Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende osilodrostat til behandling af Cushings syndrom

Vers. 1.0

Bilagsoversigt

1. Medicinrådets sundhedsøkonomiske afrapportering vedr. osilodrostat, version 1.0
2. Forhandlingsnotat fra Amgros vedr. osilodrostat
3. Høringssvar fra ansøger
4. Medicinrådets vurdering vedr. osilodrostat til behandling af Cushings syndrom, version 1.0
5. Ansøgers endelige kliniske ansøgning vedr. osilodrostat
6. Ansøgers tekniske dokument til den sundhedsøkonomiske ansøgning vedr. osilodrostat
7. Medicinrådets protokol for vurdering vedr. osilodrostat til behandling af Cushings syndrom, version 1.0

Medicinrådet

Medicinrådets sundheds-økonomiske afrapportering

Osilodrostat

Cushings syndrom

Version 1.0

Om Medicinrådet

Medicinrådet er et uafhængigt råd, som udarbejder anbefalinger og vejledninger om lægemidler til de fem regioner. Medicinrådet vurderer, om nye lægemidler og nye indikationer kan anbefales som standardbehandling, og udarbejder fælles regionale behandlingsvejledninger. Nye lægemidler vurderes i forhold til effekt, eksisterende behandling og pris. Det skal give lavere priser og lægemidler, der er til størst mulig gavn for patienterne.

Dokumentets formål

Den sundhedsøkonomiske analyse indeholder Medicinrådets vurdering af de inkrementelle omkostninger pr. patient og budgetkonsekvenserne ved anbefaling. Værdien for patienten og omkostningerne for samfundet danner grundlaget for Medicinrådets beslutning om, hvorvidt lægemidlet anbefales som mulig standardbehandling. Dette bliver sammenfattet i Medicinrådets anbefaling vedr. lægemidlet.

Den sundhedsøkonomiske analyse er udarbejdet efter *Metodevejledning for omkostningsanalyse af nye lægemidler og indikationsudvidelser i hospitalssektoren*.

Dokumentoplysninger	
Godkendelsesdato	14. december 2022
Dokumentnummer	158414
Versionsnummer	1.0

Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 15. december 2022

Indholdsfortegnelse

1. Begreber og forkortelser

AIP	Apotekernes indkøbspris
ACTH	Adrenokortikotropt hormon (*adrenocorticotropic hormone*)
DKK	Danske kroner
DRG	Diagnose Relaterede Grupper
mUFC	Gennemsnitlig fri kortisol i urinen (*mean free urinary cortisol*)
SAIP	Sygehusapotekernes indkøbspris
UFC	Frit kortisol i urinen (*urinary free cortisol*)
ULN	Øvre grænse for normalniveauet (*upper limit of normal*)

2. Konklusion

Inkrementelle omkostninger og budgetkonsekvenser
I det scenarie, Medicinrådet mener er mest sandsynligt, er de inkrementelle omkostninger for osilodrostat ca. [redacted] DKK pr. patient sammenlignet med ketoconazol, ca. [redacted] DKK pr. patient sammenlignet med metyrapon og ca. [redacted] DKK pr. patient sammenlignet med pasireotid. Når analysen er udført med apotekernes indkøbspris (AIP), er de inkrementelle omkostninger til sammenligning ca. 1.689.000 DKK pr. patient sammenlignet med ketoconazol, ca. 1.680.000 DKK pr. patient sammenlignet med metyrapon og ca. 1.614.000 DKK pr. patient sammenlignet med pasireotid.

De inkrementelle omkostninger er hovedsageligt drevet af lægemiddelomkostningerne, og den gennemsnitlige behandlingslængde for 1. linjebehandlingen er derfor en vigtig parameter. Den gennemsnitlige behandlingstid er delvist bestemt af, at patienterne i behandling med osilodrostat oplevede '*treatment escape*', hvilket er en stigning i kortisolniveauet efter at have opnået kontrol med dette. Ansøger antager i analysen, at '*treatment escape*' automatisk medfører behandlingsstop, hvilket ikke er tilfældet i dansk klinisk praksis. Det er derfor sandsynligt, at behandlingsvarigheden for osilodrostat og dermed de inkrementelle omkostninger er underestimerede.

Medicinrådet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af osilodrostat som mulig standardbehandling vil være ca. [redacted] DKK i det femte år efter en anbefaling sammenlignet med komparatorerne. Når analysen er udført med AIP, er budgetkonsekvenserne ca. 3,5 mio. DKK i det femte år.

3. Introduktion

Formålet med analysen er at estimere de gennemsnitlige inkrementelle omkostninger pr. patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af osilodrostat som mulig standardbehandling til Cushings syndrom på danske hospitaler.

Analysen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Recordati AB. Medicinrådet modtog ansøgningen den 21. april 2022.

3.1 Patientpopulation

Cushings syndrom er den kliniske tilstand, som opstår, når kroppen gennem længere tid udsættes for forhøjede mængder af binyrebarkhormon (kortisol). Kortisol dannes i binyrebarken, og syntesen stimuleres af kortikotropin (adrenokortikotropt hormon (ACTH)), som dannes i hypofysen [1]. Cushings syndrom kan skyldes forhøjet produktion af kortisol fra binyrerne (endogent Cushings syndrom), men det kan også opstå som følge af langvarig behandling med lægemidler. Patienter med Cushings syndrom kan få en række forskelligartede symptomer, fx vægtøgning, forhøjet blodtryk, nedsat muskelstyrke, psykiske forstyrrelser, blødningstendens, dårlig sårheling, øget

infektionsrisiko og knogleskørhed. Desuden har patienterne en større risiko for at udvikle diabetes.

Der er ca. 20-30 nye tilfælde om året af endogent Cushings syndrom i Danmark. Af disse antages det, at ca. 5-8 patienter er kandidater til medicinsk behandling. Denne analyse omhandler kun patienter med endogent Cushings syndrom, hvor operation i hypofysen som udgangspunkt ikke længere er en behandlingsmulighed. Dette kan være patienter, der:

- tidligere er opereret i hypofysen uden efterfølgende normalisering af kortisolniveau
- er inoperable
- har fravalgt operation i hypofysen.

Størstedelen af disse patienter behandles i dag med enten ketoconazol, metyrapon eller pasireotid, inden de gennemgår en fjernelse af begge binyrer ved en operation. Yderligere information om sygdomsområdet og behandlingerne kan findes i Medicinrådets vurderingsrapport.

3.1.1 Komparator

Medicinrådet har vurderet den kliniske værdi af osilodrostat på baggrund af følgende kliniske spørgsmål:

Klinisk spørgsmål 1:

Hvilken værdi har osilodrostat sammenlignet med ketoconazol til voksne patienter med endogent Cushings syndrom?

Klinisk spørgsmål 2:

Hvilken værdi har osilodrostat sammenlignet med metyrapon til voksne patienter med endogent Cushings syndrom?

Klinisk spørgsmål 3:

Hvilken værdi har osilodrostat sammenlignet med pasireotid til voksne patienter med endogent Cushings syndrom?

4. Vurdering af den sundhedsøkonomiske analyse

I sin ansøgning har ansøger indsendt en sundhedsøkonomisk analyse, der består af en omkostningsanalyse og en budgetkonsekvensanalyse. I omkostningsanalysen estimeres de inkrementelle omkostninger pr. patient for osilodrostat sammenlignet med hhv. ketoconazol, metyrapon og pasireotid. Medicinrådet vurderer nedenfor den sundhedsøkonomiske analyse, som ansøger har indsendt.

4.1 Antagelser og forudsætninger for modellen

Sammenligningen med de tre komparatorer er lavet på baggrund af data fra de kliniske studier som anført i Tabel 1.

Tabel 1. Oversigt over studier til at sammenligne osilodrostat med ketoconazol, metyrapon og pasireotid

	Klinisk spørgsmål 1 (vs. ketoconazol)	Klinisk spørgsmål 2 (vs. metyrapon)	Klinisk spørgsmål 3 (vs. pasireotid)
Studie til at informere om osilodrostat	LINC-3 [2]	LINC-3 [2]	LINC-3 [2]
Studier til at informere om komparatorer	Castinetti et al. 2014 [3] og Young 2018 [4]	Ceccato 2018 [5] og Daniel 2015 [6]	G2304 [7]

Ingen af studierne indeholder en direkte sammenligning mellem osilodrostat og komparatorerne. Ansøger baserer derfor effekt- og sikkerhedsparametre i den sundhedsøkonomiske model på de naive studieestimater i sammenligningerne med ketoconazol og metyrapon og laver en justeret analyse baseret på individuelle patientdata for at sammenligne LINC-3 med G2304 for sammenligningen med pasireotid.

Fagudvalget vurderer, at LINC-3 ikke er det bedst egnede studie til at estimere effekten af osilodrostat, og ville foretrække, at den sundhedsøkonomiske model var baseret på data fra LINC-4 (se Medicinrådets vurderingsrapport). Fagudvalget vurderer dog, at de kliniske resultater fra LINC-3 og LINC-4 overordnet er sammenlignelige, og forventer derfor, at det ikke har stor betydning for analysens resultater, om LINC-3 eller LINC-4 anvendes. Derfor lægges data fra LINC-3 til grund for analysen på trods af forbeholdet.

4.1.1 Modelbeskrivelse

Ansøger har indsendt en Markov-model til at estimere omkostningerne forbundet med behandlingen med osilodrostat, ketoconazol, metyrapon og pasireotid (Figur 1).

Modellen består af en række helbredsstadier, som patienten kan befinde sig i på et givent tidspunkt. Patientens bevægelse mellem de forskellige helbredsstadier bestemmes af transitionssandsynligheder, som angiver patientens sandsynlighed for at forblive i det samme helbredsstadie eller rykke videre til et andet helbredsstadie ved hver modelcyklus.

Modellen estimerer omkostninger baseret på det helbredsstadie, patienten befinder sig i, da hvert helbredsstadie er forbundet med en omkostning, der baserer sig på den behandling, patienten modtager i det pågældende stadie.

Modellen har en cykluslængde på 1 uge, hvilket ansøger argumenterer for er passende, da dette tillader fleksibilitet til at tilskrive time-to-event-data fra LINC-3 til den rette modelcyklus.

Ansøgers model består af følgende stadier:

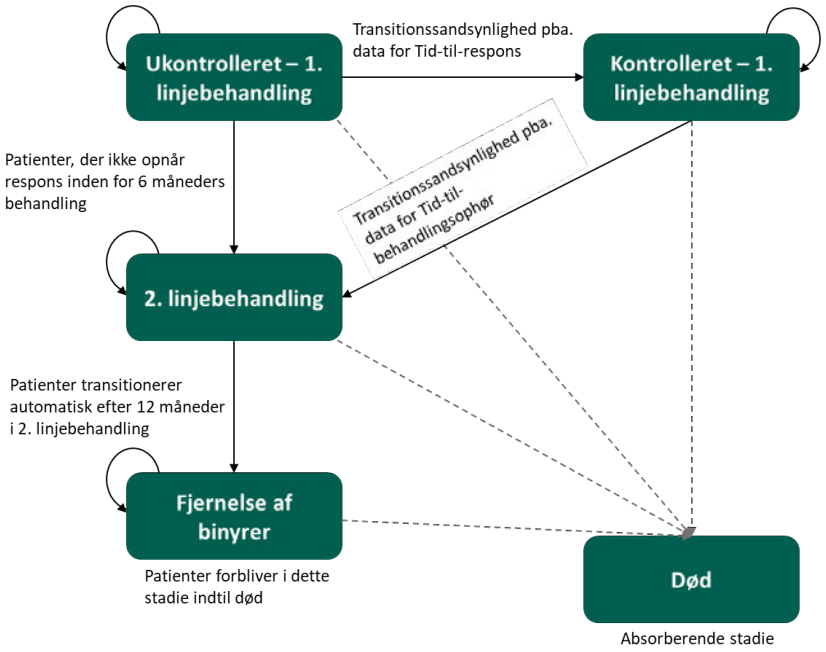
'Ukontrolleret – 1. linjebehandling': Patienter, der har forhøjet niveau af kortisol, og hvor operation af hypofysen ikke har medført en normalisering, eller hvor patienten ikke kan/vil opereres. Patienten påbegynder 1. linje medicinsk behandling med osilodrostat eller én af komparatorerne for at sænke kortisolniveauet. Alle patienter starter i dette stadium.

'Kontrolleret – 1. linjebehandling': Patienten modtager 1. linje medicinsk behandling med osilodrostat eller én af komparatorerne og har opnået normalisering af kortisolniveau. Patientens sandsynlighed for at tilgå dette stadium er afhængig af raten for komplet respons samt tid til komplet respons for den givne behandling (se 'Ansøgers modellering af tid-til-respons'). Sandsynlighederne er baseret på direkte studiedata fra LINC-3 (osilodrostat) og G2304 (pasireotid). For metyrapon og ketoconazol er sandsynlighederne baseret på en naiv sammenligning af responsrater for metyrapon (Ceccato 2018 og Daniel 2015) og ketoconazol (Castinetti 2014) med responsraterne fra LINC-3, hvorefter tid-til-komplet-respons er modelleret ud fra data for osilodrostat vha. hazard ratioer (Tabel 2).

'2. linjebehandling': Patienten har ikke tilstrækkelig kontrol med kortisolniveauet efter 1. linje medicinsk behandling og er derfor påbegyndt 2. linjebehandling. Patienter tilgår dette stadium, hvis de enten ikke opnår komplet respons inden for 6 måneders behandling, eller hvis patienten opnår komplet respons, som herefter ophører baseret på 'tid-til-behandlingsophør' (se 'Ansøgers modellering af tid-til-behandlingsophør'). Sandsynlighederne for at tilgå stadiet er baseret på studiedata fra LINC-3 (osilodrostat) og G2304 (pasireotid). For metyrapon og ketoconazol er sandsynlighederne baseret på en naiv sammenligning af andel patienter, der har ophørt behandling med ketoconazol (Young 2018 og Castinetti 2014) med tilsvarende andel fra LINC-3, hvorefter tid-til-behandlingsophør for 1. linje modelleres ud fra data for osilodrostat vha. hazard ratioer (Tabel 3) og en antagelse om, at tid-til-behandlingsophør i 1. linje er ens for ketoconazol og metyrapon. Patienten forbliver i '2. linjebehandling' i 12 måneder baseret på ansøgers antagelse.

'Fjernelse af binyrer': Patienten har ikke længere tilstrækkelig kontrol med kortisolniveauet og er ikke længere kandidat til medicinsk behandling. Patienten får fjernet begge binyrer ved en operation, hvorved patientens kortisolniveau reduceres. Patienten tilgår dette stadium efter 12 måneder i '2. linjebehandling' (se 'Ansøgers antagelser om behandlingstid for 2. linje og direkte overgang til fjernelse af binyrer'). Ansøger antager, at alle patienter i dette stadium opnår normaliseret kortisolniveau.

'Død': Patienten er død. Dette er et absorberende stadium, som patienten kan overgå til fra alle andre stadier. Patientens sandsynlighed for at tilgå dette stadium er afhængig af dødeligheden i den almene befolkning samt en tilskrevet forøget risiko for død i modellens forskellige stadier (se 'Ansøgers antagelser om risikoen for død').



Figur 1. Oversigt over Markov-modellen til at estimere omkostningerne forbundet med behandlingen af Cushings syndrom for patienter, der ikke har opnået normalisering af kortisolniveauet gennem en operation i hypofysen, eller hvor operation i hypofysen ikke har været mulig.

Medicinrådets vurdering af ansøgers model

Medicinrådet vurderer, at ansøgers model overordnet kan anvendes til at repræsentere behandlingen af patienter med endogent Cushings syndrom, der skyldes en ACTH-producerende svulst i hypofysen, og som ikke opnår en normalisering af kortisolniveau ved operation i hypofysen. Fagudvalget fremhæver, at nogle patienter har ACTH-uafhængigt Cushings syndrom eller ACTH-afhængigt Cushings syndrom, der skyldes en tumor uden for hypofysen (ektopisk Cushings syndrom), og at disse patienter følger en anderledes behandlingsalgoritme, hvor binyrerne ofte fjernes tidligere i algoritmen. Disse patienter vil normalt ikke være kandidater til længere tids behandling med osilodrostat. Fagudvalget vurderer, at ca. 75 % af patienterne har Cushings syndrom, der skyldes en ACTH-producerende svulst i hypofysen, så modellen vil være repræsentativ for størstedelen af populationen.

Fagudvalget bemærker desuden, at patienter både kan være kandidater til medicinsk behandling, hvis de tidligere er forsøgt opereret, eller hvis det er nødvendigt at opnå klinisk forbedring inden en operation af hypofysen. Den sidstnævnte population indgår ikke i modellen, men disse patienter vil typisk kun modtage midlertidig medicinsk behandling (med osilodrostat eller én af komparatorerne) (typisk 2-6 måneder), indtil operation i hypofysen er mulig. Medicinrådet forventer derfor ikke, at denne delpopulation har betydning for analysens resultat.

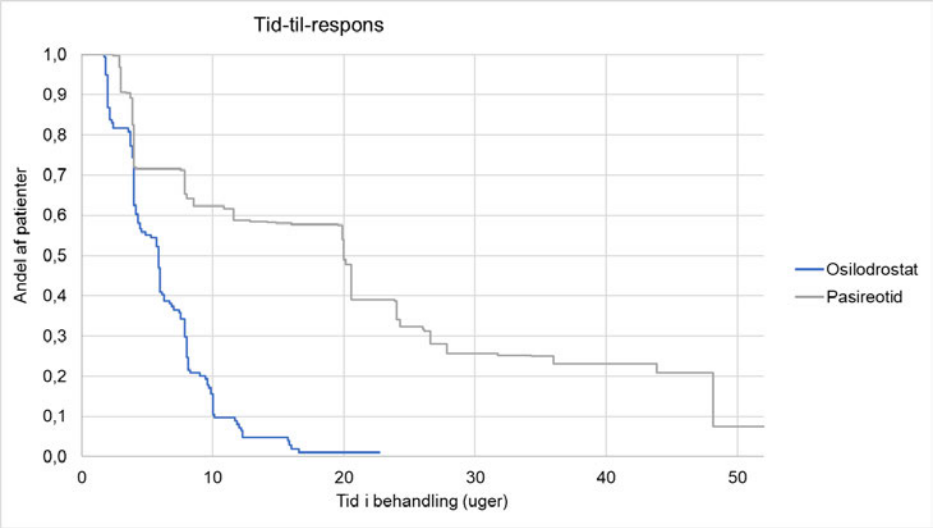
Medicinrådet accepterer ansøgers tilgang vedr. modellens opbygning.

4.1.2 Modelantagelser og -beskrivelse

Ansøger modellerer tiden i de forskellige stadier ved at anvende tid-til-respons-data fra LINC-3 og G2304 (overgang fra 'Ukontrolleret – 1. linjebehandling' til 'Kontrolleret – 1. linjebehandling') samt ekstrapolerede data for tid-til-behandlingsophør (overgang fra 'Kontrolleret – 1. linjebehandling' til '2. linjebehandling').

Ansøgers modellering af tid-til-respons

Tid-til-respons er baseret på individuelle patientdata fra LINC-3 og G2304. Nedenstående figur viser Kaplan-Meier-data for tid-til-respons.



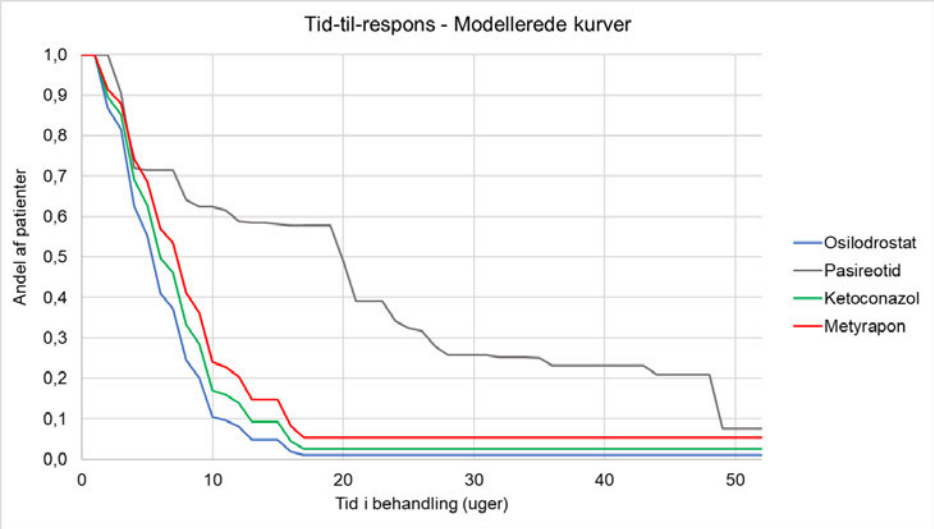
Figur 2. Kaplan-Meier-kurve, der viser tid-til-respons baseret på individuelle patientdata fra LINC-3 (osilodrostat) og G2304 (pasireotid)

Ansøger antager, at 1. linjebehandlingen stoppes for de patienter, der ikke har opnået respons efter 6 måneder, hvorefter de overgår til 2. linjebehandling. Ansøger har ikke individuelle patientdata for tid-til-respons for ketoconazol eller metyrapon. Ansøger modellerer i stedet tid-til-respons ud fra en naiv sammenligning af responsrater mellem osilodrostat og hhv. ketoconazol og metyrapon ved et enkelt opfølgningstidspunkt og finder herfra hazard ratioer ved at antage, at hazard ratioerne er konstante over tid (Tabel 2).

Tabel 2. Oversigt over hazard ratioer, som ansøger anvender til at modellere tid-til-respons for metyrapon og ketoconazol

Tidspunkt	Intervention		Komparator		Hazard ratio
	Lægemiddel (studie)	Andel patienter med komplet respons	Lægemiddel (studie)	Andel patienter med komplet respons	
3 måneder	Osilodrostat (LINC-3)	98/137	Metyrapon (Ceccato 2018 [5])	17/31	1,58
24,8 måneder	Osilodrostat (LINC-3)	64/137	Ketoconazol (Castinetti 2014 [8])	78/200	1,27

Hazard ratioerne anvendes til at modellere tid-til-respons-kurver for ketoconazol og metyrapon ud fra kurven for osilodrostat. Derved opnås nedenstående kurver (Figur 3), som ansøger anvender til at estimere tid-til-respons i modellen og derved sandsynligheden for at overgå fra modelstadiet, 'Ukontrolleret – 1. linjebehandling' til 'Kontrolleret – 1. linjebehandling' (se gennemsnitlig tid-til-respons i Tabel 5). Med de anvendte kurver estimeres det, at hhv. ca. 99 %, ca. 98 %, ca. 95 % og ca. 66 % af patienterne vil opnå respons inden for 6 måneders behandling med osilodrostat, ketoconazol, metyrapon eller pasireotid.



Figur 3. Ansøgers modellerede kurver for tid-til-respons, som anvendes til at estimere transitionssandsynligheden mellem modelstadierne, 'ukontrolleret – 1. linjebehandling' og 'kontrolleret – 1. linjebehandling'

Medicinrådets vurdering af tid-til-respons

Tid-til-respons for ketoconazol og metyrapon er modelleret ud fra hazard ratioer for ét sammenligningstidspunkt ud fra en naiv sammenligning af tre studier med meget

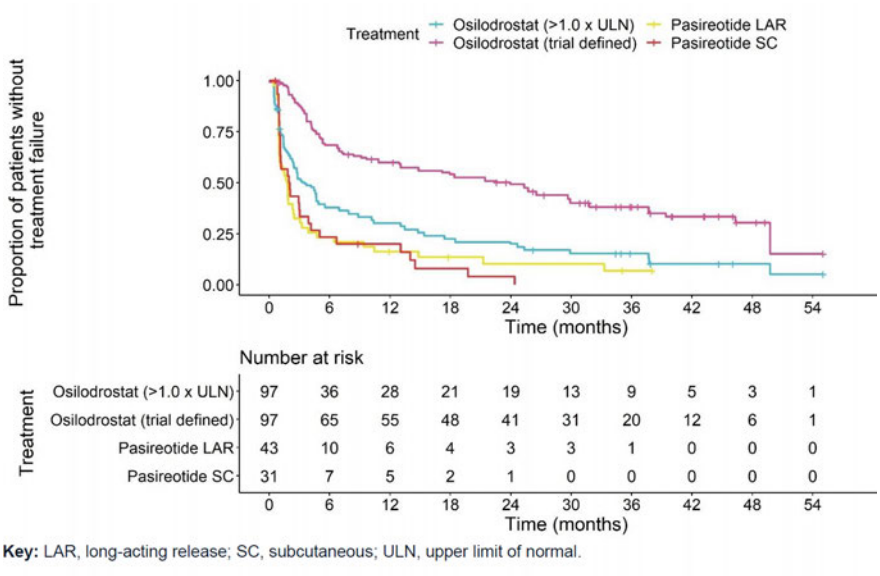
forskellig opbygning og en antagelse om, at disse hazard ratioer er konstante over tiden. Fagudvalget vurderer, at dette er usandsynligt. Fagudvalget vurderer dog ikke, at der er en bedre egnet tilgang ud fra det tilgængelige datagrundlag. Samtidig har antagelsen lille betydning for analysens resultat, og derfor accepterer Medicinrådet ansøgers fremgangsmåde.

Ansøgers modellering af tid-til-behandlingsophør

Ansøger modellerer tid-til-behandlingsophør ud fra det samlede mål '*time-to-treatment failure*' for osilodrostat. '*Time-to-treatment failure*' er ikke et defineret endepunkt i LINC-3. I stedet har ansøger lavet en samlet '*Time-to-treatment failure*'-kurve ud fra den andel patienter, der enten ophører behandling grundet bivirkninger, grundet manglende respons, dør (kun én patient) eller oplever "*treatment escape*". '*Treatment escape*' er en afgørende faktor for de samlede "*time-to-treatment failure*"-estimater. I LINC-3 defineres '*treatment escape*' som [9]:

Første tab af kontrol over gennemsnittet af frit kortisol i urinen (mean free urinary cortisol/mUFC) efter mindst et tilfælde af normalisering af UFC. Tab af kontrol defineres herefter som: Både mUFC og minimum 2 enkeltmålinger, der bidrager til mUFC, skal overstige 1,5 x øvre normalgrænse (upper limit of normal/ULN). Stigningen i UFC måtte ikke være relateret til en dosisafbrydelse eller dosisreduktion, som følge af sikkerhedshændelser. Stigningen skal forekomme efter den initiale 12-ugers titreringsperiode.

Ansøger bruger ikke denne definition i sin model, men ændrer grænsen for '*treatment escape*' til mUFC > 1 x ULN, hvilket i praksis betyder, at langt flere patienter har et '*escape event*' end rapporteret i LINC-3. Figur 4 viser Kaplan-Meier-kurven for time-to-escape.

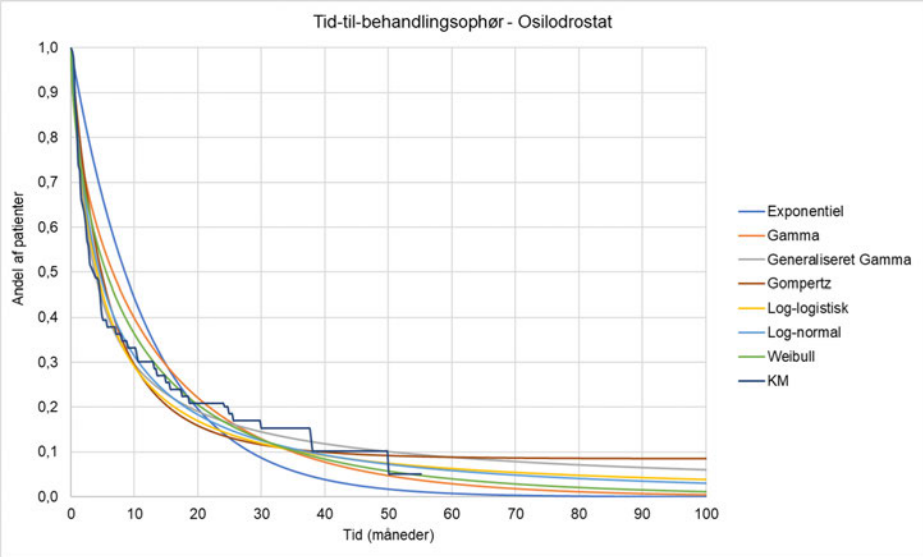


Key: LAR, long-acting release; SC, subcutaneous; ULN, upper limit of normal.

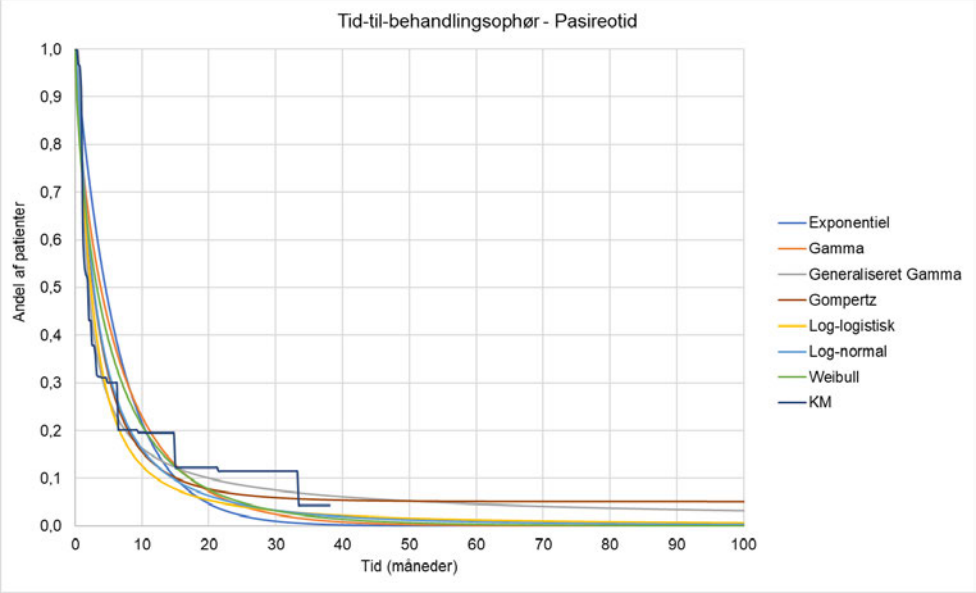
Figur 4. '*Time-to-escape*'-kurver for osilodrostat baseret på LINC-3. I LINC-3 blev der anvendt en grænseværdi på 1,5 x *upper limit of normal* (ULN) for den gennemsnitlige kortisolkoncentration i urinen (lilla kurve). Ansøger antager i stedet en grænse for escape på 1 x ULN (turkis kurve).

Ansøger argumenterer ikke for, hvorfor de anvender en grænse for '*treatment escape*', der er lavere end defineret i LINC-3. Ansøger argumenterer heller ikke for antagelsen om, at '*treatment escape*' skulle medføre behandlingsophør, hvilket ikke var tilfældet i LINC-3. For pasireotid har ansøger vægtet Kaplan-Meier-kurven ift. LINC-3-populationen.

Ansøger ekstrapolerer kurverne for tid-til-behandlingsophør ved 7 parametriske funktioner og undersøger det statiske fit. Ansøger argumenterer for, at log-normal funktionen giver det bedste statiske fit, hvis den samme ekstrapoleringsfunktion skal anvendes til både osilodrostat (Figur 5) og pasireotid (Figur 6), og vælger derfor denne.



Figur 5. Ekstrapolerede kurver for tid-til-behandlingsophør for osilodrostat ved anvendelse af *'treatment escape'* defineret som mUFC > 1 x ULN (ansøgers antagelse)



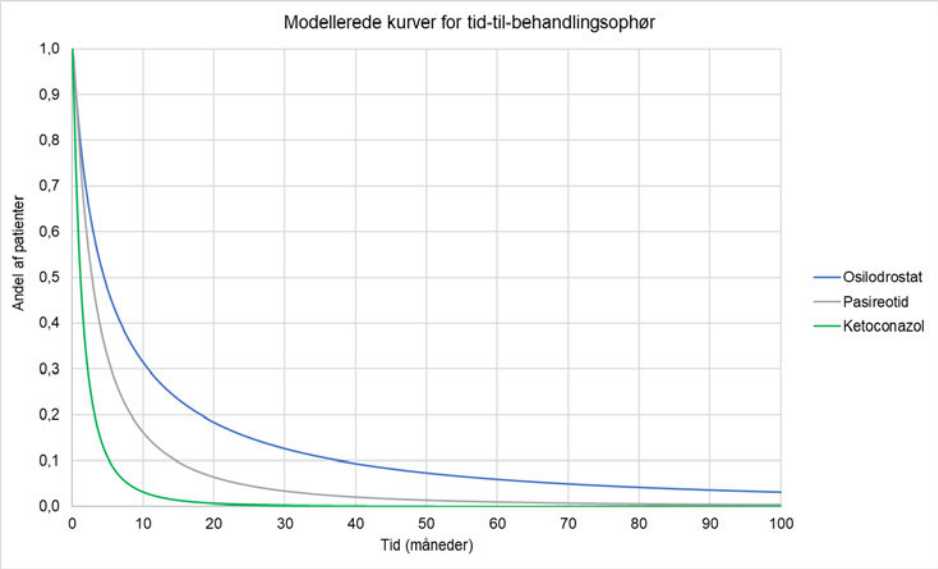
Figur 6. Ekstrapolerede kurver for tid-til-behandlingsophør for pasireotid

Ansøger estimerer tid-til-behandlingsophør for ketoconazol og metyrapon ud fra en naiv sammenligning af andelen af patienter, der ophører behandling i studierne mellem osilodrostat og ketoconazol, som de anvender til at estimere en hazard ratio mellem ketoconazol og osilodrostat (Tabel 3). Ansøger anvender hazard ratioen bestemt ved 3 måneders opfølgning til at modellere kurven for tid-til-behandlingsophør for ketoconazol ud fra kurven for osilodrostat. Herefter antager ansøger, at tid-til-behandlingsophør er ens for ketoconazol og metyrapon.

Tabel 3. Oversigt over hazard ratioer, som ansøger anvender til at modellere tid-til-behandlingsophør for metyrapon og ketoconazol

Tidspunkt	Intervention		Komparator		Hazard ratio
	Lægemiddel (studie)	Andel patienter med behandlingsophør	Lægemiddel (studie)	Andel patienter med behandlingsophør	
3 måneder	Osilodrostat (LINC-3)	19/137	Ketoconazol (Young 2018 [10])	39/108	0,33
24,8 måneder	Osilodrostat (LINC-3)	58/137	Ketoconazol (Castinetti 2014 [8])	118/160	0,41

De samlede tid-til-behandlingsophør-kurver ved anvendelse af ansøgers antagelser er vist i Figur 7.



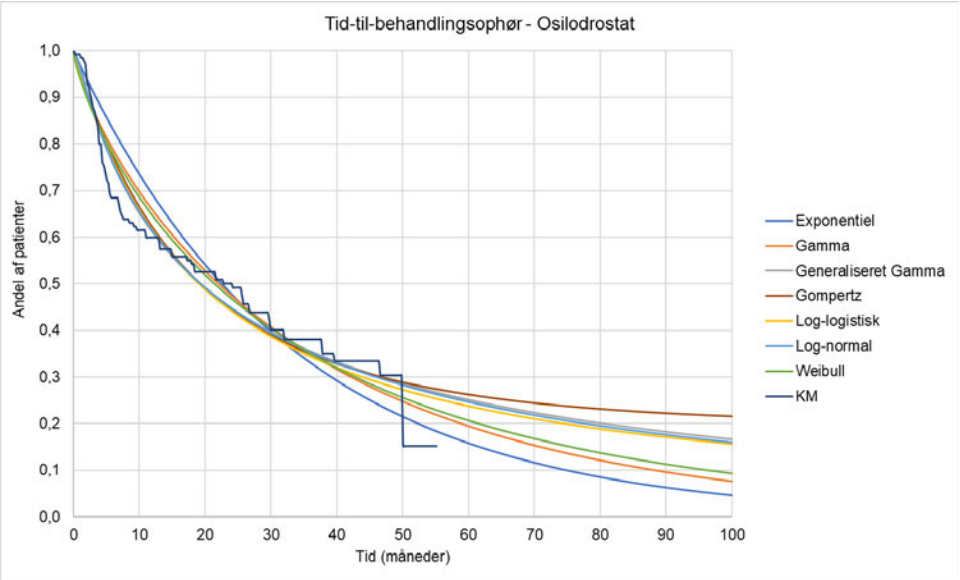
Figur 7. Modellerede kurver for tid-til-behandlingsophør baseret på ansøgers antagelser. Ansøger antager, at kurven for metyrapon er identisk med kurven for ketoconazol.

Medicinrådets vurdering af tid-til-behandlingsophør

Fagudvalget vurderer, at ansøgers estimater for tid-til-behandlingsophør er urealistiske og medfører en underestimering af omkostningerne til osilodrostat ift. den forventede effekt. Ansøger anvender et sammensat endepunkt ('*time-to-treatment failure*'), hvor '*treatment escape*' i LINC-3 har stor betydning. Fagudvalget vurderer, at dette ikke er repræsentativt for behandlingen i dansk klinisk praksis og heller ikke i overensstemmelse med de kliniske data. Fagudvalget begrunder dette med:

- '*Treatment escape*' som defineret i LINC-3 medfører ikke automatisk behandlingsophør i dansk klinisk praksis. Almindeligvis vil en måling lidt over normalniveauet ikke medføre nogen ændringer, medmindre UFC bliver ved med at stige, og i sådanne tilfælde vil man i dansk klinisk praksis almindeligvis forsøge en dosisjustering, medmindre patienten i forvejen modtager den maksimalt tolerable dosis.
- '*Treatment escape*' medførte heller ikke behandlingsstop i LINC-3. Tværtimod angives det i EPAR, at mange patienter med '*treatment escape event*' genvandt kontrollen over UFC med eller uden en øgning af osilodrostatdosis. Samtidig fremhæves det, at 66 % af patienterne, der responderede, havde opretholdt respons i minimum 6 måneder [9].
- Den gennemsnitlige tid i behandling i LINC-3 var 80,3 uger, hvilket overstiger ansøgers estimat, når *'time-to-treatment escape'* inddrages.
- I EPARen fremhæves, at der er langtidsdata for behandling af 17 patienter fra LINC-1/2. Responsdata efter 46 måneders opfølgning viser, at 58,8 % stadig opretholder komplet respons (UFC < ULN) på dette tidspunkt [9].

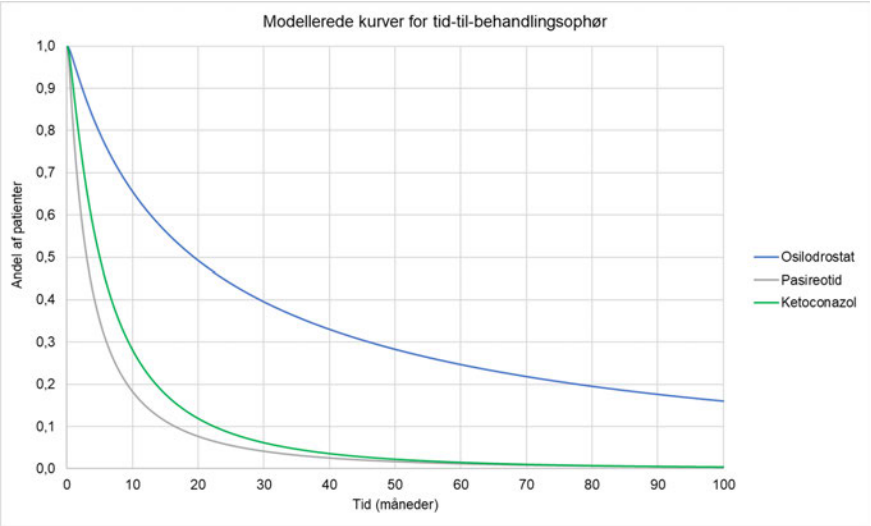
Medicinrådet ændrer ansøgers antagelse angående '*treatment escape*' til at matche definitionen i LINC-3, dvs. mUFC > 1,5 x ULN i stedet for mUFC > 1 x ULN som antaget af ansøger. Dette fjerner ikke det problematiske i, at '*treatment escape*' sættes lig med behandlingsophør, når dette ikke er almindelig praksis hverken i Danmark eller i de kliniske studier. Derfor antager Medcinrådet, at behandlingsvarigheden af osilodrostat stadig er underestimeret i Medicinrådets hovedanalyse. Det mindsker betydningen af antagelsen, når grænsen for '*treatment escape*' hæves til mUFC > 1,5 x ULN, og samtidig betyder det, at definitionen af *'treatment escape'* svarer til definitionen i det studie, som data er opsamlet fra. Kaplan-Meier-data for tid-til-behandlingsophør samt ekstrapolation af data ses i Figur 8.



Figur 8. Ekstrapolerede kurver for tid-til-behandlingsophør for osilodrostat ved anvendelse af '*treatment escape*' defineret som mUFC > 1,5 x ULN ligesom i LINC-3

Ekstrapolationen med log-normal-funktionen resulterer i det bedste statiske fit, da denne funktion resulterer i de laveste værdier for *Akaike information criteria* og *Bayesian information criteria*. Fagudvalget kan ikke udtale sig om, hvorvidt den ene ekstrapolationsfunktion er mere klinisk plausibel end de andre. Derfor anvender Medicinrådet log-normal-funktionen i sin hovedanalyse, men udfører følsomhedsanalyser for de andre ekstrapolationer. Medicinrådets antagelse om, at *'treatment escape'* skal defineres som mUFC > 1,5 x ULN, medfører en forlængelse af den gennemsnitlige behandlingstid for osilodrostat, ketoconazol og metyrapon (Tabel 6). Denne ændring vurderes at have stor betydning for analysens resultat, da behandlingsvarigheden for osilodrostat forlænges med ca. faktor 3.

De samlede tid-til-behandlingsstop-kurver i Medicinrådets hovedanalyse er vist i Figur 9.



Figur 9. Modellerede kurver for tid-til-behandlingsophør i Medicinrådets hovedanalyse. Kurven for metyrapon er identisk med kurven for ketoconazol.

Ansøgers antagelser om behandlingstid for 2. linje og direkte overgang til fjernelse af binyrer

Ved behandlingsophør af 1. linjebehandling antager ansøger, at alle patienter vil modtage 2. linjebehandling i stedet for at overgå direkte til fjernelse af binyrerne. Ansøger har ingen data til at estimere tiden i 2. linjebehandling. I stedet antager ansøger en gennemsnitlig behandlingsvarighed på 12 måneder, baseret på input fra kliniske eksperter.

Medicinrådets vurdering af antagelser om behandlingstid for 2. linje og direkte overgang til fjernelse af binyrer

Fagudvalget vurderer, at ansøgers antagelse om, at alle patienter modtager 2. linje medicinsk behandling ved manglende eller ophørt effekt af 1. linjebehandlingen, er plausibel. Fagudvalget påpeger, at nogle patienter vil få fjernet binyrerne med det samme i stedet for at gennemgå 2. linjebehandling, men det vil være meget få patienter, og fagudvalget kan ikke give et præcist estimat for dette. Derfor accepterer Medicinrådet ansøgers antagelse.

På baggrund af klinisk erfaring vurderer fagudvalget desuden, at 12 måneders gennemsnitlig behandlingsvarighed ved 2. linje medicinsk behandling virker som lang tid. Fagudvalget vurderer, at dette kan føre til en overestimering af omkostningerne ved behandling i 2. linje. Den gennemsnitlige behandlingstid har betydning for analysens resultat, da den i flere tilfælde overskrider den gennemsnitlige behandlingstid for 1. linjebehandlingen, hvorved 2. linjebehandlingen bliver betydende for de samlede omkostninger, særligt for komparatorerne. Fagudvalget kan ikke med rimelig sikkerhed estimere en mere sandsynlig gennemsnitlig behandlingstid for 2. linjebehandling. Derfor accepterer Medicinrådet ansøgers antagelse, men vil foretage en følsomhedsanalyse, hvor den gennemsnitlige behandlingstid ændres til 6 måneder.

Ansøgers antagelser om risikoen for død

LINC-3 kan ikke anvendes til at estimere risikoen for død i modellen, da der kun indtraf ét dødsfald i studiet. Ansøger anvender i stedet dødeligheden i den generelle befolkning som udgangspunkt for sandsynligheden for at overgå til stadiet død. Transitionssandsynligheden i de forskellige modelstadier varieres ved at antage en konstant mortalitetsratio ift. den generelle befolkning i hvert modelstadie (Tabel 4). Ansøger baserer mortalitetsraterne på et svensk registerstudie med 502 patienter behandlet i perioden 1987-2013 [11] og anvender dødelighed for den gennemsnitlige danske befolkning baseret på tal fra Danmarks Statistik.

Tabel 4. Mortalitetsrater ift. den generelle befolkning i forskellige modelstadier

Stadium	Mortalitetsrate	Reference
Ukontrolleret sygdom	6,9 [95 % CI: 4,3; 10]	Ragnarsson 2019 [11]
Kontrolleret sygdom	1,9 [95 % CI: 1,5; 2,3]	Ragnarsson 2019 [11]
Kontrolleret sygdom efter fjernelse af binyrerne	3,6	Ragnarsson 2019 [11] og klinisk ekspert

De fundne mortalitetsrater sammen med dødeligheden for den generelle befolkning af tilsvarende alder anvendes igennem hele modellens tidshorisont til at estimere transitionssandsynligheden for død fra alle modelstadier. Ved ansøgers antagelser resulterer dette i en gennemsnitlig overlevelse på ca. 30 år for både osilodrostat og komparatorerne.

Medicinrådets vurdering af antagelser om risikoen for død

Fagudvalget vurderer, at ansøgers estimater for dødeligheden er rimelige. Samtidig har dødeligheden i modellen minimal betydning for analysens resultater, da der ikke tilskrives terminale omkostninger ved død, og langt de fleste dødsfald forekommer, efter patienterne har gennemgået operation til fjernelse af binyrerne. Medicinrådet anvender derfor ansøgers tilgang til modellering af risikoen for død.

Konklusion angående ansøgers modelantagelser og Medicinrådets vurdering af disse

På baggrund af individuelle patientdata, naive sammenligninger og ekstrapoleringerne har ansøger estimeret den gennemsnitlige tid, patienten befinder sig i modellens stadier.

Tabel 5. Gennemsnitlig tid-til-respons og behandlingstid i 1. og 2. linje ved ansøgers antagelser uden begrænsning for tidshorisont

Behandling	Tid-til-respons	Gennemsnitlig behandlingstid i 1. linje	Gennemsnitlig behandlingstid i 2. linje
Osilodrostat	1,53 måneder	21,5 måneder	12 måneder*
Ketoconazol	1,77 måneder	4,9 måneder	

Behandling	Tid-til-respons	Gennemsnitlig behandlingstid i 1. linje	Gennemsnitlig behandlingstid i 2. linje
Metyrapon	2,02 måneder	5,1 måneder	
Pasireotid	3,75 måneder	10,4 måneder	

*Ansøger antager, at behandlingsvarigheden af 2. linjebehandlingen gennemsnitligt er 12 måneder, uanset hvilken 2. linjebehandling der administreres.

Fagudvalget vurderer, at der er stor usikkerhed forbundet med ansøgers antagelser for både tid-til-respons, tid-til-behandlingsophør og gennemsnitlig behandlingstid i 2. linje, hvilket er uddybet i afsnittene ovenfor. Kort opsummeret vurderer fagudvalget, at ansøger underestimerer den gennemsnitlige behandlingsvarighed for osilodrostat ved at antage, at '*treatment escape*' automatisk medfører behandlingsstop, og ved at anvende en grænse for '*treatment escape*', der er lavere end grænsen defineret i LINC-3. Medicinrådet ændrer derfor grænsen for '*treatment escape*', så den stemmer overens med grænsen i LINC-3. Gennemsnitlig tid-til-respons, behandlingstid i 1. linje og behandlingstid i 2. linje anvendt i Medicinrådets analyse fremgår af Tabel 6.

Tabel 6. Gennemsnitlig tid-til-respons og behandlingstid i 1. og 2. linje i Medicinrådets hovedanalyse uden begrænsning for tidshorisont

Behandling	Tid-til-respons	Gennemsnitlig behandlingstid i 1. linje	Gennemsnitlig behandlingstid i 2. linje
Osilodrostat	1,5 måneder	59,8 måneder	12 måneder*
Ketoconazol	1,8 måneder	11,8 måneder	
Metyrapon	2,0 måneder	11,8 måneder	
Pasireotid	3,8 måneder	10,4 måneder	

*Ansøger antager, at behandlingsvarigheden af 2. linjebehandlingen gennemsnitligt er 12 måneder, uanset hvilken 2. linjebehandling der administreres.

Medicinrådet accepterer ansøgers overordnede tilgang vedr. modelantagelser. Dog ændrer Medicinrådet grænsen for 'treatment escape' til at matche definitionen i LINC-3, som var mUFC > 1,5 x ULN. Medicinrådet udfører en følsomhedsanalyse, hvor grænsen for 'treatment escape' sættes til mUFC > 1 som antaget af ansøger for at illustrere betydningen af denne antagelse for analysens resultat. Medicinrådet vælger desuden at udarbejde en følsomhedsanalyse, hvor den gennemsnitlige behandlingsvarighed af 2. linjebehandlingen reduceres fra 12 til 6 måneder. Endelig udarbejder Medicinrådet følsomhedsanalyser for de forskellige ekstrapoleringsfunktioner for tid-til-behandlingsophør.

4.1.3 Analyseperspektiv

I overensstemmelse med Medicinrådets metoder har ansøger valgt et begrænset samfundsperspektiv til sin analyse. Ansøger har valgt en tidshorisont på 2 år med den begrundelse, at denne tidshorisont er mest realistisk ift. faktiske behandlingsvarigheder for sygdommen i Danmark.

Omkostninger, der ligger efter det første år, er diskonteret med en rate på 4 % pr. år.

Medicinrådets vurdering af ansøgers analyseperspektiv
Jf. Medicinrådets metodevejledning skal analysens tidshorisont være tilstrækkelig til at opfange alle væsentlige omkostninger ved interventionen og komparatorerne. Dette opnås ikke ved en tidshorisont på 2 år, hvor ca. 47 % af patienterne stadig vil være i 1. linjebehandling med osilodrostat. Medicinrådet ændrer tidshorisonten til 50 år, så modellen opfanger det fulde estimerede behandlingsforløb med osilodrostat. Fagudvalget fremhæver, at den lange tidshorisont medfører betydelig usikkerhed, og ifølge fagudvalgets kliniske erfaring med komparatorerne er det meget sjældent, at patienter er i medicinsk behandling i mere end 5 år. Fagudvalget har dog ikke erfaring med behandling med osilodrostat, og ud fra de nuværende kliniske data for osilodrostat kan det forekomme, at patienterne kan behandles i væsentlig længere tid med osilodrostat end med de nuværende behandlinger. Medicinrådet foretager dog en følsomhedsanalyse, hvori det antages, at behandlingen afsluttes efter 5 år. Medicinrådet antager i følsomhedsanalysen, at patienter, som stadig er i 1. eller 2. linjebehandling efter 5 år, ophører behandling og gennemgår fjernelse af binyrerne, da årsagen til at ophøre med behandlingen vil være, at effekten ophører.

Den ændrede tidshorisont vurderes at have stor betydning for analysens resultat.

Medicinrådet ændrer desuden diskonteringsraten til 3,5 % i år 2-35 og 2,5 % i år 36-50 ifølge Finansministeriets diskonteringsrente.

Medicinrådet ændrer diskonteringsrenten til 3,5 % i år 2-35 og 2,5 % i år 36-50. Medicinrådet ændrer ansøgers valg vedr. analyseperspektiv. Tidshorisonten i Medicinrådets hovedanalyse justeres til 50 år. Desuden foretager Medicinrådet en følsomhedsanalyse, hvor Medicinrådet antager, at alle patienter ophører behandling efter 5 år.

4.2 Omkostninger

I det følgende præsenteres ansøgers antagelser for omkostningerne i den sundhedsøkonomiske analyse af osilodrostat sammenlignet med ketoconazol, metyrapon og pasireotid. Ansøger har inkluderet lægemiddelomkostninger, hospitalsomkostninger, patientomkostninger og omkostninger til efterfølgende behandlinger. Ansøger har dog inddraget patientomkostninger for tabt arbejdsfortjeneste, hvilket ikke accepteres i Medicinrådets omkostningsanalyse, jf. Medicinrådets metodevejledning. Omkostninger relateret til tabt arbejdsfortjeneste ekskluderes derfor fra Medicinrådets hovedanalyse. Der indgår ikke patientomkostninger omfattet af Metodevejledningen i ansøgers analyse.

Omkostningerne er cyklusbestemt, hvilket betyder, at omkostningerne påregnes for hver cyklus, patienten befinder sig i stadiet.

For stadiet 'Fjernelse af binyrer' erstattes størstedelen af de cyklusbestemte omkostninger med transitionsomkostninger ved indgangen til stadiet. Disse omfatter omkostninger til fjernelse af binyrerne, uønskede hændelser og mulige komplikationer i forbindelse med operationen samt monitoreringsomkostninger i de første fire uger efter operationen. De eneste cyklusbestemte omkostninger for stadiet er hospitalsomkostninger i forbindelse med kroniske komplikationer og monitorering i den kroniske fase efter operationen.

4.2.1 Lægemiddelomkostninger

Ansøger har estimeret lægemiddelomkostninger på baggrund af apotekernes indkøbspris (AIP). Ansøger har angivet et dosisinterval for alle lægemidlerne baseret på de respektive produkters produktresuméer (se Tabel 8). Dosisintervallerne er relativt brede, hvilket skyldes, at dosis normalt titreres, indtil patienten opnår respons eller når den maksimalt tolerable dosis. Ansøger anvender de faktiske dosisdistributioner fra LINC-3 (osilodrostat) og G2304 (pasireotid) til at estimere lægemiddelomkostningerne. Den gennemsnitlige dosisdistribution i LINC-3 ses nedenfor (Tabel 7), mens de detaljerede tabeller er vist i bilaget, afsnit 10.3).

Tabel 7. Gennemsnitlig dosisdistribution af tilgængelige styrker af osilodrostat på baggrund af LINC-3

Osilodrostat	1 mg	5 mg	10 mg
Gennemsnitligt antal tabletter pr. døgn	2,11	0,54	0,58

For ketoconazol og metyrapon anvender ansøger en gennemsnitsdosis baseret på Castinetti et al. 2014 (ketoconazol) og PROMT (metyrapon) (ingen specifik reference). De gennemsnitlige doser fremgår af Tabel 8.

Medicinrådets vurdering af ansøgers antagelser vedr. lægemiddelomkostninger
Medicinrådet anvender dosisdistributionen for osilodrostat og gennemsnitsdoser for ketoconazol og metyrapon som angivet af ansøger, da fagudvalget vurderer, at disse er realistiske. Medicinrådet ændrer dosisdistributionen for pasireotid, da ansøger har antaget, at 68 % af patienterne modtager 10 mg pr. dosis. Den lavest tilgængelige styrke i Danmark er 20 mg, og fagudvalget vurderer, at alle patienter opstartes og forbliver på denne dosis. Denne ændring vurderes [redacted]

Medicinrådet har udskiftet AIP med sygehusapotekernes indkøbspris (SAIP), se Tabel 8.

Tabel 8. Anvendte lægemiddelpriser, SAIP (november 2022)

Lægemiddel	Styrke	Anbefalet dosis fra EMAs produkt-resume	Mg/dosis	Pakkings-størrelse	Pris [DKK]	Kilde
Osilodrostat	1 mg	2-30 mg 2 gange dagligt	10,7 mg*	60 stk.	[redacted]	Amgros
	5 mg				[redacted]	
	10 mg				[redacted]	
Ketoconazol	200 mg	400-1.200 mg pr. dag fordelt på 2-3 doser	800 mg	60 stk.	[redacted]	Amgros
Metyrapon	250 mg	250-6.000 mg dagligt fordelt på 3-4 doser	2.000 mg	50 stk.	[redacted]	Amgros
Pasireotid	20 mg	10-40 mg hver 4. uge	20 mg	1 stk.	[redacted]	Amgros

*Gennemsnitsdosis er udregnet pga. dosisdistributionen i LINC-3. I den sundhedsøkonomiske analyse anvendes gennemsnitsdosis for osilodrostat ikke til at udregne lægemiddelomkostningerne. I stedet anvendes den faktiske dosisfordeling (se Tabel 7 og Tabel 27), da den faktiske kombination af tabletstyrker har betydning for de samlede omkostninger.

Medicinrådet accepterer ansøgers valg vedr. lægemiddelomkostninger, men ændrer doseringen af pasireotid, så den svarer til den tilgængelige styrke i Danmark.

4.2.2 Hospitalsomkostninger

Ansøger inkluderer administrationsomkostninger, monitoreringsomkostninger, bivirkningsomkostninger, omkostninger til behandling af komorbiditet og omkostninger i forbindelse med operation for fjernelse af binyrerne.

Administrationsomkostninger

Ansøger har inkluderet administrationsomkostninger for pasireotid i form af en månedlig intramuskulær injektion. Ansøger har prissat dette ud fra priserne for sygebesøg i Södra Regionsvårdsnämnden, Sverige. De øvrige lægemidler administreres oralt, og ansøger antager, at dette ikke medfører omkostninger.

Medicinrådets vurdering af ansøgers antagelser vedr. administrationsomkostninger

Medicinrådet accepterer ansøgers antagelser om, at der er administrationsomkostninger forbundet med pasireotid, men ikke ved osilodrostat, ketoconazol eller metyrapon. Medicinrådet vælger at anvende en DRG-takst på 1.954 DKK (MDC10 1-dagsgruppe, pat.

mindst 7 år) til estimering af administrationsomkostninger for pasireotid. Ændringen har lille betydning for analysens resultat.

Medicinrådet accepterer ansøgers tilgang vedr. administrationsomkostninger, men erstatter enhedsomkostningen for intramuskulær injektion med omkostningen fra DRG-taksten 2022.

Monitoreringsomkostning

Ansøger inkluderer monitoreringsomkostninger, afhængigt af hvilket helbredsstadie patienten befinder sig i. Enhedsomkostningerne er de samme i de forskellige stadier, men frekvensen varieres med helbredsstadiet (se Tabel 9). Overordnet set er monitoreringsfrekvensen størst i stadierne med ukontrolleret sygdom og lavest efter fjernelse af binyrerne. Ansøger baserer enhederne og frekvensen af disse på input fra kliniske eksperter.

Medicinrådets vurdering af ansøgers antagelser vedr. monitoreringsomkostninger

Fagudvalget vurderer, at de medtagne monitoreringsomkostninger er relevante, men at frekvenserne i nogle tilfælde ikke stemmer overens med dansk klinisk praksis. Fx kommer patienter med kontrolleret sygdom oftere til kontrol end antaget af ansøger, og patienter, der har fået fjernet binyrerne, kommer til kontrol hver uge i de første 28 dage. Medicinrådet har justeret frekvenserne i ansøgers antagelser, og værdierne anvendt i Medicinrådets hovedanalyse fremgår af Tabel 9. Denne ændring vurderes at have minimal betydning for analysens resultat. Desuden har Medicinrådet indsat omkostninger i 2022-priser.

Tabel 9. Oversigt over monitoreringsomkostninger i Medicinrådets hovedanalyse

Ressource	Årlig frekvens ved ukontrol-leret sygdom	Årlig frekvens ved kontrol-leret sygdom	Årlig frekvens ved kronisk fase efter fjernelse af binyrer	Antal enheder i de første 28 dage efter fjernelse af binyrer	Enheds-omkost-ning	Kilde
Konsultation ved endokri-nolog	8	4	2	4	525 DKK (30 minutter, overlæge)	Medicin-rådets værdisæt-ning af enhedsom-kostninger
Konsultation ved anden læge	5	2	2	0	525 DKK (30 minutter, overlæge)	Medicin-rådets værdisæt-ning af enhedsom-kostninger

Ressource	Årlig frekvens ved ukontrol-leret sygdom	Årlig frekvens ved kontrol-leret sygdom	Årlig frekvens ved kronisk fase efter fjernelse af binyrer	Antal enheder i de første 28 dage efter fjernelse af binyrer	Enheds-omkost-ning	Kilde
Ambulato-risk besøg*	8	2	2	0	1.954 DKK	DRG 2022 – 10MA98 - MDC10 1-dagsgrup-pe, pat. mindst 7 år
Skadestue-besøg	3	2	0,5	0,25	2.185 DKK	Antaget samme som hospi-talsindlægg else (DRG 2022)
Hospitals-indlæggelse	18	4	1	4	2.185 DKK	DRG 2022 – takst udover trimpunk-tet
Hjerne MRI-scanning	2	0,5	1	0	2.057 DKK	DRG 2022 – 30PR03 – MR-scanning, ukompli-ceret
ACTH-test	8	4	2	1	95 DKK	Rigshospi-talets labportal (ACTH)
24 timers UFC-test	6	0	0	0	1.104 DKK	Rigshospi-talets labportal (UCORTFRI)
Serum kortisoltest	16	6	1	1	62 DKK	Rigshospi-talets labportal (CORT45)

Ressource	Årlig frekvens ved ukontrol-leret sygdom	Årlig frekvens ved kontrol-leret sygdom	Årlig frekvens ved kronisk fase efter fjernelse af binyrer	Antal enheder i de første 28 dage efter fjernelse af binyrer	Enheds-omkost-ning	Kilde
Test for natrium, kalium og kreatinin	18	8	2	2	39 DKK (13 + 13 + 13 DKK)	Rigshospi-talets labportal (K, NA og CREA)
Testosteron-test	1	2	1	0	46 DKK	Rigshospi-talets labportal (TESTO)
Leverfunk-tionstest	1	2	2	1	41 DKK (14 + 13 + 14 DKK)	Rigshospi-talets labportal (ASAT, ALAT og BILI)
Test af glucose-niveau	4	2	2	10	13 DKK	Rigshospi-talets labportal (GLU)

*Udover kontrolbesøg ved endokrinolog eller anden læge.

Medicinrådet accepterer ansøgers tilgang vedr. monitoreringsomkostninger, men justerer nogle af frekvenserne og enhedsomkostningerne, så de følger de nyeste takster (DRG-2022, Rigshospitalets laboratorieportal 2022 og Medicinrådets værdisætning af enhedsomkostninger 2022).

Bivirkningsomkostninger

Ansøger har inkluderet omkostninger forbundet med bivirkninger ved osilodrostat og pasireotid på baggrund af bivirkningsopgørelserne i LINC-3 [2] (osilodrostat) og G2304 [7] (pasireotid). Bivirkningsfrekvenser er ikke opgjort i studierne af ketoconazol og metyrapon, og ansøger antager i stedet, at bivirkningsfrekvenserne er identiske med frekvenserne for osilodrostat. Ansøger anvender bivirkninger af grad 3 eller højere i modellen. Ansøger anvender individuelle patientdata fra de to kliniske studier til at bestemme det totale antal events af hver inkluderet bivirkning. Herefter anvender ansøger den totale eksponeringstid i studierne til at omregne antal events til en fast rate pr. modelcyklus (se Tabel 10). Raten pr. modelcyklus ganges herefter med enhedsomkostningen for at finde omkostningen pr. cyklus for hver inkluderet bivirkning. Ansøger har baseret enhedsomkostningerne på DRG 2021 for adrenal insufficiens,

diabetes mellitus, levertoksicitet og hypertension, mens de resterende bivirkninger takseres som et besøg hos egen læge.

Ansøger har desuden angivet komplikationer ved fjernelse af binyrerne som bivirkningsomkostninger.

Medicinrådets vurdering af ansøgers antagelser vedr. bivirkningsomkostninger
Medicinrådet accepterer ansøgers tilgang til estimering af bivirkningsomkostninger. Fagudvalget kan ikke vurdere, om ansøgers antagelse angående ens bivirkningsfrekvens ved osilodrostat, ketoconazol og metyrapon er plausibel, da der ikke findes systematisk opgjorte bivirkningsfrekvenser for komparatorerne under lignende forhold. Medicinrådet erstatter enhedsomkostningerne i ansøgningen med DRG-takster fra 2022 for alle de inkluderede bivirkninger, da Medicinrådet antager, at bivirkningerne er behandlingskrævende, i og med at de er af grad ≥ 3. For de bivirkninger, hvor ansøger har antaget besøg hos egen læge, antager Medicinrådet et ambulant besøg (10MA98).

Bivirkningsfrekvenser og anvendte takster kan ses i Tabel 10.

Medicinrådet omgrupperer omkostningerne til komplikationer ved fjernelse af binyrerne, så de ikke fremgår som bivirkningsomkostning, men i stedet som engangsomkostninger relateret til fjernelse af binyrerne (se afsnittet Engangsomkostninger relateret til fjernelse af binyrerne).

Tabel 10. Rapporterede bivirkningsfrekvenser ved behandling med osilodrostat og pasireotid samt enhedsomkostninger for bivirkningerne. Bivirkningsfrekvenserne ved behandling med ketoconazol og metyrapon antages at være de samme som for osilodrostat.

	Osilodrostat Frekvens pr. modelcyklus	Pasireotid Frekvens pr. modelcyklus	DRG-kode	Takst
Mavesmerter	0,00008021	0,0002	1.954 DKK	DRG 2022 – 10MA98 - MDC10 1-dags-gruppe, pat. mindst 7 år
Adrenal insufficiens	0,0006	0,0002	24.875 DKK	DRG 2022 – 10MA05 - Hypofyse-, binyre-, gonade- og andre endokrine sygdomme
Øget alanin aminotransferase	0,0000	0,0002	1.954 DKK	DRG 2022 – 10MA98 - MDC10 1-dagsgruppe, pat. mindst 7 år

	Osilodrostat Frekvens pr. modelcyklus	Pasireotid Frekvens pr. modelcyklus	DRG-kode	Takst
Øget blodsukker	0,0001	0,0002	1.954 DKK	DRG 2022 – 10MA98 - MDC10 1-dags-gruppe, pat. mindst 7 år
Diabetes Mellitus	0,0000	0,0014	31.594 DKK	DRG 2022 – 10MA03 – Diabetes mellitus
Hypokortisolisme	0,0009	0,0000	1.954 DKK	DRG 2022 – 10MA98 - MDC10 1-dags-gruppe, pat. mindst 7 år
Hyperglykæmi	0,0000	0,0018	1.954 DKK	DRG 2022 – 10MA98 - MDC10 1-dags-gruppe, pat. Mindst 7 år
Hypertension	0,0006	0,0003	16.630 DKK	DRG 2022 – 05MA11 – Hypertension
Hypokaliæmi	0,0002	0,0000	1.954 DKK	DRG 2022 – 10MA98 – MDC10 1-dags-gruppe, pat. mindst 7 år
Kvalme	0,0002	0,0002	1.954 DKK	DRG 2022 – 10MA98 - MDC10 1-dags-gruppe, pat. mindst 7 år
Opkast	0,0002	0,0000	1.954 DKK	DRG 2022 – 10MA98 - MDC10 1-dags-gruppe, pat. mindst 7 år
Totale bivirknings-omkostninger pr. modelcyklus	-	-	– Osilodrostat, ketoconazol og metyrapon = 30 DKK – Pasireotid = 60 DKK	-

Medicinrådet har erstattet enhedsomkostningerne med gældende DRG-takster. Denne ændring vurderes at have minimal betydning for analysens resultat.

Medicinrådet accepterer ansøgers tilgang vedr. bivirkningsomkostninger, men erstatter enhedsomkostningerne for de enkelte bivirkninger med DRG-takster fra 2022.

Omkostninger til behandling af komorbiditet

Cushings syndrom medfører en række komorbiditeter, som enten kan være akutte begivenheder eller kroniske tilstande. Ansøger inkluderer dette som en omkostning knyttet til modelstadierne, '*Uncontrolled - on initial Tx*', '*Controlled – on initial tx*', '*Subsequent medical treatment*' og '*Bilateral adrenalectomy*'.

Ansøger anvender studiedata fra LINC-3 til at estimere frekvensen af akutte og kroniske komorbiditeter i stadiet 'Ukontrolleret – 1. linjebehandling'. Ansøger har inddraget de uønskede hændelser i LINC-3, der matchede beskrivelserne af de relevante komorbiditeter (se Tabel 12), og omregnet frekvenserne for de akut opståede komorbiditeter til en ugentlig frekvens ud fra den totale hyppighed og patienternes samlede tid uden sygdomskontrol. Forekomsten af kroniske komorbiditeter blev estimeret ud fra forekomsten i patientpopulationen ved baseline. Ansøger har derefter estimeret de tilsvarende forekomster for akutte og kroniske komorbiditeter i stadiet 'Kontrolleret – 1. linjebehandling' vha. relative risiko-rater for komorbiditeterne ved ukontrolleret over for kontrolleret sygdom fundet i litteraturen. Derved finder ansøger en samlet omkostning for komorbiditeter pr. modelcyklus, som patienterne tilskrives, alt efter om de har kontrolleret eller ukontrolleret sygdom.

De samme rater for komorbiditet anvendes i helbredsstadierne '2. linjebehandling' og 'Fjernelse af binyrer'. Mens patienterne er i disse helbredsstadier, fordeles de mellem hhv. kontrolleret og ukontrolleret sygdom, afhængigt af de publicerede responsrater fra de kliniske studier (se Tabel 11).

Tabel 11. Oversigt over responsrater og kilder, som ansøger anvender til at estimere andelen af patienter i 2. linjebehandling, der har hhv. kontrolleret og ukontrolleret sygdom

2. linjebehandling	Responsrate	Kilde
Osilodrostat	67,9 %	LINC-3 [2]
Ketoconazol	48,5 %	Castinetti et al. 2014 [3]
Metyrapon	43 %	Daniel 2015 [6]
Pasireotid	41,9 %	G2304 [7]
Fjernelse af binyrer	100 %	Ansøgers antagelse baseret på klinisk ekspert

Medicinrådets vurdering af ansøgers antagelser vedr. omkostninger til behandling af komorbiditeter

Medicinrådet vurderer, at der er flere usikkerheder i ansøgers antagelser. Fx antages responsraterne fra de kliniske studier at være gældende i hele perioden med efterfølgende behandling, og patienterne antages at fortsætte i efterfølgende behandling uanset responset. Derudover er det usikkert, om de rapporterede relative risikorater mellem ukontrolleret og kontrolleret sygdom er repræsentative for populationen i dansk klinisk praksis. Omkostningerne til behandling af komorbiditet udgør dog en meget lille del af de samlede omkostninger ved osilodrostat og komparatorerne, og de nævnte usikkerheder har derfor minimal betydning for analysens resultat. Medicinrådet anvender derfor raterne og omkostningerne til behandling af komorbiditet som antaget af ansøger, men udskifter priserne med DRG-takster fra 2022 og erstatter omkostningen for knogleskørhed med DRG-taksten – 10MA02 - Knoglemetaboliske- og kalksygdomme.

Tabel 12. Oversigt over relevante komorbiditeter samt frekvenser og enhedsomkostninger for disse anvendt i Medicinrådets hovedanalyse

Komorbiditet	Rate pr. modelcyklus ved ukontrolleret sygdom	Relativ risiko mellem ukontrolleret og kontrolleret sygdom	Rate pr. modelcyklus ved kontrolleret sygdom	Enheds-omkostning	Kilde
Akutte					
Kardiovas-kulære hændelser	0,01	1,5	0,007	41.334 DKK	DRG 2022 – 05MP53
Kroniske					
Diabetes	0,036	1,8	0,023	31.594 DKK	DRG 2022 – 10MA03
Metabolisk syndrom	0,036	1,5	0,023	1.954 DKK	DRG 2022 – 10MA98 - MDC10 1-dagsgruppe, pat. mindst 7 år
Angst	0,007	1,4	0,005	58.972 DKK	*Vestergaard 2020* [12]
Depression	0,007	1,3	0,005	77.832 DKK	*Vestergaard 2020* [12]
Knogle-skørhed	0,037	3,7	0,010	33.125 DKK	DRG-taksten – 10MA02 – Knoglemeta-boliske- og

Komorbiditet	Rate pr. modelcyklus ved ukontrolleret sygdom	Relativ risiko mellem ukontrolleret og kontrolleret sygdom	Rate pr. modelcyklus ved kontrolleret sygdom	Enheds-omkostning	Kilde
					kalksygdom-me
Muskel-svaghed	0,036	1,5	0,23	1.954 DKK	DRG 2022 – 10MA98 - MDC10 1-dagsgruppe, pat. mindst 7 år

Medicinrådet accepterer ansøgers tilgang, men erstatter de anvendte DRG-takster for enhedsomkostningerne med DRG-takster fra 2022 og anvender DRG-takst som enhedsomkostning for knogleskørhed.

Engangsomkostninger relateret til fjernelse af binyrerne

Ansøger antager, at fjernelse af binyrerne medfører en række engangsomkostninger, der tilskrives i det øjeblik, patienten overgår til helbredsstadiet. Ansøger inkluderer disse under hhv. lægemiddelomkostninger (selve operationsomkostningen) og bivirkningsomkostninger (omkostninger til komplikationer opstået under operationen). Ansøger anvender DRG-takster til at prissætte operationerne og de opståede komplikationer, bortset fra kroniske smerter efter operation, hvor ansøger antager, at dette ikke medfører en betydende omkostning, da det behandles med almindelig smertestillende medicin.

Medicinrådets vurdering af ansøgers antagelser vedr. engangsomkostninger relateret til fjernelse af binyrerne

Medicinrådet har bibeholdt omkostningerne som antaget af ansøger, men har omgrupperet dem til dette afsnit. Desuden har Medicinrådet erstattet ansøgers enhedsomkostninger med DRG-takster for 2022. Derudover har Medicinrådet accepteret ansøgers antagelser. Transitionsomkostningerne kan ses i Tabel 13.

Tabel 13. Transitionsomkostninger anvendt i Medicinrådets hovedanalyse ved fjernelse af binyrerne

Procedure/komplikation	Andel, der tilskrives omkostningen ved transitionen	Enhedsomkostning [DKK]	Kilde
Operation til fjernelse af binyrer	100 %	78.387	DRG 2022 – 10MP02

Procedure/komplikation	Andel, der tilskrives omkostningen ved transitionen	Enhedsomkostning [DKK]	Kilde
Komplikationer ved operation			
Nelson syndrom	25 %	24.111	DRG 2022 – 01MP06
Infektion i operationssår	10 %	35.699	DRG 2022 – 18MA03
Kroniske smerter efter operation	5 %	0	Ansøgers antagelse

Medicinrådet accepterer ansøgers tilgang, men erstatter enhedsomkostningerne med DRG-takster fra 2022.

4.2.3 Efterfølgende behandling

Ansøger inkluderer omkostninger til efterfølgende behandling, da ansøger antager, at alle patienter bliver behandlet medicinsk efter behandlingssvigt på den første behandlingslinje, inden patienten får bortopereret binyrerne. Ansøger antager, at patienter behandlet med osilodrostat i 1. linje behandles med ketoconazol (50 %) eller metyrapon (50 %) i 2. linje, mens patienterne behandlet med komparatorerne i 1. linje behandles med osilodrostat (50 %) eller metyrapon/ketoconazol (50 %). Ansøger antager, at behandlingslængden i alle tilfælde er 12 måneder, og respons på behandlingen indgår udelukkende ift. at estimere omkostninger til behandling af komorbiditet, mens patienterne er i 2. linjebehandling (se 'Omkostninger til behandling af komorbiditet').

Medicinrådets vurdering af ansøgers antagelser vedr. efterfølgende behandling
Medicinrådet har ændret fordelingen af lægemidler til efterfølgende behandling. Dette skyldes, at Medicinrådet ikke har vurderet osilodrostat til behandling af patienter med tidligere behandlingssvigt, og at osilodrostat heller ikke anvendes til dette i klinikken på nuværende tidspunkt. Patienterne omfordeles derfor på baggrund af fagudvalgets kliniske erfaring (Tabel 14). Denne ændring har stor betydning for analysens resultat.

Tabel 14. Fordeling af 2. linjebehandling efter ophør af 1. linjebehandlingen anvendt i Medicinrådets hovedanalyse

Efterfølgende behandling	Behandling i 1. linje			
	Osilodrostat	Ketoconazol	Metyrapon	Pasireotid
Osilodrostat	0 %	0 %	0 %	0 %
Ketoconazol	50 %	0 %	50 %	50 %
Metyrapon	50 %	50 %	0 %	50 %
Pasireotid	0 %	50 %	50 %	0 %

Dosis og priser for den efterfølgende behandling er uændret ift. 1. linjebehandling (Tabel 8). Fagudvalget bemærker, at den gennemsnitlige behandlingstid på 12 måneder virker høj på baggrund af deres kliniske erfaringer samt den gennemsnitlige behandlingstid ved 1. linjebehandling (Tabel 5) og de antagne responsrater (Tabel 11). Fagudvalget kan dog ikke estimere en mere præcis gennemsnitlig behandlingstid, da det drejer sig om få patienter i klinisk praksis. Derfor anvender Medicinrådet ansøgers antagelse i hovedanalysen, men Medicinrådet foretager en følsomhedsanalyse, hvor den gennemsnitlige behandlingstid justeres til 6 måneder. Endelig bemærker fagudvalget, at det er usikkert, om alle patienter modtager 2. linjebehandling inden fjernelse af binyrer. Fagudvalget vurderer dog, at størstedelen af patienterne vil modtage 2. linjebehandling, og derfor anvender Medicinrådet ansøgers antagelse.

Medicinrådet accepterer ansøgers tilgang vedr. efterfølgende behandling, men ændrer fordelingen af, hvilken behandling patienterne modtager, så ingen patienter modtager osilodrostat som efterfølgende behandling. Desuden udfører Medicinrådet en følsomhedsanalyse, hvor den gennemsnitlige behandlingsvarighed reduceres fra 12 til 6 måneder.

4.3 Følsomhedsanalyser

Formålet med følsomhedsanalyserne er at undersøge usikkerhederne i analysen og de økonomiske konsekvenser af at justere de parametre, der er usikre.

Ansøger har ikke udarbejdet følsomhedsanalyser. Medicinrådet har dog valgt at udføre følsomhedsanalyser, hvor effekten af variation i forskellige parametre undersøges. Følgende følsomhedsanalyser er udført:

Tabel 15. Følsomhedsanalyser og beskrivelse

Følsomhedsanalyse	Beskrivelse
Følsomhedsanalyse 1 – Antagelse om, at alle patienter ophører med medicinsk behandling efter 5 år.	Analysens tidshorisont reduceres til 5 år. Umiddelbart inden år 5 flyttes alle patienter i fortsat medicinsk behandling til helbredsstadiet 'fjernelse af binyrer'.
Følsomhedsanalyse 2 – '*Treatment escape*' ved mUFC > 1 x ULN	Grænsen for '*treatment escape*' sættes til mUFC > 1 x ULN som antaget af ansøger. Medicinrådet vurderer, at dette ikke er et plausibelt scenarie, men udfører analysen for at illustrere betydningen af antagelsen.
Følsomhedsanalyse 3 – Ekstrapolation af tid-til-behandlingsophør med eksponentiel funktion	Ekstrapolationsfunktionen for tid-til-behandlingsophør for både osilodrostat og pasireotid ændres fra log-normal til eksponentiel.
Følsomhedsanalyse 4 – Ekstrapolation af tid-til-behandlingsophør med gamma-funktion	Ekstrapolationsfunktionen for tid-til-behandlingsophør for både osilodrostat og pasireotid ændres fra log-normal til gamma.
Følsomhedsanalyse 5 – Ekstrapolation af tid-til-behandlingsophør med generaliseret gamma-funktion	Ekstrapolationsfunktionen for tid-til-behandlingsophør for både osilodrostat og pasireotid ændres fra log-normal til generaliseret gamma.
Følsomhedsanalyse 6 – Ekstrapolation af tid-til-behandlingsophør med Gompertz-funktion	Ekstrapolationsfunktionen for tid-til-behandlingsophør for både osilodrostat og pasireotid ændres fra log-normal til Gompertz.
Følsomhedsanalyse 7 – Ekstrapolation af tid-til-behandlingsophør med log-logistisk funktion	Ekstrapolationsfunktionen for tid-til-behandlingsophør for både osilodrostat og pasireotid ændres fra log-normal til log-logistisk.
Følsomhedsanalyse 8 – Ekstrapolation af tid-til-behandlingsophør med Weibull-funktion	Ekstrapolationsfunktionen for tid-til-behandlingsophør for både osilodrostat og pasireotid ændres fra log-normal til Weibull.
Følsomhedsanalyse 9 – Ændring af den gennemsnitlige behandlingstid ved 2. linje medicinsk behandling	Det antages, at den gennemsnitlige behandlingstid for 2. linje medicinsk behandling er 6 måneder i stedet for 12 måneder.

4.4 Opsummering af basisantagelser

I Tabel 16 opsummeres basisantagelserne i hhv. ansøgers og Medicinrådets hovedanalyse.

Tabel 16. Basisantagelser for ansøgers og Medicinrådets hovedanalyse

Basisantagelser	Ansøger	Medicinrådet
Tidshorisont	2 år	50 år
Diskonteringsrate	4 %	3,5 % i år 2-35 2,5 % i år 36-50
Inkluderede omkostninger	Lægemiddelomkostninger Hospitalsomkostninger Omkostninger til efterfølgende behandlinger Omkostninger til behandling af komorbiditet Patientomkostninger (tabt arbejdsfortjeneste)	Lægemiddelomkostninger Hospitalsomkostninger Omkostninger til efterfølgende behandlinger Omkostninger til behandling af komorbiditet
Dosering	Osilodrostat: fordeling baseret på LINC-3 Ketoconazol: 800 mg pr. døgn Metyrapon: 2.000 mg pr. døgn Pasireotid: fordeling baseret på G2304	Osilodrostat: fordeling baseret på LINC-3 Ketoconazol: 800 mg pr. døgn Metyrapon: 2.000 mg pr. døgn Pasireotid: 20 mg hver 4. uge
Behandlingslinje	1. linje efter operation af hypofysen eller ved fravalg af operation	1. linje efter operation af hypofysen eller ved fravalg af operation
Gennemsnitlige behandlingslængder i 1. linje	Osilodrostat: 21,5 måneder Ketoconazol: 4,9 måneder Metyrapon: 5,1 måneder Pasireotid: 10,4 måneder	Osilodrostat: 59,8 måneder Ketoconazol: 11,8 måneder Metyrapon: 11,8 måneder Pasireotid: 10,4 måneder
Stopregel	Ophør grundet uønskede hændelser, død, manglende effekt efter 6 måneders behandling eller '*treatment escape*' defineret som mUFC > 1 x ULN	Ophør grundet uønskede hændelser, død, manglende effekt efter 6 måneders behandling eller '*treatment escape*' defineret som mUFC > 1,5 x ULN (som i LINC-3)
Parametriske funktioner for *'time-to-treatment failure'* Intervention: Komparatorer:	Osilodrostat: log-normal Ketoconazol: HR på 0,33 ift. osilodrostat Metyrapon: Samme som ketoconazol Pasireotid: log-normal	Osilodrostat: log-normal Ketoconazol: HR på 0,33 ift. osilodrostat Metyrapon: Samme som ketoconazol Pasireotid: log-normal

Basisantagelser	Ansøger	Medicinrådet
Estimering af overlevelse	Anvender en stadiespecifik konstant mortalitetsratio ift. den almene befolkning: Ukontrolleret sygdom: 6,9 Kontrolleret sygdom: 1,9 Kontrolleret sygdom efter fjernelse af binyrer: 3,6	Anvender en stadiespecifik konstant mortalitetsratio ift. den almene befolkning: Ukontrolleret sygdom: 6,9 Kontrolleret sygdom: 1,9 Kontrolleret sygdom efter fjernelse af binyrer: 3,6
Inkludering af spild	Ja	Ja
Transitioner mellem helbredsstadier i modellen	Fra 'ukontrolleret - 1. linjebehandling' til 'kontrolleret - 1. linjebehandling': Tid-til-respons-data for osilodrostat (LINC-3) og pasireotid (G2304) samt modellering vha. hazard ratio ift. respons med osilodrostat for ketoconazol og metyrapon. Fra 'kontrolleret - 1. linjebehandling' til '2. linjebehandling': tid-til-behandlingsophør for osilodrostat (LINC-3) og pasireotid (G2304) samt modellering vha. hazard ratio ift. andel, der ophører behandling med osilodrostat for ketoconazol og metyrapon. Fra '2. linjebehandling til 'Fjernelse af binyrer': Patienten flyttes automatisk til fjernelse af binyrerne efter 12 måneder i 2. linjebehandling. Overgang til død fra alle stadier: Fast sandsynlighed, afhængig af helbredsstadie og alder, modelleret ud fra dødeligheden i den almene befolkning og en mortalitetsratio tilknyttet det enkelte stadie.	Fra 'ukontrolleret - 1. linjebehandling' til 'kontrolleret - 1. linjebehandling': Tid-til-respons-data for osilodrostat (LINC-3), og pasireotid (G2304) samt modellering vha. hazard ratio ift. respons med osilodrostat for ketoconazol og metyrapon. Fra 'kontrolleret - 1. linjebehandling' til '2. linjebehandling': tid-til-behandlingsophør for osilodrostat (LINC-3) og pasireotid (G2304) samt modellering vha. hazard ratio ift. andel, der ophører behandling med osilodrostat for ketoconazol og metyrapon. Fra '2. linjebehandling til 'Fjernelse af binyrer': Patienten flyttes automatisk til fjernelse af binyrerne efter 12 måneder i 2. linjebehandling. Overgang til død fra alle stadier: Fast sandsynlighed, afhængig af helbredsstadie og alder, modelleret ud fra dødeligheden i den almene befolkning og en mortalitetsratio tilknyttet det enkelte stadie.

5. Resultater

5.1 Resultatet af Medicinrådets hovedanalyse

Medicinrådets hovedanalyse bygger på samme antagelser som ansøgers hovedanalyse med undtagelse af de væsentligste ændringer, der fremgår af Tabel 16.

Ved anvendelsen af osilodrostat bliver den gennemsnitlige inkrementelle omkostning pr. patient [redacted] DKK ift. ketoconazol, [redacted] DKK ift. metyrapon og [redacted] DKK ift. pasireotid i Medicinrådets hovedanalyse. Det er særligt lægemiddelomkostningerne for osilodrostat, der driver analysernes resultater. Omkostningerne er størst i starten af behandlingsforløbet. Efter år 30 øges de inkrementelle omkostninger kun marginalt.

Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient 1.689.000 DKK ift. ketoconazol, 1.680.000 DKK ift. metyrapon og 1.614.000 DKK ift. pasireotid.

Resultaterne fra Medicinrådets hovedanalyse er præsenteret i Tabel 17 (over for ketoconazol), Tabel 18 (over for metyrapon) og Tabel 19 (over for pasireotid).

Tabel 17. Resultatet af Medicinrådets hovedanalyse ved sammenligning med ketoconazol (klinisk spørgsmål 1), DKK, diskonterede tal

	Osilodrostat [DKK]	Ketoconazol [DKK]	Inkrementelle omkostninger [DKK]
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	698.833	691.303	7.529
Efterfølgende behandling	[redacted]	[redacted]	[redacted]
Totale omkostninger	[redacted]	[redacted]	[redacted]

Tabel 18. Resultatet af Medicinrådets hovedanalyse ved sammenligning med metyrapon (klinisk spørgsmål 2), DKK, diskonterede tal

	Osilodrostat [DKK]	Metyrapon [DKK]	Inkrementelle omkostninger [DKK]
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	698.833	691.025	7.807
Efterfølgende behandling	[redacted]	[redacted]	[redacted]
Totale omkostninger	[redacted]	[redacted]	[redacted]

Tabel 19. Resultatet af Medicinrådets hovedanalyse ved sammenligning med pasireotid (klinisk spørgsmål 3), DKK, diskonterede tal

	Osilodrostat [DKK]	Pasireotid [DKK]	Inkrementelle omkostninger [DKK]
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	698.833	709.622	-10.790
Efterfølgende behandling	[redacted]	[redacted]	[redacted]
Totale omkostninger	[redacted]	[redacted]	[redacted]

5.1.1 Resultatet af Medicinrådets følsomhedsanalyser

Ved samme antagelser som i Medicinrådets hovedanalyse for meromkostninger har Medicinrådet udført en følsomhedsanalyse på parametrene listet i Tabel 20.

Tabel 20. Resultatet af Medicinrådets følsomhedsanalyser sammenlignet med hovedanalysen, DKK

Scenarie	Inkrementelle omkostninger [DKK]
Resultatet af hovedanalysen	Over for ketoconazol: [redacted] Over for metyrapon: [redacted] Over for pasireotid: [redacted]
Følsomhedsanalyse 1 – Antagelse om, at alle patienter ophører med medicinsk behandling efter 5 år	Over for ketoconazol: [redacted] Over for metyrapon: [redacted] Over for pasireotid: [redacted]
Følsomhedsanalyse 2 – '*Treatment escape*' ved mUFC > 1 x ULN	Over for ketoconazol: [redacted] Over for metyrapon: [redacted] Over for pasireotid: [redacted]
Følsomhedsanalyse 3 – Ekstrapolation af tid-til-behandlingsophør med eksponentiel funktion	Over for ketoconazol: [redacted] Over for metyrapon: [redacted] Over for pasireotid: [redacted]
Følsomhedsanalyse 4 – Ekstrapolation af tid-til-behandlingsophør med gamma-funktion	Over for ketoconazol: [redacted] Over for metyrapon: [redacted] Over for pasireotid: [redacted]

Scenarie	Inkrementelle omkostninger [DKK]
Følsomhedsanalyse 5 – Ekstrapolation af tid-til-behandlingsophør med generaliseret gamma-funktion	Over for ketoconazol: [redacted] Over for metyrapon: [redacted] Over for pasireotid: [redacted]
Følsomhedsanalyse 6 – Ekstrapolation af tid-til-behandlingsophør med Gompertz-funktion	Over for ketoconazol: [redacted] Over for metyrapon: [redacted] Over for pasireotid: [redacted]
Følsomhedsanalyse 7 – Ekstrapolation af tid-til-behandlingsophør med log-logistisk funktion	Over for ketoconazol: [redacted] Over for metyrapon: [redacted] Over for pasireotid: [redacted]
Følsomhedsanalyse 8 – Ekstrapolation af tid-til-behandlingsophør med Weibull-funktion	Over for ketoconazol: [redacted] Over for metyrapon: [redacted] Over for pasireotid: [redacted]
Følsomhedsanalyse 9 – Ændring af den gennemsnitlige behandlingstid ved 2. linje medicinsk behandling	Over for ketoconazol [redacted] Over for metyrapon: [redacted] Over for pasireotid: [redacted]

6. Budgetkonsekvenser

Budgetkonsekvenserne pr. år er baseret på antagelsen om, at osilodrostat vil blive anbefalet som mulig standardbehandling. Man ser derfor på to scenarier:

- Osilodrostat bliver anbefalet som mulig standardbehandling af Medicinrådet til indikationen, som denne analyse omhandler.
- Osilodrostat bliver ikke anbefalet som mulig standardbehandling.

Budgetkonsekvenserne udgør forskellen mellem de samlede omkostninger i de to scenarier.

6.1 Estimat af patientantal og markedsandel

Ansøger har antaget, at der vil være ca. 25 patienter om året, der ved anbefaling vil være kandidater til behandling med osilodrostat. Ansøger baserer dette på det totale antal patienter, der årligt diagnosticeres med endogent Cushings syndrom ifølge Medicinrådets protokol for vurdering vedrørende osilodrostat til behandling af Cushings syndrom. Ansøger antager desuden, at patienterne vil være i medicinsk behandling i 2 år, så det totale patientantal i år 1 er 25, mens det i år 2-5 er 50. Ansøger antager, at

osilodrostat har et markedsoptag på 8 % i år 1, 16 % i år 2, 20 % i år 3, 30 % i år 4 og 34 % i år 5.

Medicinrådets vurdering af ansøgers budgetkonsekvensanalyse
Fagudvalget er blevet konsulteret i forhold til patientantal, hvis osilodrostat anbefales som mulig standardbehandling, og hvis ikke osilodrostat anbefales. Fagudvalget estimerer, at 8 patienter pr. år forventes at være kandidater til behandling med osilodrostat til den pågældende indikation. Det skyldes, at kun ca. en tredjedel af de nydiagnosticerede patienter skønnes at være kandidater til medicinsk behandling, jf. Medicinrådets protokol for vurdering vedrørende osilodrostat til behandling af Cushings syndrom. Derudover vurderer fagudvalget, at ansøgers markedsoptag for osilodrostat er underestimeret. Fagudvalget vurderer, at markedsoptaget vil være 50 % for osilodrostat i år 1-5, og at det resterende marked vil være ligeligt fordelt mellem ketoconazol og metyrapon. Fagudvalgets samlede estimerede antal af nydiagnosticerede patienter ses i Tabel 21.

Tabel 21. Medicinrådets estimat af antal nye patienter pr. år

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Osilodrostat	4	4	4	4	4
Ketoconazol	2	2	2	2	2
Metyrapon	2	2	2	2	2
Pasireotid	0	0	0	0	0
			Anbefales ikke		
Osilodrostat	0	0	0	0	0
Ketoconazol	3	3	3	4	4
Metyrapon	3	3	3	2	2
Pasireotid	2	2	2	2	2

Medicinrådet har udført sin egen budgetkonsekvensanalyse, hvor antallet af nye patienter er ændret til 8 patienter pr. år, hvoraf de 4 behandles med osilodrostat.

6.2 Medicinrådets budgetkonsekvensanalyse

Medicinrådet har korrigeret følgende estimater i sin budgetkonsekvensanalyse i forhold til ansøgers budgetkonsekvensanalyse:

- 8 nye patienter pr. år.

- 50 % markedsoptag for osilodrostat i år 1-5.

Medicinrådet estimerer, at anvendelse af osilodrostat vil resultere i budgetkonsekvenser på ca. [redacted] DKK i det femte år efter en anbefaling. Resultatet er præsenteret i Tabel 22.

Er analysen udført med AIP, bliver budgetkonsekvenserne ca. 3,5 mio. DKK i år 5.

Tabel 22. Medicinrådets analyse af totale budgetkonsekvenser, DKK, ikke-diskonterede tal

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

7. Diskussion

Behandling med osilodrostat er forbundet med inkrementelle omkostninger ca. [redacted] DKK pr. patient sammenlignet med ketoconazol, ca. [redacted] DKK pr. patient sammenlignet med metyrapon og ca. [redacted] DKK pr. patient sammenlignet med pasireotid. De inkrementelle omkostninger er næsten udelukkende drevet af lægemiddelomkostningerne for osilodrostat. De øgede lægemiddelomkostninger skyldes både, at lægemidlet er dyrere end komparatorerne pr. gennemsnitlig månedlige dosis, og at behandlingsvarigheden forventes at være væsentlig længere for osilodrostat end komparatorerne (ca. 60 måneder for osilodrostat, 12 måneder for ketoconazol og metyrapon og 10 måneder for pasireotid). Dermed er de øgede inkrementelle omkostninger også udtryk for en forventet bedre og længevarende klinisk effekt af osilodrostat end komparatorerne i form af kontrol af patientens kortisolniveau. Behandlingsvarigheden er usikker, da estimaterne for denne i høj grad er påvirket af, at ansøger antager, at patienterne ophører med behandling, hvis der opstår '*treatment escape*', hvilket betyder, at patientens kortisolniveau overstiger en vis grænse, efter patienten tidligere har opnået normaliseret kortisolniveau. Grænsen for '*treatment escape*' blev i det kliniske studie af osilodrostat (LINC-3) defineret som 1,5 x øvre grænse for normalniveauet, men i ansøgers analyse er denne grænse sænket til 1 x øvre grænse for normalniveauet. Grænsen for '*treatment escape*' har stor betydning for den gennemsnitlige behandlingsvarighed, hvor ansøgers antagelse medfører, at den gennemsnitlige behandlingsvarighed for osilodrostat reduceres fra ca. 60 måneder til ca. 22 måneder. Medicinrådet illustrerer dette i en følsomhedsanalyse, hvor anvendelsen af 1 x øvre grænse for normalniveauet som '*treatment escape*' medfører, at de inkrementelle omkostninger reduceres til ca. [redacted] DKK pr. patient, [redacted] DKK pr. patient og [redacted] DKK pr. patient over for hhv. ketoconazol, metyrapon og pasireotid. Medicinrådet anser ikke dette for et plausibelt scenarie, da fagudvalget afviser, at man i

klinisk praksis vil stoppe behandlingen af patienter i respons, hvis deres kortisolniveau kortvarigt overstiger den øvre grænse for normalniveauet. Fagudvalget vurderer, at dette i stedet oftere medfører en øgning af dosis, medmindre patienten i forvejen modtager den maksimalt tolererede dosis. Derfor er der en stor sandsynlighed for, at behandlingsvarigheden og dermed omkostningerne for osilodrostat er underestimerede i Medicinrådets hovedanalyse, selvom grænsen for '*treatment escape'* er sat til 1,5 x øvre grænse for normalniveauet. Medicinrådet har ikke adgang til data for behandlingsophør uden hensyntagen til '*treatment escape'* eller til de faktiske behandlingsforløb for patienter, der oplevede '*treatment escape*' i de kliniske studier. Derfor kan Medicinrådet ikke estimere det forventede behandlingsforløb i dansk klinisk praksis uden hensyntagen til '*treatment escape*'.

Modellens tidshorisont har stor betydning for analysens resultat. Medicinrådet anvender en tidshorisont på 50 år i hovedanalysen, for at modellen kan opfange alle relevante meromkostninger ved behandlingen med osilodrostat ift. komparatorerne. Fagudvalget vurderer ud fra klinisk erfaring, at meget få patienter er i medicinsk behandling for Cushings syndrom i mere end 5 år. I Medicinrådets hovedanalyse er ca. 25 % af patienterne behandlet med osilodrostat stadig i 1. linjebehandling efter 5 år. Medicinrådet har derfor foretaget en følsomhedsanalyse, hvor det antages, at disse patienter efter 5 år stopper behandling og overgår til fjernelse af binyrerne. Der er dog stor usikkerhed om denne antagelse, da fagudvalgets kliniske erfaring er baseret på behandling med komparatorerne, og de kliniske studiedata indikerer, at effekten af osilodrostat kan vare betydeligt længere end effekten for komparatorerne. Ved følsomhedsanalysen reduceres de inkrementelle omkostninger til [redacted] DKK pr. patient sammenlignet med ketoconazol, [redacted] DKK pr. patient sammenlignet med metyrapon og [redacted] DKK pr. patient sammenlignet med pasireotid.

Fagudvalget fremhæver, at der desuden er store usikkerheder angående flere af antagelserne i modellen, fx behandlingsvarigheden for 2. linjebehandling, der antages at være 12 måneder uagtet responsraten ved behandlingen uden nærmere begrundelse, og tid-til-respons, der for ketoconazol og metyrapon er baseret på en naiv sammenligning af responsrater med responsraten for osilodrostat til et bestemt tidspunkt, hvorefter det antages, at en hazard ratio til dette tidspunkt er repræsentativt for hele tidsforløbet. Disse antagelser har dog mindre betydning for analysens resultater, hvorfor Medicinrådet anvender antagelserne på trods af usikkerheden.

8. Referencer

1. Dansk endokrinologisk selskab. National behandlingsvejledning: Cushings syndrom [internet]. 2018. Tilgængelig fra: https://endocrinology.dk/nbv/hypofyse-og-binyresygdomme/cushings-syndrom/

2. Pivonello R, Fleseriu M, Newell-Price J, Bertagna X, Findling J, Shimatsu A, et al. Efficacy and safety of osilodrostat in patients with Cushing's disease (LINC 3): a multicentre phase III study with a double-blind, randomised withdrawal phase. Lancet Diabetes Endocrinol. 2020;8(9):748–61.

3. Castinetti F, Guignat L, Giraud P, Muller M, Kamenicky P, Drui D, et al. Ketoconazole in Cushing's disease: is it worth a try? J Clin Endocrinol Metab. 2014;99(5):1623–30.

4. Young J, Bertherat J, Vantyghem MC, Chabre O, Senoussi S, Chadarevian R, et al. Hepatic safety of ketoconazole in Cushing's syndrome: results of a Compassionate Use Programme in France. Eur J Endocrinol. 2018;178(5):447–58.

5. Ceccato F, Zilio M, Barbot M, Albiger N, Antonelli G, Plebani M, et al. Metyrapone treatment in Cushing's syndrome: a real-life study. Endocrine. 2018;62(3):701–11.

6. Daniel E, Aylwin S, Mustafa O, Ball S, Munir A, Boelaert K, et al. Effectiveness of metyrapone in treating cushing's syndrome: A retrospective multicenter study in 195 patients. Journal of Clinical Endocrinology and Metabolism. 2015;100(11):4146–54.

7. Lacroix A, Gu F, Gallardo W, Pivonello R, Yu Y, Witek P, et al. Efficacy and safety of once-monthly pasireotide in Cushing's disease: a 12 month clinical trial. Lancet Diabetes Endocrinol. 2018;6(1).

8. Castinetti F, Guignat L, Giraud P, Muller M, Kamenicky P, Drui D, et al. Ketoconazole in Cushing's disease: is it worth a try? J Clin Endocrinol Metab. 2014;99(5):1623–30.

9. European Medicines Agency (EMA). Isturisa - EPAR. 2020;31(November 2019).

10. Young J, Bertherat J, Vantyghem MC, Chabre O, Senoussi S, Chadarevian R, et al. Hepatic safety of ketoconazole in Cushing's syndrome: results of a Compassionate Use Programme in France. Eur J Endocrinol. 2018;178(5):447–58.

11. Ragnarsson O, Olsson DS, Papakokkinou E, Chantzichristos D, Dahlqvist P, Segerstedt E, et al. Overall and disease-specific mortality in patients with cushing disease: A Swedish nationwide study. Journal of Clinical Endocrinology and Metabolism. 2019;104(6):2375–84.

12. Vestergaard SV, Rasmussen TB, Stallknecht S, Olsen J, Skipper N, Sørensen HT, et al. Occurrence, mortality and cost of brain disorders in Denmark: a population-based cohort study. BMJ Open. 2020;10(11):e037564.

9. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	14. december 2022	Godkendt af Medicinrådet.

10. Bilag

10.1 Resultatet af ansøgers hovedanalyse

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient [redacted] DKK ift. ketoconazol, [redacted] DKK ift. metyrapon og [redacted] DKK ift. pasireotid over en tidshorisont på 2 år. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 23, Tabel 24 og Tabel 25.

Tabel 23. Resultatet af ansøgers hovedanalyse ift. ketoconazol, DKK, diskonterede tal

	Osilodrostat [DKK]	Ketoconazol [DKK]	Inkrementelle omkostninger [DKK]
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	[redacted]	[redacted]	[redacted]
Efterfølgende behandling	[redacted]	[redacted]	[redacted]
Patientomkostninger	[redacted]	[redacted]	[redacted]
Totale omkostninger	[redacted]	[redacted]	[redacted]

Tabel 24. Resultatet af ansøgers hovedanalyse ift. metyrapon, DKK, diskonterede tal

	Osilodrostat [DKK]	Metyrapon [DKK]	Inkrementelle omkostninger [DKK]
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	[redacted]	[redacted]	[redacted]
Efterfølgende behandling	[redacted]	[redacted]	[redacted]
Patientomkostninger	[redacted]	[redacted]	[redacted]
Totale omkostninger	[redacted]	[redacted]	[redacted]

Tabel 25. Resultatet af ansøgers hovedanalyse ift. pasireotid, DKK, diskonterede tal

	Osilodrostat [DKK]	Pasireotid* [DKK]	Inkrementelle omkostninger [DKK]
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	[redacted]	[redacted]	[redacted]

	Osilodrostat [DKK]	Pasireotid* [DKK]	Inkrementelle omkostninger [DKK]
Efterfølgende behandling	[redacted]	[redacted]	[redacted]
Patientomkostninger	[redacted]	[redacted]	[redacted]
Totale omkostninger	[redacted]	[redacted]	[redacted]

*Resultaterne i afsnittet er ansøgers estimat af de inkrementelle omkostninger pr. patient. Dog har der været fejl i den indsendte ansøgning, hvor prisen på pasireotid, 10 mg var sat til 0, hvilket medførte en underestimering af omkostningen til lægemidlet. Denne har Medicinrådet rettet. Derfor stemmer resultaterne ikke overens med resultaterne præsenteret i ansøgers tekniske dokument.

10.2 Resultatet af ansøgers budgetkonsekvensanalyse

Ansøger har inkluderet de samme omkostninger i budgetkonsekvensanalysen, som er inkluderet i omkostningsanalysen, dog uden patientomkostninger. Ansøger har udført budgetkonsekvensanalysen ud fra en anden metode, end Medicinrådet anvender. Derfor har Medicinrådet udført sin egen budgetkonsekvensanalyse, men med ansøgers antagelser om patientantal, markedsandele, behandlingsvarighed, tidshorisont og enhedsomkostninger.

Herved estimeres, at anvendelse af osilodrostat vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 26.

Tabel 26. Ansøgers hovedanalyse for totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

10.3 Dosisdistribution for osilodrostat og pasireotid

Tabel 27. Dosisdistribution af osilodrostat i LINC3. Den daglige dosis af osilodrostat er fordelt over to doser, hvilket der er taget højde for i tabletsammensætningen for at opnå den daglige dosis.

Daglig dosis	Antal tabletter			Fordeling i LINC-3
	1 mg	5 mg	10 mg	
1 mg	1	-	-	9 %

Daglig dosis	Antal tabletter			Fordeling i LINC-3
	1 mg	5 mg	10 mg	
2 mg	2	-	-	14 %
3 mg	3	-	-	4 %
4 mg	4	-	-	16 %
5 mg	5	-	-	0 %
6 mg	6	-	-	9 %
7 mg	7	-	-	0 %
8 mg	8	-	-	1 %
9 mg	4	1	-	0 %
10 mg	-	2	-	16 %
11 mg	1	2	-	1 %
12 mg	2	2	-	1 %
13 mg	3	2	-	0 %
14 mg	4	2	-	6 %
15 mg	5	2	-	1 %
16 mg	6	2	-	0 %
17 mg	7	2	-	0 %
18 mg	8	2	-	0 %
19 mg	4	3	-	0 %
20 mg	-	-	2	14 %
21 mg	1	-	2	0 %
22 mg	2	-	2	0 %

Daglig dosis	Antal tabletter			Fordeling i LINC-3
	1 mg	5 mg	10 mg	
23 mg	3	-	2	0 %
24 mg	4	-	2	0 %
25 mg	5	-	2	0 %
26 mg	6	-	2	0 %
27 mg	7	-	2	0 %
28 mg	8	-	2	0 %
29 mg	4	1	2	0 %
30 mg	-	2	2	2 %
31 mg	1	2	2	0 %
32 mg	2	2	2	0 %
33 mg	3	2	2	0 %
34 mg	4	2	2	0 %
35 mg	5	2	2	0 %
36 mg	6	2	2	0 %
37 mg	7	2	2	0 %
38 mg	8	2	2	0 %
39 mg	4	3	2	0 %
40 mg	-	-	4	4 %
41 mg	1	-	4	0 %
42 mg	2	-	4	0 %
43 mg	3	-	4	0 %

Daglig dosis	Antal tabletter			Fordeling i LINC-3
	1 mg	5 mg	10 mg	
44 mg	4	-	4	0 %
45 mg	5	-	4	0 %
46 mg	6	-	4	0 %
47 mg	7	-	4	0 %
48 mg	8	-	4	0 %
49 mg	4	1	4	0 %
50 mg	-	2	4	0 %
51 mg	1	2	4	0 %
52 mg	2	2	4	0 %
53 mg	3	2	4	0 %
54 mg	4	2	4	0 %
55 mg	5	2	4	0 %
56 mg	6	2	4	0 %
57 mg	7	2	4	0 %
58 mg	8	2	4	0 %
59 mg	4	-	5	0 %
60 mg	-	-	6	1 %
Gennemsnitligt antal tabletter pr. døgn	2,11	0,54	0,58	

Tabel 28. Dosisdistribution af pasireotid i G2304. Distributionen er lavet på baggrund af de patienter, der blev randomiseret til en startdosis på 10 mg

Dosis pr. administration	Fordeling i G2304
10 mg	68 %
20 mg	0 %
30 mg	20 %
40 mg	12 %
60 mg	0 %

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

29.11.2022

MGK/ECH

Forhandlingsnotat

Dato for behandling i Medicinrådet	14.12.2022
Leverandør	Recordati
Lægemiddel	Isturisa (osilodrostat)
Ansøgt indikation	Cushings syndrom

Forhandlingsresultat

Amgros har opnået følgende pris på Isturisa (osilodrostat):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke/dosis/form	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Isturisa (osilodrostat)	1 mg	60 stk.	11.890	[redacted]	[redacted]
Isturisa (osilodrostat)	5 mg	60 stk.	47.568	[redacted]	[redacted]
Isturisa (osilodrostat)	10 mg	60 stk.	49.948	[redacted]	[redacted]

Prisen er ikke betinget af Medicinrådets anbefaling.

[redacted]

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

I Tabel 2 nedenfor ses de årlige lægemiddelomkostninger for de lægemidler, der indgår i Medicinrådets vurderingsrapport.

Tabel 2: Sammenligning af lægemiddelomkostninger

Lægemiddel	Styrke	Dosisdistribution	Pakningsstørrelse	Pakningspris SAIP (DKK)	Antal pakninger/år	Årlige lægemiddelomkostninger SAIP pr. år (DKK)
Isturisa* (osilodrostat)	1 mg	2,11 tabletter per dag	60 stk.	[redacted]	~13	[redacted]
	5 mg	0,54 tabletter per dag	60 stk.	[redacted]	~3	
	10 mg	0,58 tabletter per dag	60 stk.	[redacted]	~3	
Ketoconazole** HRA (ketoconazol)	200 mg	400-1.200 mg pr. dag fordelt på 2-3 doser/ tabletter	60 stk.	[redacted]	~24	[redacted]
Metopirone*** (metyrapon)	250 mg	250-6.000 mg dagligt fordelt på 3-4 doser/ kapsler	50 stk.	[redacted]	~58	[redacted]
Signifor**** (pasireotid)	20 mg	10-40 mg hver 4. uge/ IV	1 stk.	[redacted]	~13	[redacted]

**Gennemsnitligt antal tabletter pr. døgn (Medicinrådets sundhedsøkonomiske afrapportering, tabel 7), 1 mg: 2,11 tabletter, 5 mg: 0,54 tabletter, 10 mg: 0,58 tabletter*
***Antager en gennemsnitsdosis på 800mg per dag*
****Antager en gennemsnitsdosis på 2000 mg per dag*
*****Antager en gennemsnitsdosis på 20 mg hver 4 uge.*

Status fra andre lande

Norge: Anbefales ikke [1]
Sverige: Ingen information fundet
England: Ingen information fundet

Konklusion

[redacted]

[1] Osilodrostat (Isturisa) (nyemetoder.no)

Recordati would like to thank the Danish Medicines Council (DMC) for the assessment report on osilodrostat (Isturisa®) for the treatment of Cushing's Syndrome. In the following, you will find our comments on the assessment report.

Recordati understand that due to the lack of head-to-head data it is difficult to categorize the added value. Recordati wishes to ask the DMC to consider the high level of quality from the indirect comparisons versus metyrapone and pasireotide, as well as the advantageous safety profile versus metyrapone and ketoconazole.

Safety of osilodrostat versus ketoconazole and metyrapone

The DMC states in the assessment that safety versus pasireotide is comparable, however highlights the risk of developing type 2 diabetes with pasireotide. Recordati would like to also emphasis the advantages of osilodrostat in terms of safety versus ketoconazole and metyrapone.

Question 1 (page 22)

Firstly, ketoconazole has been withdrawn from the European markets for some time due to safety concerns, and currently has a warning regarding drug interactions stated in the SmPC. Secondly, ketoconazole received a black box warning from the FDA. It should be also highlighted that:

- Based on clinical trials, significantly fewer patients treated with osilodrostat compared to ketoconazole discontinued treatment due to adverse events. In 12 weeks 2.1% of patients on osilodrostat (LINC-4) and 13.2% of patients on ketoconazole (Castinetti 2008) discontinued treatment due to AEs. During full study periods 6/48 (13%) patients discontinued osilodrostat (LINC-4) and 41/160 (26%) patients discontinued ketoconazole due to adverse events.
- Due to the known hepatotoxicity of ketoconazole, the treatment must not be initiated in patients with liver enzymes levels above 2 times the upper limit of normal.
- There is long contraindication list for ketoconazole according to SmPC.
- Ketoconazole is characterized by numerous drug to drug interactions which can result in potentially life-threatening adverse reactions. Drugs that cannot be concomitantly used are for example CYP3A4 metabolised HMG-CoA reductase inhibitors, solifenacin, tolvaptan, and eplerenone. In CS, a multiorgan disease, this limits the possibility of symptom respectively comorbidity treatment dramatically.

Despite not being able to categorize the safety data due to the lack of good quality evidence for ketoconazole, Recordati wishes the DMC to acknowledge that osilodrostat has a better safety profile compared to ketoconazole.

The report (page 20) states that the committee does not know how many adverse events are related to the disease or to the patient's disease. The comparison of adverse events rates between osilodrostat and placebo, indirectly answers the question regarding adverse events related to the treatment.

Based on Gadelha 2022 the most common AEs during the placebo-controlled period included decreased appetite, arthralgia, and nausea. Grade 3/4 AEs occurred in 20.8% and 20.0% of osilodrostat and placebo recipients, respectively; hypertension was most common (8.3% osilodrostat vs 16.0% placebo). Only 1 patient discontinued because of an AE (arthralgia). During the placebo-controlled period, 77.1% of osilodrostat and 60.0% of placebo recipients received ≥ 1 concomitant

medication; the most common concomitant medications (> 5% in either arm) were acetaminophen (osilodrostat 10.4% vs placebo 8.0%), ranitidine, and ibuprofen (both 6.3% vs 0%).

Bearing in mind that the first 12 weeks are crucial to assess the safety profile of osilodrostat (up-titration period) and that the rate of Grade 3/4 AEs was similar between the treatment arms, it can be concluded that the most serious adverse events are attributed to disease symptoms.

Osilodrostat versus placebo

A summary of safety outcomes up to Week 12 from LINC-4 is presented in the table below. There was no statistically significant difference between osilodrostat and placebo for the proportion of patients who experienced any AE, any Grade ≥ 3 AE, any treatment related AE and any severe adverse events (SAE). There was also no statistically significant difference between osilodrostat and placebo for the proportion of patients who discontinued treatment due to an AE (DISCAE).

Table 1 Osilodrostat vs placebo (LINC-4): Summary of adverse events up to Week 12

	Risk Difference (95% CI); p value	**Relative Risk (95% CI); p value**	**Odds Ratio (95% CI); p value**
Any AE	0.04 (-0.08; 0.16); p = 0.5327	1.04 (0.91; 1.19); p = 0.5375	2.00 (0.26; 15.12); p = 0.5018
Any Grade ≥ 3 AE	0.01 (-0.19, 0.20); p = 0.9330	1.04 (0.40, 2.72); p = 0.9335	1.05 (0.32, 3.50); p = 0.9334
Treatment related AE	0.18 (-0.05; 0.42); p = 0.1275	1.42 (0.87; 2.33); p = 0.1634	2.12 (0.79; 5.67); p = 0.1335
Any SAE	0.00 (-0.09; 0.10); p = 0.9727	1.04 (0.10; 10.94); p = 0.9729	1.04 (0.09; 12.10); p = 0.9728
DISCAE	0.02 (-0.05; 0.09); p = 0.5680	1.58 (0.07; 37.35); p = 0.7777	1.61 (0.06; 40.98); p = 0.7729

Additionally, below you find a table overview from the final CSR document for LINC-4 reporting on adverse events suspected to be study drug related. [redacted]

Question 2

On page 29, the committee states that the Daniel et al. 2015 retrospective study included limited information regarding adverse events and mainly gastrointestinal problems. To provide a better picture of metyrapone's safety profile, Recordati would like to emphasise that the PROMPT (prospective study investigating metyrapone) did show the drug related adverse events. Information regarding this study was included in the submission dossier, however not reflected upon in the report. The most common AEs with metyrapone in PROMPT were nausea (24%), decreased appetite (18%), fatigue (14%), headache (10%), peripheral edema (6.0%), hypokalemia (6.0%) and hypertension (6.0%). Reversible adrenal insufficiency occurred in 6 (12%) patients. 14% of patients (7/50) experienced at least one AE that led to a dose interruption or dose adjustment. (Nieman et al. 2021)

The naïve (indirect) comparisons for safety outcomes can be informed by LINC-4 and PROMPT. There was generally no statistically significant difference between the treatments for the proportion of patients experiencing AEs. However, significantly fewer patients treated with osilodrostat (4.2%) experienced a SAE compared to metyrapone (20%), with the difference reaching statistical significance (RR 0.21, 95% CI: 0.05; 0.90; p=0.0359).

Overall conclusion

As the committee concluded, due to the nature of the disease, patients will experience certain adverse events. However, the treatments also come with their own adverse events. The data shows that osilodrostat not only has a better safety profile versus pasireotide, but also better than ketoconazole and metyrapone and, that it is not statistically significantly different from placebo in LINC-4 with its upfront placebo comparison. Recordati respectfully asks the Council to consider this evidence.

Indirect treatment comparisons with metyrapone and pasireotide

Question 2

Recordati observed that the committee did not consider the PROMPT study in the assessment of osilodrostat versus metyrapone, a study that did not came up in the protocol search string (dated July 2021), however, was identified separately in 2022. PROMPT is the only available prospective study for metyrapone and ought to, as a higher quality of evidence, be considered for this comparative assessment. Recordati had shared PROMPT's CSR synopsis as published in the EU Clinical Trials Register for full transparency with the committee. Therefore, Recordati kindly requests the DMC to reconsider the conclusion that the quality of evidence for metyrapone versus osilodrostat is rated as very low. This would be appropriate based on one retrospective study for metyrapone (i.e. Daniel 2015), but not in the case of available results for a prospective study which, in addition, enabled Recordati to perform an indirect treatment comparison.

Following this, the submitted matching adjusted indirect comparison (MAIC) of osilodrostat versus metyrapone based on PROMPT was not considered in the assessment report. The MAIC is based on patient level data from osilodrostat and aggregated data from a prospective study of good quality for metyrapone (PROMPT). The approach of a MAIC and propensity weighted analysis are supported by NICE (NICE documents TSD17 and TSD18). For the Committee's decision making it is of importance to

acknowledge that the MAIC shows osilodrostat to be a more effective option than metyrapone for patients with CS. The difference is substantial in every presented scenario and cannot be attributed to any methods bias. In the tables below, which are the same as in the application, it is shown that osilodrostat is more efficacious than metyrapone.

Table 2 MAIC results, complete response at Week 12

Scenario		Patients with CR (n/N [%])		OR (95% CI [robust SE])		RR (95% CI)
Imputation method	mUFC match	Osilodrostat (LINC-4)	Metyrapone (PROMPT)	Naïve	Adjusted	Adjusted
LOCF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: CI, confidence interval; CR, complete response; ESS, effective sample size; HR, hazard ratio; LOFC, last observation carried forward; mUFC, mean urinary free cortisol; OR, odds ratio; SE, standard error.

Notes: OR > 1 na RR > 1 favour osilodrostat; Green highlight indicated results which significantly favour osilodrostat.

Table 3 MAIC results, complete response at Week 36

Scenario		Patients with CR (n/N [%])		OR (95% CI [robust SE])		RR (95% CI)
Imputation method	mUFC match	Osilodrostat (LINC-4)	Metyrapone (PROMPT)	Naïve	Adjusted	Adjusted
LOCF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: CI, confidence interval; CR, complete response; ESS, effective sample size; HR, hazard ratio; LOFC, last observation carried forward; mUFC, mean urinary free cortisol; OR, odds ratio; SE, standard error.

Notes: OR > 1 na RR > 1 favour osilodrostat; Green highlight indicated results which significantly favour osilodrostat.

Given that the MAIC is based on two prospective trials (with one RCT), the quality of evidence cannot be considered as very low. The evidence is relevant for the decision making and Recordati kindly requests the Council to acknowledge the improved normalization of cortisol with osilodrostat versus metyrapone.

On page 26, the report states that differences in baseline mUFC levels between the studies might impact the share of patients who achieve mUFC normalization in the different studies.

Recordati has submitted two indirect comparisons: A propensity score weighted ITC for osilodrostat vs. pasireotide and a matching adjusted ITC vs metyrapone. These analyses by definition adjust for any significant baseline differences between the studies. Moreover, identifying prognostic factors and treatment confounders was a key element of both analyses. Among significant prognostic factors were age, sex and time since diagnosis, but not the baseline mUFC, which means that odds for

normalization do not depend on baseline mUFC values. Baseline mUFC was included in the ITCs as a parameter for matching populations, but only because it was a stratification variable in Lacroix 2018 study.

Additionally, the available osilodrostat RCTs (LINC-3 and LINC-4) suggest that no clear relationship can be established between the baseline mUFC value and patients' mUFC normalization. This is depicted in the below figures from the LINC-3 and LINC-4 trials.

Figure 1 LINC-3: baseline vs 24 weeks mUFC levels (Pivonello 2020)

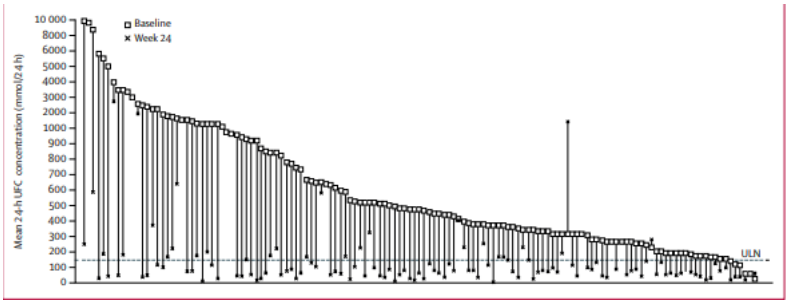
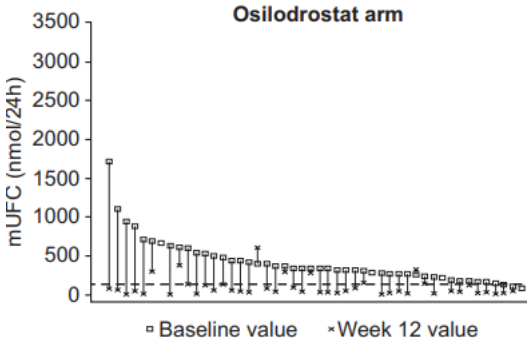


Figure 2 LINC-4: baseline vs 12 weeks mUFC levels (Gadelha 2022)



Question 3

Regarding question 3 (page 39), relating to the comparison between osilodrostat and pasireotide, the committee bases their conclusions only on the descriptive comparison, whereas the submitted patient level data (PLD) population adjusted ITC was not considered to strengthen the relative effectiveness comparison. The committee deemed the adjusted comparison analysis only as supplementary, because it was not considered to provide a more accurate picture than the descriptive review. Given that this is a statistical analysis based on accepted methods by NICE, Recordati wishes to emphasise the relevance of the results. In NICE guidelines it is clearly indicated that if patient level data from RCTs are used for both compared interventions, the credibility and accuracy of such analysis is high, as it is easy to match patients according to baseline characteristics. The results show osilodrostat to have significantly more patients achieving complete response at week 12 and at longest follow up versus pasireotide LAR and pasireotide sc. The committee states that in absence of comparative data, the quality of evidence is considered very low. Given that a comparative analysis based on patient level data from prospective RCTs is provided in the submission, Recordati believes that the quality of data cannot be considered as very low.

General remarks on evidence quality

Given the rarity of the condition, the reimbursement dossier is based on a significant number of studies including large numbers of observed patients. The overall assessment is based on 14 studies,

including 2 RTCs for osilodrostat and 2 RCTs for pasireotide. Additionally, for metyrapone one prospective (PROMPT) and one observational study (Daniel et al 2015) and for ketoconazole two observational studies (Castinetti 2008, Castinetti 2014) were included. A few other supporting studies (long term and real-world data) were also described, which strengthens the conclusions.

According to the DMC methodology, the quality of evidence definition 'very low' is applicable if new studies are very likely to change the conclusion.

Given the submitted wealth and quality of evidence, particularly in a rare disease, Recordati believes that new studies are very unlikely to change the following conclusions from Medicine Council Assessment:

- "Treatment with osilodrostat overall results in more patients achieving normalisation of cortisol than treatment with ketoconazole, metyrapone and pasireotide".
- "… osilodrostat has a more benign side effect profile compared to pasireotide, as the risk of developing type 2 diabetes is lower among patients receiving osilodrostat".

All studies for pasireotide, including two RTCs and three nRCT single arm studies, report significantly lower rates of normalization compared to osilodrostat studies. It is therefore unlikely that any potential new study can change the conclusion. The same logic applies to osilodrostat's comparisons to metyrapone and ketoconazole. It is also unlikely that any additional study for osilodrostat would report a higher risk of developing type 2 diabetes, with RCTs and long-term outcomes (LINC1/LINC-2/LINC-3) being available.

Economic appraisal

Treatment escape

In the report, the Committee states that treatment escape does not automatically lead to treatment cessation, given that this is not the case in Danish clinical practice. The council changes the treatment escape definition to match that of LINC-3 (>1.5 ULN instead of applicant's >1.0 ULN). (Page: 6, 14, 15, 17 of the economic appraisal)

According to published literature (Pivonello 2015) the main objectives for the treatment of CS include: 1) normalization of cortisol secretion; 2) reversal of the clinical picture; 3) prevention or recovery of the concomitant comorbidities and clinical complications; and 4) long-term disease control without disease recurrence. The article also states that "it is clear that the normalization of cortisol secretion improves mortality, most likely because of the positive effects on the clinical comorbidities associated with CD including cardiovascular disease, metabolic syndrome, infectious diseases, and neuropsychiatric disorders, which affect quality of life and represent the important risk of death for patients with CD." These conclusions are consistent with the main clinical guideline (Fleseriu 2021) and other sources indicating that patients with persistently elevated cortisol level have significantly increased standard mortality rates compared to patients normalized (6.9 vs. 1.9) (Clayton 2011, Ragnarsson 2019). According to the algorithm for management of Cushing's (Fleseriu 2021) a different drug should be started if only partial control is achieved with the current medical therapy. If cortisol does not normalise but a reduction or some clinical improvement is seen, combination therapy can be considered.

It has been validated by the KOLs worldwide that the decrease in mUFC with partial response is not enough to consider patients as normalized and does not yet provide health benefits. It is certainly true in clinical practice, as also indicated by the experts of the Committee, that some patients might continue therapies with currently available treatment options with slightly elevated mUFC levels, however this practice is likely driven by short-term therapies (e.g. bridging to 2nd surgery or adrenalectomy) and possibly a necessity due to today's scarce alternatives with limited efficacy. With osilodrostat, pasireotide LAR and bilateral adrenalectomy (as a last resort treatment) available to the patients and taking into consideration that CS is a chronic disease, it should be assumed that physicians will not be willing to keep patients on suboptimal treatment for longer periods in 1st line medical treatment (e.g. ≥2 years) which expose them to a more elevated risk of clinical consequences, comorbidities and, ultimately, death.

In LINC-3, treatment escape was defined as mUFC > 1.5 x ULN, whereas in LINC-4 this was > 1.3 x ULN. This definition is however strictly connected with the inclusion criteria of both studies (mUFC above 1.5 x and 1.3 x ULN respectively) and it is therefore both logic and coherent. It allows to detect "zero effect" of drug, but it is not appropriate for the estimation of time on treatment in the real-world setting. The inclusion criteria above 1.0 x ULN was introduced for practical reasons: to power the trial and to be able to detect significant difference between intervention and comparator.

Additionally, for methodological reasons, it was not feasible to design a study where patients would be withdrawn from therapies at treatment escape as this would lead to bias in maintaining randomization and interpretation of results.

In the pasireotide studies, Colao 2012 and Lacroix 2018, time to treatment escape has been defined as the duration of the first response, which is defined as the period starting from the date of the patient's first normalization (mUFC ≤ 1.0 x ULN) up to the date when the patient attained a mUFC > 1.0 x ULN for the first time. No other parameter has been reported, which can be alternatively used as a proxy to calculate time to treatment escape. As a result, we can reliably compare osilodrostat with pasireotide only with the treatment escape definition of >1.0xULN as has been used in the economic analysis. In the scenario proposed by the DMC, patients are treated with osilodrostat until mUFC > 1.5 x ULN and with pasireotide until > 1.0 x ULN, which results in the incremental cost of osilodrostat vs pasireotide to be vastly overestimated. An appropriate comparison can only be derived when for both interventions the same definition of treatment escape, defined as >1.0 ULN is used. This definition of treatment escape also aligns with the long-term therapeutic goals of CS.

Time horizon

The Medical Council has changed the time horizon to 50 years, as it is believed that model would then capture the full estimated course of treatment with osilodrostat (page 22 of Economic appraisal).

Recordati recognizes that it is important to have a time horizon that would capture all relevant aspects to the treatment. According to clinical expert, in Danish clinical practice, pharmacological treatment lasts for a maximum of 2 to 3 years before undergoing BLA, which validates a time horizon of 2-5 years as capturing all relevant costs and benefits. Therefore, a 2 to maximum 5 year-time-horizon is suitable for the cost analysis.

This is also consistent with international clinical guidelines (Fleseriu 2021) pointing to a period of 3-4 years for treating patients from failure of initial pituitary surgery to adrenal surgery (BLA). Introducing

the longer time horizon of 50 years does not reflect the expected average time of CS medical treatment. A longer time horizon would also require building a much more complex structure of the model and including additional costs of adrenal insufficiency and complications patients would experience after BLA. Such costs categories are playing key role in longer time horizon as most patients in the model transition to BLA health state after a couple of years.

Treatment of adrenal insufficiency, omitted in the health economic model, aims to replace hormonal deficiency, using mainly glucocorticoids, as well as mineralocorticoids and, optionally, adrenal androgens. Replacement therapy is lifelong and challenging in terms of potential serious adverse events (Papierska 2015).

The current model includes only Nelson syndrome and wound infection treatment costs related to BLA, which are the most common side effects of BLA itself and not of adrenal insufficiency caused by BLA. The current model structure would underestimate both the costs associated with BLA over a longer time period (e.g. 50 years horizon) but also the QoL impact that patients would experience from the side effects due to the replacement therapy as well as the lack of the circadian rhythm of cortisol secretion.

Medicinrådet

Medicinrådets vurdering vedrørende osilodrostat til behandling af Cushings syndrom

Version 1.0

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

Medicinrådet vurderer, om nye lægemidler og indikationsudvidelser skal anbefales som mulig standardbehandling. Medicinrådet udarbejder også behandlingsvejledninger og rekommandationer for anvendelse af medicin på sygehusene. Derudover kan Medicinrådet tage andre typer sager op, der handler om medicinanvendelse.

Om vurderingsrapporten

Vurderingsrapporten indeholder Medicinrådets vurdering af, hvilken værdi lægemidlet har for patienten i forhold til nuværende standardbehandling.

Værdien for patienten og omkostningerne for samfundet danner grundlaget for Medicinrådets beslutning om, hvorvidt lægemidlet anbefales som mulig standardbehandling. Dette bliver sammenfattet i Medicinrådets anbefaling vedr. lægemidlet.

Lægemidlet er vurderet efter *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, som du kan finde på Medicinrådets hjemmeside under siden Metoder.

Dokumentoplysninger	
Godkendelsesdato	23. november 2022
Dokumentnummer	156646
Versionsnummer	1.0

Indholdsfortegnelse

Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 24. november 2022

1. Medicinrådets konklusion

Medicinrådet vurderer, at værdien af osilodrostat til Cushings syndrom sammenlignet med ketoconazol, metyrapon og pasireotid ikke kan kategoriseres. Rådet vurderer dog, at behandling med osilodrostat samlet medfører, at flere patienter opnår normalisering af kortisol end ved behandling med ketoconazol, metyrapon og pasireotid.

Medicinrådet vurderer, at osilodrostat sammenlignet med pasireotid har en mere skånsom bivirkningsprofil, da risikoen for at udvikle type 2-diabetes er mindre blandt patienter, der modtager osilodrostat. På det nuværende datagrundlag er det ikke muligt at vurdere, om der er forskelle i bivirkninger mellem behandling med osilodrostat og hhv. ketoconazol og metyrapon.

Data for pasireotid og osilodrostat peger i retning af, at begge behandlinger øger livskvaliteten, men fagudvalget kan på det nuværende datagrundlag ikke vurdere, om der er en klinisk relevant forskel mellem behandlingerne. Der er ikke data for livskvalitet for behandling med ketoconazol og metyrapon, og effekten kan derfor ikke vurderes.

Vurderingerne er baseret på evidens af meget lav kvalitet.

MEDICINRÅDET KATEGORISERER LÆGEMIDLERS VÆRDI I EN AF FØLGENDE KATEGORIER:

- **Stor merværdi:** Der er påvist en stor forbedring i effektforhold i forhold til gældende standardbehandling, eksempelvis markant forbedret overlevelse, markant reduktion i forekomsten af alvorlige symptomer og/eller alvorlige bivirkninger.
- **Moderat merværdi:** Der er påvist en moderat forbedring i forhold til gældende standardbehandling, eksempelvis moderat forbedret overlevelse, moderat reduktion i forekomsten af symptomer og/eller bivirkninger.
- **Lille merværdi:** Der er påvist en lille forbedring i forhold til gældende standardbehandling, eksempelvis en dokumenteret forbedret overlevelse, en reduktion i forekomsten af symptomer og/eller bivirkninger.
- **Merværdi af ukendt størrelse:** Der er påvist en forbedring i forhold til gældende standardbehandling, men størrelsen af forbedring kan ikke bestemmes. Lægemidlets merværdi er som minimum lille, men kunne også være moderat eller stor.
- **Ingen dokumenteret merværdi:** Der er ikke påvist en merværdi i forhold til gældende standardbehandling. Omvendt tyder den tilgængelige evidens heller ikke på, at der er en negativ værdi.
- **Negativ værdi:** Der er påvist en negativ værdi i forhold til gældende standardbehandling.

I nogle situationer er det ikke muligt at kategorisere lægemidlets samlede værdi. De situationer opstår, når evidensgrundlaget for vurderingen er for usikkert til at kategorisere værdien jf. Medicinrådets metoder (fx på grund af usikkerheder omkring effektforhold og spinkelt datagrundlag). Medicinrådet konkluderer da, at samlet værdi ikke kan kategoriseres. Medicinrådet vil i disse tilfælde argumentere for, om der er grund til at formode, at det nye lægemiddel er dårligere eller evt. bedre end gældende standardbehandling, eller der ikke er grund til at skelne mellem behandlingerne. Det sker på baggrund af det foreliggende datagrundlag og fagudvalgets kliniske erfaring. Vurderingen er forbundet med større usikkerhed end vurderinger, hvor lægemidlets værdi kan kategoriseres.

MEDICINRÅDET VURDERER KVALITETEN AF DE DATA, DER LIGGER TIL GRUND FOR VURDERINGEN AF LÆGEMIDLET (EVIDENSENS KVALITET) I EN AF FØLGENDE GRADE-KATEGORIER:

- **Høj:** Nye studier vil med meget lav sandsynlighed ændre konklusionen.
- **Moderat:** Nye studier vil med lav sandsynlighed ændre konklusionen.
- **Lav:** Nye studier vil med moderat sandsynlighed ændre konklusionen.
- **Meget lav:** Nye studier vil med høj sandsynlighed ændre konklusionen.

2. Begreber og forkortelser

ACTH: Adrenokortikotropt hormon

EMA: Det Europæiske Lægemiddelagentur (*European Medicines Agency*)

EPAR: *European Public Assessment Report*

EUnetHTA: *European Network for Health Technology Assessment*

FDA: *The Food and Drug Administration*

FINOSE: Finland, Norge og Sveriges samarbejde om medicinske teknologivurderinger

GRADE: System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)

HTA: Medicinsk teknologivurdering (*Health Technology Assessment)*

IQWIG: *The Institute for Quality and Efficiency in Healthcare*

ITT: *Intention-to-treat*

MKRF: Mindste klinisk relevante forskel

NICE: *The National Institute for Health and Care Excellence*

PICO: Population, intervention, komparator og effektmål (*Population, Intervention, Comparison and Outcome)*

PP: *Per Protocol*

RR: Relativ risiko

SMD: *Standardized Mean Difference*

mUFC: *Mean Urinary Free Cortisol*

ULN: *Upper Limit of Normal*

3. Introduktion

Formålet med Medicinrådets vurdering af osilodrostat til endogent Cushings syndrom er at vurdere den værdi, lægemidlet har sammenlignet med dansk standardbehandling.

Vurderingen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Recordati. Medicinrådet modtog ansøgningen den 14. september 2022.

De kliniske spørgsmål er:

1. Hvilken værdi har osilodrostat sammenlignet med ketoconazol til voksne patienter med endogent Cushings syndrom?
2. Hvilken værdi har osilodrostat sammenlignet med metyrapon til voksne patienter med endogent Cushings syndrom?
3. Hvilken værdi har osilodrostat sammenlignet med pasireotid til voksne patienter med endogent Cushings syndrom?

3.1 Cushings syndrom

Cushings syndrom er den kliniske tilstand, som fremkommer, når kroppen gennem længere tid udsættes for forhøjede mængder af binyrebarkhormon (kortisol). Kortisol dannes i binyrebarken, og syntesen stimuleres af kortikotropin (adrenokortikotropt hormon (ACTH)), som dannes i hypofysen [1].

Cushings syndrom kan skyldes en øget produktion af kortisol fra binyrerne (endogent Cushings syndrom) eller opstå som følge af langvarig behandling med lægemidler, som indeholder binyrebarkhormon (eksogent Cushings syndrom).

Denne protokol omhandler udelukkende endogent Cushings syndrom. Endogent Cushings syndrom kan yderligere opdeles i to grupper:

- ACTH-afhængigt Cushings syndrom, som skyldes:
    - en ACTH-producerende svulst i hypofysen (kaldet Cushings sygdom) – ca. 75 % af patienterne
      eller
    - en ACTH-producerende svulst uden for hypofysen (ektopisk Cushings syndrom) – ca. 5 % af patienterne.
- ACTH-uafhængigt Cushings syndrom, som skyldes:
    - en autonom kortisolproduktion fra binyrebarken, som skyldes en godartet eller ondartet kortisolproducerende svulst i en eller begge binyrer – ca. 20 % af patienterne.

Kortisolreceptorer findes i det meste af kroppens væv, hvorfor symptombilledet hos patienterne er meget bredt, se Tabel 3-1.

Tabel 3-1. Symptomer og kliniske fund ved Cushings syndrom [1]

Udseende	Vægtøgning med især abdominal fedme, måneansigt, tyrenakke (buffalo hump), pletorisk udseende (tomatansigt), tynde ekstremiteter
Hjerte/kar	Forhøjet blodtryk forhøjet niveau af lipider og triglycerider, øget forekomst af type 2-diabetes, tromboemboliske episoder
Kønsorganer	Akne og hirsutisme (unormal hårvækst hos kvinder), blødningsforstyrrelser, impotens
Muskler	Nedsat muskelstyrke, muskelsvaghed og muskelsmerter
Mentale	Psykiske forstyrrelser fra let irritabilitet til depression, mani eller psykoser, generel utilpashed og kognitive problemer, træthed
Hud	Tynd og skrøbelig hud med blødningstendens og dårlig sårheling, tendens til perifere ødemer
Skelet	Smerter, knogleskørhed
Andet	Øget infektionstendens

De forskellige symptomer ved Cushings syndrom og medfølgende multiorgansygdomme skyldes det kronisk forhøjede kortisolniveau og i enkelte tilfælde co-produktion af androgener (mandlige kønshormoner) i binyrerne [2–6]. Insulinsekretion og -sensitivitet påvirkes i negativ retning med risiko for udvikling af type 2-diabetes [7], som sammen med dyslipidæmi (lipidforstyrrelser) og forhøjet blodtryk øger risikoen for alvorlig hjertekarsygdom og øget mortalitet [6]. Øget kortisolniveau er også en stærk prædiktor for udvikling af knogleskørhed. Det skyldes, at det høje kortisolniveau både direkte og indirekte påvirker knogledensiteten ved blandt andet at hæmme genopbygning af knoglemasse [8]. Risikoen for infektioner øges også, idet kortisol har brede og potente immunsupprimerende effekter [9]. Symptomerne præsenterer sig gennem måneder til år, og der er stor variation både i udbredelse og alvorlighed hos de enkelte patienter.

Tilstanden er sjælden, og i Danmark er der ca. 20-30 nye tilfælde af endogent Cushings syndrom om året, men der er usikkerhed ved dette estimat. Tilstanden er hyppigst i 20-50 års-alderen og hyppigere hos kvinder end hos mænd. Der er stor forskel på, hvornår i sygdomsforløbet patienterne diagnosticeres, da sygdommen præsenterer sig individuelt, og de enkelte symptomer kan forveksles med andre sygdomme. Mistanke om Cushings syndrom opstår typisk på baggrund af mønstergenkendelse af symptomerne og hos personer med en atypisk klinisk præsentation (fx debut i ung alder) af flere af de kendte følgesygdomme [1].

Ubehandlet forværres sygdommen, og patienterne har høj dødelighed på grund af hjertekarsygdomme og den øgede risiko for infektioner. Prognosen hos patienterne er dog god, forudsat at behandlingen startes tidligt. Cushings syndrom har betydelig negativ effekt på patienternes livskvalitet, som skyldes både ændret udseende såvel som

kortisols indvirkning på psyken, og patienterne oplever ofte vedvarende psykiske senfølger, selv efter behandling er iværksat [1,10].

3.2 Osilodrostat

Osilodrostat er en kortisolsyntesehæmmer (adrenal steroidsyntesehæmmer). Det er en potent hæmmer af 11β-hydroxylase (CYP11B1), som er det enzym, der er ansvarlig for det sidste trin i syntesen af kortisol i binyrerne. CYP11B1-hæmning er forbundet med ophobning af forstadier til kortisol (11-deoxycortisol) og dermed en acceleration af adrenal syntese, herunder androgener (mandlige kønshormoner) [11]. Osilodrostat hæmmer også CYP11B2, som er ansvarlig for syntesen af aldosteron [12].

Osilodrostat findes som tabletter i styrkerne 1 mg, 5 mg og 10 mg. Den anbefalede startdosis er 2 mg osilodrostat to gange dagligt. Dosis kan titreres gradvist på baggrund af den enkelte patients respons og tolerance, med det mål at opnå normale kortisolniveauer. Den sædvanlige vedligeholdelsesdosis i kliniske studier varierer mellem 2 og 7 mg to gange dagligt. Den anbefalede maksimumdosis af osilodrostat er 30 mg to gange dagligt [13].

Osilodrostat har indikation til behandling af endogent Cushings syndrom hos voksne.

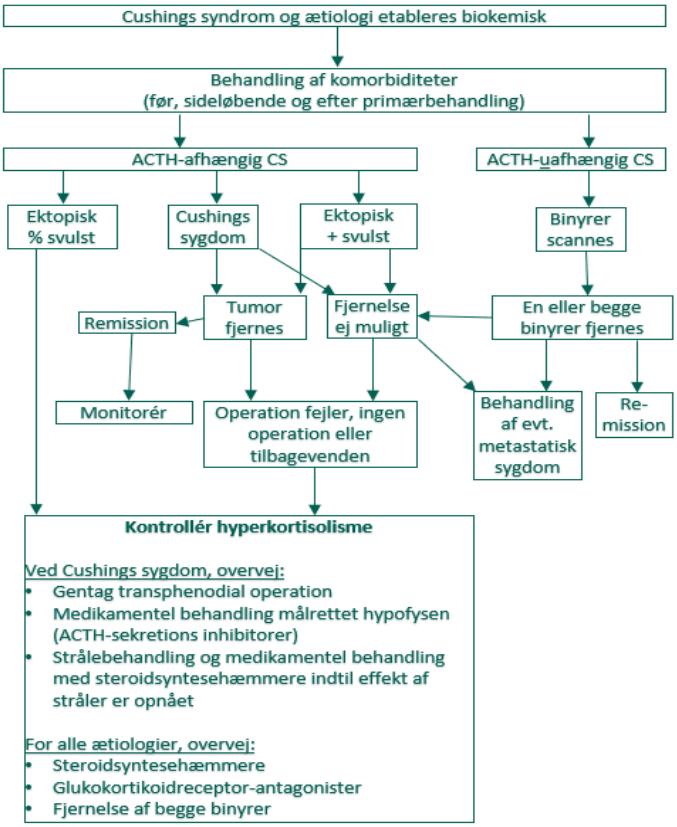
osilodrostat (Isturisa) modtog *orphan drug status* af EMA i 2014 og fik markedsføringstilladelse i EU i januar 2020.

Evidensen bygger primært på data fra et randomiseret fase 3-studie, som kun inkluderer patienter med Cushings sygdom (hypofysær). Det er dog EMAs vurdering – på baggrund af osilodrostats virkningsmekanisme – at behandlingen forventes at være effektiv hos alle former for endogent Cushings syndrom. Ekstrapolation af effekten til patienter med de øvrige former af endogent Cushings syndrom antages derfor af EMA som værende ukontroversiel [12].

3.3 Nuværende behandling

Den primære behandling af både ACTH-afhængigt og ACTH-uafhængigt Cushings syndrom er kirurgi, hvor den hormonproducerende svulst fjernes. Ved succesfuld operation vil patienterne få fjernet deres kortisoloverskud, og med tiden normaliseres kroppens udseende og funktion. Selv efter en vellykket operation tager det dog typisk lang tid, før patienterne genvinder deres normale funktionsniveau såvel fysisk som psykisk. På grund af risiko for tilbagefald (specielt for Cushings sygdom) er der behov for livslang endokrinologisk kontrol.

Udover primær kirurgi består de yderligere behandlingsmodaliteter af re-operation, medicinsk behandling, strålebehandling mod hypofyselejet og/eller fjernelse af begge binyrer, se Figur 3-1.



Figur 3-1. Behandlingsalgoritme ved Cushings syndrom [14]

Medicinsk behandling

Medicinsk behandling anvendes i Danmark til at kontrollere kortisolniveauet i disse situationer:

- Når en kirurgisk fjernelse af svulsten ikke lykkes eller ikke er mulig (ca. 25 % af patienterne med Cushings sygdom). Behandlingen er typisk midlertidig, indtil definitiv behandling er mulig (strålebehandling, fjernelse af begge binyrer eller gentaget hypofyseoperation).
- Før operation for at kontrollere et betydende forhøjet kortisolniveau og dermed opnå klinisk bedring hos patienter med svære komplikationer (ca. 10 % af patienter med Cushings syndrom).
- Metastatisk Cushings syndrom.

Den medicinske behandling er ofte kun midlertidig, typisk 2-6 måneder, og kun i sjældne tilfælde (10 %) vil patienterne fortsætte i livslang behandling. Fagudvalget vurderer, at ca. 5-8 patienter om året er kandidater til medicinsk behandling.

Valg af medicinsk behandling

Der er flere tilgængelige lægemidler, som kan anvendes i den kortisolhæmmende behandling af Cushings syndrom [1]. Behandlingerne gives enten alene eller i kombination efter behov:

- Hæmmere af binyrebarkens hormonproduktion (adrenale steroidsyntese-hæmmere): Ketoconazol, metyrapon, mitotan og etomidat.
  Kan anvendes til behandling af alle former af Cushings syndrom.
  Mitotan anvendes i Danmark kun til patienter med metastatisk sygdom.
  Etomidat anvendes udelukkende i intensivt regi (ikke markedsført i Danmark).

- Hæmmere af ACTH-sekretionen: Cabergolin og pasireotid.
  Kan anvendes til behandling af Cushings sygdom, hvorimod effekten er uafklaret ved ektopisk Cushings sygdom. I Danmark anvendes udelukkende pasireotid (cabergolin er ikke markedsført til indikationen i Danmark).

- Glukokortikoid receptorantagonist: Mifepriston.
  Kan anvendes til behandling af alle typer Cushings syndrom (ikke markedsført til indikationen i Danmark). Anvendes sjældent på grund af risiko for overdosering.

På grund af patientgruppens heterogene præsentation af symptomer og kliniske fund samt komorbiditeter er der ikke en klart defineret medicinsk standardbehandling i Danmark. Fagudvalget vurderer, at den medicinske behandling i klinisk praksis består af ketoconazol, metyrapon og pasireotid. Valg af præparat afhænger af klinisk erfaring og en individuel helhedsvurdering af patienten samt præparaternes bivirkningsprofil. Den kliniske erfaring med ketoconazol og metyrapon er lang (> 30 år), men evidensen består af retrospektive opgørelser og *case-reports*, der primært inkluderer patienter med Cushings sygdom [15,16]. Den kliniske erfaring med pasireotid er kortere, men evidensen består af randomiserede fase 3-studier [17].

Behandlingsstrategien er enten *block-replacement*-terapi ved behov for en hurtig effekt eller en normaliseringsstrategi. Ved *block-replacement*-terapi tilstræbes det at reducere det endogene kortisolniveau til et lavt niveau og supplere med hydrokortison i substitutionsdoser for at undgå binyrebarkinsufficiens. Ved normaliseringsstrategi tilstræbes eukortisolisme (fysiologisk kortisolniveau med normal døgnvariation).

Doseringen af lægemidlerne justeres individuelt efter patientens kortisolniveau og afhængigt af tolerabilitet. Ved behandling med en steroidsyntesehæmmer skal kortisolniveauerne monitoreres med få ugers mellemrum i starten. Ved behandling med pasireotid anbefales klinisk evaluering efter to måneders behandling.

Lægemidlerne har en høj grad af interaktioner med andre lægemidler. Blandt andet er ketoconazol en kraftig hæmmer af enzymet CYP3A4. CYP3A4 er med til at omsætte en lang række lægemidler i kroppen, hvorfor det er vigtigt at have opmærksomhed på dette ved opstart og under behandling [15].

Fjernelse af binyrerne antages dog fortsat at være den primære behandling af Cushings syndrom.

Øvrig behandling
Udover en normalisering af kortisolniveauet er behandlingsmålet ved Cushings syndrom også at behandle komorbiditeter og den mangel på binyrebarkhormon

(binyrebarkinsufficiens), som typisk opstår efter fjernelse af en hormonproducerende svulst.

Behandling af komorbiditet
Cushings syndrom er som anført associeret med en lang række komorbiditeter (kardiovaskulær sygdom, knogleskørhed, diabetes og psykiske symptomer), som behandles før, sideløbende og efter behandling af primær sygdom [1]. Behandlingen sker som udgangspunkt i endokrinologisk regi parallelt med kontrolbesøg for den primære sygdom.

Behandling af binyrebarkinsufficiens
Efter en vellykket primær operation af hypofysen og ved *block-replacement*-terapi vil patienterne næsten altid få binyrebarkinsufficiens. Der er ligeledes risiko for binyrebarkinsufficiens ved medicinsk normaliseringsstrategi specielt i stresssituationer. Der kan dog opleves symptomer trods substitution med fysiologiske doser hydrokortison.

Symptomer omfatter kvalme, anoreksi, vægttab og mere uspecifikke symptomer såsom træthed, udmattelse og influenzalignende muskel- og ledsmerter. Nogle patienter udvikler depression, angst og panik. Symptomlindring opnås ved at øge substitutionsdosis, men det er omvendt vigtigt at reducere dosis igen, når det er muligt, for at undgå påført Cushings syndrom [1]. Patienterne skal derfor informeres om og uddannes i at genkende tegn og symptomer på binyrebarkinsufficiens.

4. Metode

Medicinrådets protokol for vurdering vedrørende osilodrostat til Cushings syndrom beskriver sammen med *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, hvordan Medicinrådet vil vurdere lægemidlets værdi for patienterne.

5. Resultater

5.1 Klinisk spørgsmål 1

5.1.1 Litteratur

Nedenfor beskriver og vurderer Medicinrådet den litteratur, som ansøger har anvendt i sin endelige ansøgning.

Ansøger har søgt litteratur med søgestrengen fra protokollen og har udvalgt 6 fuldtekstartikler, der beskriver 4 kliniske studier samt to retrospektive studier.

Tabel 5-1. Oversigt over studier inkluderet klinisk spørgsmål 1

Publikationer	Klinisk forsøg	NCT-nummer	Population
Randomized trial of osilodrostat for the treatment of Cushing's disease. [18]	LINC-4	NCT02697734	Patienter med Cushings sygdom
Efficacy and safety of osilodrostat in patients with Cushing's disease (LINC 3): a multicentre phase III study with a doubleblind, randomised withdrawal phase. [19]	LINC-3	NCT02180217	Patienter med Cushings sygdom
LCI699, a potent 11β-hydroxylase inhibitor, normalizes urinary cortisol in patients with Cushing's disease: results from a multicenter, proof-of-concept study. [20]	LINC-1 (core study); LINC-2 (extension study)	NCT01331239	Patienter med Cushings sygdom
Osilodrostat, a potent oral 11β-hydroxylase inhibitor: 22-week, prospective, Phase II study in Cushing's disease. [21]	LINC-2	NCT01331239	Patienter med Cushings sygdom
A multicenter, phase 2 study to evaluate the efficacy and safety of osilodrostat, a new 11β-hydroxylase inhibitor, in Japanese patients with endogenous Cushing's syndrome other than Cushing's disease. [22]	C1201	NCT02468193	Japanske patienter med endogen Cushings syndrom, undtagen Cushings sygdom forårsaget af binyretumor/hyperplasi eller ektopisk adrenokortikotropisk hormonsyndrom.
Ketoconazole in Cushing's disease: is it worth a try? Castinetti et al 2014 [23]	-	-	Patienter med Cushings sygdom
Ketoconazole revisited: a preoperative or postoperative treatment in Cushing's disease. Castinetti et al 2008 [24]	-	-	Patienter med Cushings sygdom

Der præsenteres kun data fra LINC-3 og LINC-4 for osilodrostat, da disse studier bedst belyser effekten af osilodrostat. Dette skyldes, at disse studier er randomiserede fase III-studier, og fagudvalget mener ikke, at de øvrige studier bidrager med yderligere information.

Der præsenteres kun data fra Castinetti et al. 2014, da patientpopulationen fra Castinetti et al. 2008 er meget lille og ikke bidrager med yderligere information.

Studiebeskrivelser

LINC-4

LINC-4 er et randomiseret, fase 3-studie, der løber over 48 uger, startende med en 12-ugers dobbeltblindet placebokontrolleret periode. Resten af studiet er single-arm open-label.

Der blev inkluderet 73 patienter, hvoraf 48 fik osilodrostat i de første 12 uger. De patienter, der var randomiseret til placebo, skiftede til osilodrostat efter uge 12, og alle patienterne fik osilodrostat indtil uge 48, hvorefter de havde mulighed for at fortsætte i en opfølgende fase, som fortsatte indtil uge 84.

Patienter kunne deltage i studiet, hvis de:

- Oplevede vedholdende eller tilbagevendende Cushings sygdom efter tidligere at have været opereret eller fået stråling for en svulst i hypofysen, samt patienter der ikke kunne eller ville opereres.
- Patienter, der havde modtaget glukokortikoid substitutionsterapi efter operation, skulle være stoppet i mindst en uge eller efter 5 halveringstider, inden de kunne deltage i studiet.
- Patienter med nydiagnosticeret Cushings sygdom kunne kun inkluderes, hvis de ikke var kandidater til operation.

Patienter kunne ikke deltage i studiet, hvis de:

- Havde pseudo-Cushings syndrom.
- Havde en arvelig grund til hormon-overudtryk.
- Havde Cushings syndrom pga. ektopisk ACTH-sekretion eller ACTH-uafhængig Cushings syndrom.
- Havde ukontrolleret forhøjet blodtryk, diabetes, som ikke var velbehandlet, hjerteproblemer, nedsat nyrefunktion, leversygdom, malign sygdom, risikofaktorer for QTc-forlængelse eller Torsade de Pointes, eller kompression af chiasma opticum.
- Vurderedes at have behov for operation indenfor de 12 første uger af forsøget.

LINC-3

LINC-3 er et randomiseret, dobbeltblindet fase 3-studie med en udvaskningsfase. Studiet startede med en 24-ugers open-label, single-arm, dosistitreringsfase, som evaluerede effekt og sikkerhed af behandling med osilodrostat for patienter med Cushings sygdom, hvorefter patienterne randomiseredes til osilodrostat eller placebo.

Der blev inkluderet 137 patienter, som i de første 12 uger modtog mellem 2 og 30 mg osilodrostat to gange dagligt i en open-label fase. I uge 12-26 fik patienterne den dosis, de var titreret til. I uge 26 blev 71 patienter randomiseret til enten osilodrostat eller placebo. De resterende 46 patienter fortsatte osilodrostat som open-labelbehandling. De randomiserede patienter, som fik placebo, skiftede til osilodrostat efter uge 34, og alle patienterne fik osilodrostat indtil uge 48, hvor behandlingen stoppede.

Inklusionskriterierne var de samme som i LINC-4, med undtagelse af følgende kriterier:

- Patienter, der tidligere har været opereret, kunne tidligst inkluderes i studiet efter mindst 30 dage.
- Patienter, der tidligere har fået strålebehandling, kunne inkluderes i studiet, hvis der var gået 2 år (stereotaktisk strålekirurgi) eller 3 år (almindelig stråling) fra sidste strålebehandling.

Eksklusionskriterierne var de samme som i LINC-4.

Castinetti et al. 2014

Castinetti et al. 2014 er et retrospektivt kohortestudie med 200 franske patienter, som har modtaget behandling med ketoconazol. Patienterne er inddelt i tre grupper: Præ-kirurgisk (n = 40), behandlingsnaive (n = 32) og 2. linjebehandling (n = 128) (behandling efter enten en operation eller strålebehandling). Gruppen af patienter, der opnår komplet respons, behandles i 27,6 måneder (± 36,4).

Patienter kunne deltage i studiet, hvis de:

- Var blevet behandlet med ketoconazol som eneste behandling mod aktiv Cushings sygdom.

Der er ikke listet eksklusionskriterier.

Tabel 5-2. Baselinekarakteristika for studiepopulationerne anvendt til besvarelsen af klinisk spørgsmål 1

	LINC-4 (n = 73)	LINC-3 (n = 137)	Castinetti et al. 2014 (n = 200)
Alder, median år (interval)	39,0 (19,0-67,0)	40,0 (19-70)	41,9 (gennemsnit) (8-87)
Antal kvinder, n (%)	61 (83,6)	106 (77)	156 (78)
Tidligere opereret, n (%)	64 (87,7)	120 (88)	144 (72)
Tidligere medicinsk behandling, n (%)	45 (61,6)	102 (74)	-
UFC ved baseline (nmol/24 timer), median (interval)	340,3 (221,3-518,8; 2,5xULN)	476 (314-919; 3,4xULN)	4,1 ± 5,3 x ULN (1,1-40)
Tidligere strålebehandling af hypofysen, n (%)	9 (12,3)	22 (16)	47 (23,6)
BMI (kg/m2), median	-	28,8	-

ULN = upper limit of normal.

5.1.2 Databehandling og analyse

I dette afsnit er ansøgers datagrundlag, databehandling og analyse for hvert effektmål beskrevet.

Ansøger har indsendt data for normalisering af kortisolniveau og sikkerhed fra LINC-4 og LINC-3 for osilodrostat og i Castinetti et al. 2014 og Castinetti et al. 2008 for ketoconazol. Data for livskvalitet er kun tilgængeligt for osilodrostat.

Det er ikke muligt at foretage en direkte eller indirekte analyse baseret på en statistisk analyse, da osilodrostat er sammenlignet med placebo i kliniske studier, hvorimod studierne af ketoconazol er retrospektive og uden kontrolgrupper.

Analyserne af forskelle i effekt og sikkerhed mellem de to behandlinger er derfor baseret på deskriptive sammenligninger, og der er ikke justeret for evt. forskelle i studiepopulationer.

Det er ikke muligt at sammenligne patienterne i studierne, da der er meget begrænset studiedata. Patienterne i Castinetti et al. 2014 har en højere median UFC-værdi ved baseline, og fagudvalget vurderer, at det kan betyde, at der er forskel på, hvor svært det er at opnå normalisering af UFC-niveauet i de forskellige studier. Fagudvalget bruger data fra LINC-4-studiet og fra Castinetti et al. 2014 i sammenligningen og bruger de øvrige studier supplerende. Fagudvalget vurderer, at LINC-3 og LINC-4 er sammenlignelige, men foretrækker at baserer vurderingen på data fra LINC-4, da studiedesignet gør det lettere at vurdere effekten i dette studie.

5.1.3 Evidensens kvalitet

Da sammenligningen mellem osilodrostat og ketoconazol er baseret på en deskriptiv sammenligning, har Medicinrådet ikke anvendt GRADE til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen.

Fraværet af sammenligneligt data fra randomiserede kliniske studier medfører, at Medicinrådet vurderer evidensens kvalitet som meget lav.

Vurdering af risikoen for bias ved LINC-4 fremgår af Bilag 1.

5.1.4 Effektestimater og kategorier

I tabellen herunder fremgår resultaterne fra de forskellige studier, den samlede kategori og den samlede kvalitet af evidensen for klinisk spørgsmål 1.

Tabel 5-3 . Resultater for klinisk spørgsmål 1

Effektmål	Målenhed (MKRF)	Vigtighed	opfølgning	Osilodrostat (LINC-4)		Ketoconazol
				Osilodrostat (n = 48)	Placebo (n = 25)	Castinetti et al. 2014 (n = 200)
Normalisering af kortisolniveau	Andel patienter, der opnår et komplet respons på koncentration af gennemsnitlig kortisol i døgnurin (mUFCa < ULNb) (20 %-point)	Vigtigt	Uge 4	Ikke opgjort	Ikke opgjort	Ikke opgjort
			Uge 12	37/48 (77,1 %)	2/25 (8 %)	Ikke opgjort
			Uge 48	50/73 (68,5 %)		Ikke opgjort
			Varierende tidspunkter			48,5 %
Livskvalitet	CushingQoL Questionnaire. Gennemsnitlig forskel fra baseline (10,1 point)	Vigtigt	Uge 48	12,0 (95 % CI: 8,2; 15,9)		Ikke opgjort
Bivirkninger	Andel patienter, der oplever behandlingskrævende bivirkninger (10 %-point)	Vigtigt		95,8 %	84,0 %	Ikke opgjort
	Deskriptiv gennemgang			Se gennemgang		Se gennemgang
Konklusion						
Samlet kategori for lægemidlets værdi		Kan ikke kategoriseres.				
Kvalitet af den samlede evidens		Meget lav.				

CI = konfidensinterval, HR = Hazard Ratio, OR = Odds Ratio, RR = relativ risiko.

Normalisering af kortisolniveau
Som beskrevet i protokollen er effektmålet normalisering af kortisolniveau vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi mange af patienternes symptomer og følgesygdomme til deres Cushings syndrom vil normaliseres med et normalt kortisolniveau. Det er således et surrogatmål, som giver muligheden for at vurdere behandlingens afledte effekter på symptomer og følgesygdomme.

Måleenheden er: Andel patienter, der opnår et komplet respons på koncentration af gennemsnitlig kortisol i døgnurin, hvor komplet respons er defineret som døgnurin-kortisol ≤ øverste grænse for normalniveau (ULN). Fagudvalget har ønsket data efter 4 uger, 12 uger og med længst mulig opfølgningstid.

4 uger
Der er hverken data for osilodrostat eller ketoconazol vedr. normalisering af kortisol efter 4-ugers behandling.

12 uger
Efter 12 uger havde 37 ud af 48 (77,1 %) patienter opnået normalisering af kortisol i LINC-4. Der er heller ikke her data fra komparatorstudiet (se Tabel 5-4).

Længst mulig opfølgningstid
Det længste opfølgningstidspunkt i LINC-4 var 48 uger. På det tidspunkt havde 50 ud af 73 (68,5 %) patienter komplet respons på behandling med osilodrostat. Da Castinetti et al. er et retrospektivt studie, er den længste opfølgning varierende for de inkluderede patienter. Det er registreret, at 48,5 % opnåede normalisering af kortisol ved varierende tidspunkter. Disse patienter havde en gennemsnitlig behandlingslængde på 27,6 måneder (± 36,4 måneder). Behandlingslængden for patienter i delvist respons var 18,2 måneder (± 29,2 måneder), og for dem uden respons (fald i UFC under 50 %) var behandlingslængden 9,7 måneder (± 14,9 måneder).

Værdien af osilodrostat overfor ketoconazol kan ikke kategoriseres for normalisering af kortisol, fordi der mangler komparative data. Ved den længst mulige opfølgningstid peger data i retning af, at flere patienter i behandling med osilodrostat opnår normalisering af kortisol end patienter i behandling med ketoconazol. Opfølgningstiden er dog meget forskellig i de to studier, hvilket gør sammenligningen af resultaterne usikker.

Livskvalitet
Som beskrevet i protokollen er effektmålet livskvalitet vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi patienternes livskvalitet er stærkt forringet som følge af symptomer og følgesygdomme. Fagudvalget betragter derfor effektmålet som vigtigt for vurderingen.

I LINC-4 blev livskvaliteten målt med CushingsQoL ved uge 12 - som var sidste opfølgning inden patienterne i placebo-armen overgik til behandling med osilodrostat. Ændringen i livskvalitet for patienterne, der fik placebo, var 6,2 point (95 % CI: 1,7; 10,6) ift. baseline, mens den for patienter behandlet med osilodrostat var 8,6 point (95 % CI: 3,5; 13,7).

Forskellen i livskvalitet efter uge 12 var altså 2,4 point. Livskvaliteten blev også målt efter 48 uger, hvor livskvaliteten var steget med 12,0 point (95 % CI: 8,2; 15,9) ift. baseline. På det tidspunkt blev alle patienter behandlet med osilodrostat, og det er derfor ikke muligt at lave en sammenligning ift. placebo. Forskellen efter 12 uger er ikke over den mindste klinisk relevante forskel, og livskvaliteten er ikke opgjort for komparatorstudiet.

Værdien af osilodrostat overfor ketoconazol kan ikke kategoriseres for livskvalitet, fordi der mangler komparative data, og fagudvalget kan ikke vurdere, om der er forskel mellem behandlingerne på det nuværende datagrundlag, hvad angår livskvalitet.

Bivirkninger

Som beskrevet i protokollen er effektmålet bivirkninger vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi det har betydning for den enkelte patients livskvalitet og for compliance. Ansøger har indsendt data for uønskede hændelser, og fagudvalget ved derfor ikke, hvor mange af de uønskede hændelser der er relateret til behandlingen, og hvor mange der er symptomer fra patienternes sygdom.

Kvantitativ sammenligning

I LINC-4 oplevede 95,8 % af patienterne, der modtog osilodrostat, mindst én behandlingskrævende uønsket hændelse. Der er ingen data for ketoconazol.

Deskriptiv gennemgang

I Tabel 5-4 ses en opgørelse over uønskede hændelser for osilodrostat efter de første 12 placebokontrolledere uger samt for hele studiet.

Tabel 5-4. Opgørelse over uønskede hændelser fra LINC-4-studiet

	Placebo-kontrolleret periode		Hele studiet
	Osilodrostat (n = 48)	Placebo (n = 25)	Alle patienter[a] (n = 73)
Alle uønskede hændelser	46 (95,8)	23 (92,0)	73 (100)
Alvorlige uønskede hændelser	2 (4,2)	1 (4,0)	8 (11)
Uønskede hændelser, der ledte til ophør	1 (2,1)	0	8 (11)
Mest almindelige uønskede hændelser i studiet (> 20 % af alle patienter)			
Nedsat appetit, antal (%)	18 (37,5)	4 (16,0)	33 (45,2)
Ledsmerter, antal (%)	17 (35,4)	2 (8,0)	33 (45,2)
Udmattelse, antal (%)	12 (25,0	4 (16,0)	28 (38,4)

	Placebo-kontrolleret periode		Hele studiet
	Osilodrostat (n = 48)	Placebo (n = 25)	Alle patienter[a] (n = 73)
Kvalme, antal (%)	15 (31,3)	3 (12,0)	27 (37,0)
Hovedpine, antal (%)	7 (14,6)	6 (24,0)	24 (32,9)
Muskelsmerter, antal (%)	11 (22,9)	1 (4,0)	19 (26,0)
Svimmelhed, antal (%)	9 (18,8)	4 (16,0)	19 (26,0)
Adrenal insufficiens, antal (%)	7 (14,6)	0	18 (24,7)
Forøget testosteron i blodet, antal (%)	5 (10,4)	0	18 (24,7)
Diarré, antal (%)	10 (20,8)	0	17 (23,3)
Forhøjet blodtryk, antal (%)	8 (16,7)	7 (28,0)	16 (21,9)
Asteni, antal (%)	11 (22,9)	0	15 (20,5)
Øvre luftvejsinfektion, antal (%)	5 (10,4)	0	15 (20,5)

Inkluderer alle data indtil data cut-off (da den sidste patient afsluttede eller afbrød hovedundersøgelsen); median (interval) osilodrostateksponering var 70,0 (2,0-112,7) uger. A) Indeholder ikke data for placebo-modtagere indsamlet i løbet af den 12-ugers randomiserede periode. Patienter med flere sværhedsgrader for en uønsket hændelse tælles kun under den maksimale grad.

De væsentligste uønskede hændelser i Castinetti et al. 2014 var øgede leverenzymer hos 30/190 (15,8 %), gastrointestinale problemer hos 25/190 (13,1 %), adrenal insufficiens hos 10/190 (5,4 %) og kløe hos 7/190 (3,7 %).

Tabel 5-5. Uønskede hændelser, der ledte til yderligere behandling (LINC-4)

	Osilodrostat (n = 489)		Placebo (n = 25)		Alle patienter (n = 73)	
Kategori	**Alle grader n (%)**	**Grad ≥ 3 n (%)**	**Alle grader n (%)**	**Grad ≥ 3 n (%)**	**Alle grader n (%)**	**Grad ≥ 3 n (%)**
Uønskede hændelser, der krævede yderligere behandling	46 (95,8)	18 (37,5)	21 (84,0)	4 (16,0)	67 (91,8)	22 (30,1)

Forekomst af behandlingskrævende uønskede hændelser kan være et udtryk for alvorlig toksicitet af lægemidlet, og disse kan have væsentlig indvirkning på patienternes helbred og velbefindende. Hos patienter med Cushings syndrom, som i forvejen er i forhøjet risiko for kardiovaskulære, metaboliske og infektiøse komplikationer, vil bivirkninger svarende til disse systemer forværre sygdommen yderligere. I Tabel 5-4 ses, at 21,9 % af patienterne i LINC-4-studiet får forhøjet blodtryk, 24,7 % får forøget testosteron i blodet, 24,7 % får adrenal insufficiens, og 20,5 % får infektioner i de øvre luftveje. I Tabel 5-5 ses det, at 95,8 % af patienterne havde behov for yderligere behandling som følge af uønskede hændelser. Fagudvalget vurderer derfor, at der kan være betydelige uønskede hændelser ved behandling med osilodrostat. Det er usikkert, hvor mange af de uønskede hændelser der er behandlingsrelaterede, da det ikke er opgjort.

I EMAs produktresumé står:

hæmning af CYP11B1 er forbundet med akkumulering af forstadier til adrenale steroider og testosteronøgning. I et klinisk studie med osilodrostat steg de gennemsnitlige testosteronniveauer hos kvindelige patienter fra at ligge højt i normalområdet ved baseline til at ligge over den øvre normalgrænse. Stigningen forsvandt ved afbrydelse af behandlingen. Stigningen i testosteronniveauet var forbundet med milde til moderate tilfælde af hirsutisme eller akne hos en undergruppe af patienter. ACTH-værdier 10-gange over den øvre normalgrænse blev observeret hos nogle patienter med Cushings sygdom behandlet med osilodrostat i de kliniske studier og kan være associeret med cortisolværdier under den nedre normalgrænse.

I et QT-studie var osilodrostat forbundet med en dosisafhængig forlængelse af QT-intervallet (gennemsnitlig estimeret maksimal QTcF-øgning på +5,3 ms ved den højeste anbefalede dosis på 30 mg), hvilket kan forårsage hjertearytmier. Der bør foretages et EKG før opstart af behandling med osilodrostat, inden for én uge efter behandlingsstart og ved klinisk behov herefter. Hvis QTc-intervallet overstiger 480 ms før eller under behandling, anbefales det at konsultere en kardiolog. Midlertidig dosisreduktion eller afbrydelse kan være nødvendig [25].

Fagudvalget bemærker, at langtidsopfølgning viser, at ACTH-koncentrationen stiger fra en median på 1,1×øvre normalniveau ved baseline, til 3,0×øvre normalniveau ved uge 48, 3,6×øvre normalniveau ved uge 72 og 3,5× øvre normalniveau ved behandlingsophør. Vekslende ændring af hypofysetumoren er rapporteret, samt et enkelt tilfælde af Nelsons syndrom. I lighed med behandling med de øvrige steroidgenese-hæmmere, skal ACTH og hypofysetumor ved behandling med osilodrostat monitoreres [26].

Behandlingen med ketoconazol medfører primært leverpåvirkning, adrenal insufficiens og gastrointestinale problemer. Fagudvalget bemærker, at der er opgjort meget få uønskede hændelser i det retrospektive studie og mener ikke, at der er sammenlignelighed mellem studierne, da kriterierne for indsamling af data i de retrospektive studier ikke er klare.

Værdien af osilodrostat overfor ketoconazol kan ikke kategoriseres for bivirkninger, fordi der mangler komparative data, og fagudvalget kan ikke vurdere, om der er forskel mellem behandlingerne på det nuværende datagrundlag, hvad angår bivirkninger.

5.1.5 Fagudvalgets konklusion

Fagudvalget vurderer, at den samlede værdi af osilodrostat sammenlignet med ketoconazol til patienter med Cushings syndrom ikke kan kategoriseres, fordi der mangler komparative data. Fagudvalget vurderer, at der formentlig er en større andel patienter, der opnår et komplet respons ved behandling med osilodrostat, men kan ikke vurdere om der er forskel, hvad angår livskvalitet eller sikkerhed.

5.2 Klinisk spørgsmål 2

5.2.1 Litteratur

Nedenfor beskriver og vurderer Medicinrådet den litteratur, som ansøger har anvendt i sin endelige ansøgning.

Ansøger har søgt litteratur med søgestrengen fra protokollen og har udvalgt 5 fuldtekstartikler, der beskriver 4 kliniske studier samt et retrospektivt studie. De artikler, der benyttes til at vurdere osilodrostat, blev beskrevet i klinisk spørgsmål 1 (se afsnit 5.1.1). Herunder beskrives det studie, der bruges til at vurdere effekten af metyrapon.

Tabel 5-6. Oversigt over studier inkluderet klinisk spørgsmål 2

Publikationer	Klinisk forsøg	NCT-nummer	Population
Effectiveness of Metyrapone in Treating Cushing's Syndrome: A Retrospective Multicenter Study in 195 Patients. [27]	-	-	195 patienter med Cushings syndrom, 115 patienter med cushings sygdom, 37 patienter med ektopisk ACTH-syndrom, 43 patienter med ACTH-uafhængig sygdom

Studiebeskrivelser

LINC-4 er beskrevet i afsnit 5.1.1.

Daniel et al. 2015

Daniel et al. 2015 er et retrospektivt studie med 195 patienter fra England og Wales. Studiet omfattede patienter med Cushings syndrom, som blev behandlet med metyrapon mellem 1997 og 2013. De fleste patienter havde Cushings sygdom (115 patienter, heraf 37 med makroadenom), mens de resterende havde ektopisk ACTH-syndrom (37), binyrebarkcarcinom (10), benign binyresygdom (30), binyreadenom, ACTH

-uafhængig makronodulær adrenal hyperplasi (2) og primær pigmenteret nodulær adrenal hyperplasi (1). Den gennemsnitlige behandlingslængde i studiet var 18,6 måneder, og 29 patienter fik kombinationsbehandling med metyrapon og primært ketokonazol eller mitotan.

Patienter kunne deltage i studiet, hvis de:

- Var diagnosticeret med Cushings syndrom.

Der er ikke listet eksklusionskriterier.

Tabel 5-7. Baselinekarakteristika

	LINC-4 (n = 73)	Daniel et al. 2015 (n = 195)
Alder, median år (interval)	39,0 (19,0–67,0)	49,6 (± 15,7) gennemsnit
Andel kvinder, n (%)	61 (83,6)	85/115 (74)
Tidligere opereret, n (%)	64 (87,7)	-
Tidligere medicinsk behandling, n (%)	45 (61,6)	-
UFC ved baseline (nmol/24 timer), median (interval)	340,3 (221,3-518,8; 2,5xULN)	1483 (537 µg/24 h) (n = 37)
Tidligere strålebehandling af hypofysen, n (%)	9 (12,3)	-
BMI (kg/m^2), median	-	-

5.2.2 Databehandling og analyse

I dette afsnit er ansøgers datagrundlag, databehandling og analyse for hvert effektmål beskrevet.

Ansøger har indsendt data for normalisering af kortisolniveau, sikkerhed og livskvalitet er undersøgt fra LINC-4 for osilodrostat. Der er kun data for normalisering af kortisol for metyrapon fra Daniel et al. 2015.

Det er ikke muligt at foretage en direkte eller indirekte analyse baseret på en statisk analyse. Osilodrostat er sammenlignet med placebo i kliniske studier, hvorimod studiet af metyrapon er retrospektivt og uden kontrolgruppe. Analyserne af forskelle i effekt og sikkerhed mellem de to behandlinger er derfor baseret på deskriptive sammenligninger. Der er ikke justeret for evt. forskelle i studiepopulationer.

Det er ikke muligt at sammenligne patienterne i studierne, da der er meget begrænset data vedr. baselinekarakteristika i Daniel et al. 2015. Patienterne i Daniel et al. 2015 har en højere median UFC-værdi ved baseline, og fagudvalget vurderer, at det kan betyde, at der er forskel på, hvor svært det er at opnå normalisering af UFC-niveauet i de forskellige studier. UFC-værdien ved baseline er kun opgjort på baggrund af målinger i 37 af patienterne i studiet, hvilket medfører usikkerhed i sammenligningen.

5.2.3 Evidensens kvalitet

Da sammenligningen mellem osilodrostat og metyrapon er baseret på en deskriptiv sammenligning, har Medicinrådet ikke anvendt GRADE til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen.

Fraværet af data fra randomiserede kliniske studier medfører, at Medicinrådet vurderer evidensens kvalitet som meget lav.

5.2.4 Effektestimater og kategorier

I tabellen herunder fremgår resultaterne fra de forskellige studier, den samlede kategori og den samlede kvalitet af evidensen for klinisk spørgsmål 2.

Tabel 5-8. Resultater for klinisk spørgsmål 2

Effektmål	Målenhed (MKRF)	Vigtighed	Opfølgning	Osilodrostat (LINC-4)		Metyrapon
				Osilodrostat (n = 48)	Placebo (n = 25)	Daniel et al. 2015 (n = 195)
Normalisering af kortisolniveau	Andel patienter, der opnår et komplet respons på koncentration af gennemsnitlig kortisol i døgnurin (mUFCa < ULNb) (20 %-point)	Vigtigt	Uge 4	Ikke opgjort	Ikke opgjort	Ikke opgjort
			Uge 12	37/48 (77,1 %)	2/25 (8 %)	Ikke opgjort
			Uge 48	50/73 (68,5 %)		Ikke opgjort
			Varierende tidspunkter			43%
Livskvalitet	CushingQoL Questionnaire. Gennemsnitlig forskel fra baseline (10,1 point)	Vigtigt	Uge 48	12,0 (95 % CI: 8,2; 15,9)		Ikke opgjort
Bivirkninger	Andel patienter, der oplever behandlingskrævende bivirkninger (10 %-point)	Vigtigt		95,8 %	84,0 %	Ikke opgjort
	Deskriptiv gennemgang			Se gennemgang		Se gennemgang
Konklusion						
Samlet kategori for lægemidlets værdi		Kan ikke kategoriseres.				
Kvalitet af den samlede evidens		Meget lav.				

CI = konfidensinterval, HR = Hazard Ratio, OR = Odds Ratio, RR = relativ risiko.

Normalisering af kortisolniveau

4 uger
Der er hverken data for osilodrostat eller metyrapon vedr. normalisering af kortisol efter 4-ugers behandling.

12 uger
Efter 12 uger havde 37 ud af 48 (77,1 %) patienter opnået normalisering af kortisol i LINC-4. Der er heller ikke her data fra komparator-studiet (se Tabel 5-8).

Længst mulig opfølgningstid
Det længste opfølgningstidspunkt i LINC-4 var 48 uger. På det tidspunkt havde 50 ud af 73 (68,5 %) patienter komplet respons på behandling med osilodrostat. Da Daniel et al. er et retrospektivt studie, er den længste opfølgning varierende for de inkluderede patienter. Det er registreret, at 43 % opnår normalisering af kortisol ved varierende tidspunkter, det er dog uklart, hvordan effektmålet er opgjort, da der i ansøgningen står "*UFC ≤ upper limit of normal ULN for the assey used*", men det er ikke nærmere specificeret, hvordan det er målt. Derudover har 29 patienter fået kombinationsterapi med tillæg af yderligere kortisolnedsættende lægemidler.

Værdien af osilodrostat overfor metyrapon kan ikke kategoriseres for normalisering af kortisol, fordi der mangler komparative data. Ved den længst mulige opfølgningstid peger data i retning af, at flere patienter i behandling med osilodrostat opnår normalisering af kortisol end patienter i behandling med metyrapon.

Livskvalitet
Livskvaliteten i LINC-4 viser ikke en forskel over den mindste klinisk relevante forskel i den placebokontrollerede periode af studiet (se afsnit 5.1.4), og livskvaliteten er ikke opgjort for komparatorstudiet.

Værdien af osilodrostat overfor metyrapon kan ikke kategoriseres for livskvalitet, fordi der mangler komparative data, og fagudvalget kan ikke vurdere, om der er forskel mellem behandlingerne på det nuværende datagrundlag, hvad angår livskvalitet.

Bivirkninger

Kvantitativ sammenligning
I LINC-4 oplevede 95,8 % af patienterne, der modtog osilodrostat, mindst én behandlingskrævende uønsket hændelse. Der er ingen data for metyrapon.

Deskriptiv gennemgang
I Tabel 5-4 ses en opgørelse over uønskede hændelser for osilodrostat efter de første 12 placebokontrolledere uger samt for hele studiet.

De væsentligste uønskede hændelser i Daniel et al. var gastrointestinale problemer (23 %) og adrenal insufficiens (7 %).

I Tabel 5-4 ses, at 21,9 % af patienterne i LINC-4 studiet får forhøjet blodtryk, 24,7 % får forøget testosteron i blodet, 24,7 % får adrenal insufficiens, og 20,5 % får infektioner i de øvre luftveje. I Tabel 5-5 ses det, at 91,8 % af patienterne havde behov for yderligere behandling som følge af bivirkninger. Fagudvalget vurderer derfor, at der er betydelige bivirkninger ved behandling med osilodrostat.

Behandlingen med metyrapon medfører primært gastrointestinale problemer. Fagudvalget bemærker, at der er opgjort meget få bivirkninger i det retrospektive studie og mener ikke, at der er sammenlignelighed mellem studierne, da kriterierne for indsamling af data i de retrospektive studier ikke er klare.

Værdien af osilodrostat overfor metyrapon kan ikke kategoriseres for bivirkninger, fordi der mangler komparative data, og fagudvalget kan ikke vurdere, om der er forskel mellem behandlingerne på det nuværende datagrundlag, hvad angår bivirkninger.

5.2.5 Fagudvalgets konklusion

Fagudvalget vurderer, at den samlede værdi af osilodrostat sammenlignet med metyrapon til patienter med Cushings syndrom ikke kan kategoriseres, fordi der mangler komparative data. Fagudvalget vurderer, at der formentlig er en større andel patienter, der opnår et komplet respons ved behandling med osilodrostat.

5.3 Klinisk spørgsmål 3

5.3.1 Litteratur

Nedenfor beskriver og vurderer Medicinrådet den litteratur, som ansøger har anvendt i sin endelige ansøgning.

Datagrundlaget for osilodrostat er det samme som i klinisk spørgsmål 1 og 2 (se afsnit 5.1.1). Herunder beskrives de studier, der bruges til at vurdere effekten af pasireotid.

Der præsenteres kun data fra G2304 for pasireotid, da dette studie er det bedste til at belyse effekten af pasireotid i klinisk praksis. Dette skyldes dels, at studiet har den længste blindede periode, og dels, at studiet undersøger den formulering, der oftest bruges i dansk klinisk praksis.

To af komparatorstudierne (B2208 og Pivonello 2019 et al.) er fravalgt, fordi de er små og ukontrollerede og ikke bidrager med væsentlig yderligere information. Derudover præsenteres studierne B2305 og SEASCAPE ikke i gennemgangen af effektestimater, da disse studier ikke bidrager med yderligere væsentlige informationer.

Tabel 5-9. Oversigt over studier inkluderet i klinisk spørgsmål 3

Publikationer	Klinisk forsøg	NCT-nummer	Population
Long-term efficacy and safety of once-monthly pasireotide in Cushing's disease: A Phase III extension study. [28] Efficacy and safety of once-monthly pasireotide in Cushing's disease: a 12 month clinical trial. [29]	G2304	NCT01374906	Patienter med Cushings sygdom
A 12-Month Phase 3 Study of Pasireotide in Cushing's Disease. [30] Long-term treatment of Cushing's disease with pasireotide: 5-year results from an open-label extension study of a Phase III trial. [31] Pasireotide can induce sustained decreases in urinary cortisol and provide clinical benefit in patients with Cushing's disease: results from an open-ended, open-label extension trial. [32] Treatment effectiveness of pasireotide on health-related quality of life in patients with Cushing's disease. [33]	B2305	NCT00434148	Patienter med Cushings sygdom
Safety and efficacy of subcutaneous pasireotide in patients with Cushing's disease: Results from an open-label, multicenter, single-arm, multinational, expanded-access study. [34]	SEASCAPE	NCT01582061	Patienter med Cushings sygdom
The medical treatment with pasireotide in Cushing's disease: an Italian multicentre experience based on "real-world evidence". [35]	-	-	Patienter med Cushings sygdom
Extended treatment of Cushing's disease with pasireotide: Results from a 2-year, Phase II study. [36]	CSOM230B2208	NCT00088608	Patienter med Cushings sygdom

Studiebeskrivelser
LINC-4 er beskrevet i afsnit 5.1.1

G2304
G2304 er et randomiseret, dobbeltblindet fase 3-studie, der undersøger effekt og sikkerhed af pasireotid til patienter med Cushings sygdom. Patienter i studiet blev randomiseret 1:1 til at modtage enten 10 mg (n = 74) eller 30 mg (n = 76) pasireotid hver 28. dag i fire måneder. Dosis kunne herefter justeres ved måned 4, 7 og 9. Efter 12 måneder ophørte blindingen, og patienterne kunne fortsætte behandlingen indtil måned 36.

Det primære endemål var andelen af patienter, der opnåede et komplet respons på koncentration af gennemsnitlig kortisol i døgnurin ved måned 7, uagtet evt. dosisjustering. Sekundære endemål var sikkerhed samt andel af patienter, der opnåede et komplet respons på koncentration af gennemsnitlig kortisol i døgnurin ved måned 7 uden dosisforøgelse ved måned 4. Data blev analyseret efter ITT-princippet.

Patienter kunne deltage i studiet, hvis de:

- havde en svulst i hypofysen, der var større end 6 mm, bekræftet med en magnetisk resonansscanning (MR-scanning), eller
- havde en svulst i hypofysen, der var mindre end 6 mm, men havde tegn på hypofysær overproduktion af ACTH med gradient > 3 ved sinus petrosus sampling
- havde en svulst, der producerede ACTH efter tidligere at have været opereret for en svulst i hypofysen.

Patienter kunne ikke deltage i studiet, hvis de:

- var kandidater til kirurgisk behandling af hypofysen
- havde fået strålebehandling af hypofysen inden for de seneste ti år
- havde modtaget behandling med mitotan inden for det seneste år
- havde kirurgisk behandlingskrævende synsfeltsudfald pga. kompression af chiasma opticum
- havde ukontrolleret diabetes
- havde symptomatisk galdesten
- eller havde alvorlig lever- eller hjertesygdom.

Tabel 5-10. Baselinekarakteristika i LINC-4 og G2304.

	LINC-4 (n = 73)	G2304 (n = 150)
Alder, år i gennemsnit (interval)	41,2 (19; 67)	38,5 (ikke opgivet)
Antal kvinder, n (%)	61 (83,6)	118 (79)
Median tid siden diagnose, måneder (interval)	67,4 (interval: 6,0; 257,7)	22,3 (IQR: 6,6; 62,5)
Antal tidligere opereret, n (%)	64 (67,7)	123 (82)
Antal, der tidligere har fået medicinsk behandling, n (%)	45 (61,6)	62 (41)
Gennemsnitlig UFC over 24 timer ved baseline (nmol/24 timer), median (IQR)	Median: 340,3 (221,3; 518,8)	10 mg: 409,8 (IQR: 287,6-632,5) 30 mg: 371,6 (IQR: 268,5-593,7)
Tidligere strålebehandling af hypofysen, n (%)	9 (12,3)	Ikke opgjort

UFC: *urinary free cortisol*, IQR: *interquartile range*, ULN: *upper limit of normal.*

Populationerne i LINC-4 og G2304 er sammenlignelige og afspejler generelt de patienter, der vil være kandidater til behandling i Danmark. Den væsentligste forskel fra studierne til dansk klinisk praksis er, at de fleste patienter, der modtager kortisolsænkende behandling i Danmark, bliver opereret for den bagvedlæggende årsag til den forhøjede kortisol efter 1-3 måneder. Hos patienterne i studierne var operation ikke indiceret, og studierne har derfor rekrutteret patienter, hvor behandling over lang tid er forventet. Fagudvalget vurderer ikke, at dette har en betydning for lægemidlernes effekt på reduktion af kortisol.

5.3.2 Databehandling og analyse

I dette afsnit er ansøgers datagrundlag, databehandling og analyse for hvert effektmål beskrevet.

Ansøger har indsendt data fra de ovennævnte studier for alle relevante effektmål. Da der ikke forelægger data for bivirkninger, er sikkerhed opgjort som uønskede hændelser for både osilodrostat og pasireotid.

Ansøger har udført en *adjusted comparison* med udgangspunkt i data fra LINC-3, LINC-4, G2304 og B2304 for effektmålet normalisering af kortisol. I analysen har ansøger justeret data i G2304 og B2304 for alder, race, UFC, tiden siden diagnose, tidligere operation af hypofysen samt tidligere behandling, så data vægtes til at afspejle populationerne i LINC-3 og LINC-4.

Ansøger har også foretaget en deskriptiv sammenligning af data fra de enkelte studier.

Medicinrådets vurdering tager udgangspunkt i den deskriptive gennemgang af effektmålene. Ansøgers *adjusted comparison*-analyse bruges kun supplerende, da Medicinrådet ikke finder, at analysen giver et mere retvisende billede af osilodrostats effekt end den deskriptive gennemgang.

5.3.3 Evidensens kvalitet

Da sammenligningen mellem osilodrostat og pasireotid er baseret på en deskriptiv sammenligning, har Medicinrådet ikke anvendt GRADE til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen.

Fraværet af komparative data medfører, at Medicinrådet vurderer evidensens kvalitet som meget lav.

Vurdering af risikoen for bias ved LINC-4 og G2304 fremgår af Bilag 1

5.3.4 Effektestimater og kategorier

I tabellen herunder fremgår en oversigt og resultaterne fra den deskriptive sammenligning, den samlede kategori for lægemidlets værdi og den samlede kvalitet af evidensen for klinisk spørgsmål 3.

Tabel 5-11. Resultater for klinisk spørgsmål 3

Effektmål	Målenhed (MKRF)	Vigtighed	opfølgning	Osilodrostat (LINC-4)		Pasireotid (G2304)	
				Osilodrostat (n = 48)	Placebo (n = 25)	10 mg (n = 74)	30 mg (n = 76)
Normalisering af kortisolniveau	Andel patienter, der opnår et komplet respons på koncentration af gennemsnitlig kortisol i døgnurin (mUFCa < ULNb) (20 %-point)	Vigtigt	Uge 4	Ikke opgjort	Ikke opgjort	Ikke opgjort	Ikke opgjort
			Uge 12	37/48 (77,1 %)	2/25 (8 %)	27,9 %	35,1 %
			Uge 48	50/73 (68,5 %)		Samlet gruppe: 30 %	
Livskvalitet	CushingQoL Questionnaire. Gennemsnitlig forskel fra baseline (10,1 point)	Vigtigt	Uge 48	12,0 (95 % CI: 8,2; 15,9)		6,4 point (95 % CI: 1,3; 11,6)	7,0 point (95 % CI: 3,0; 10,9)
Bivirkninger	Andel patienter, der oplever behandlingskrævende bivirkninger (10 %-point)	Vigtigt		95,8 %	84,0 %	Samlet gruppe: 96,7 %	
	Deskriptiv gennemgang			Se gennemgang		Se gennemgang	
	Konklusion						
	Samlet kategori for lægemidlets værdi	Kan ikke kategoriseres.					
	Kvalitet af den samlede evidens	Meget lav.					

CI = konfidensinterval, HR = Hazard Ratio, OR = Odds Ratio, RR = relativ risiko.

Normalisering af kortisol

4 uger
Ansøger har hverken leveret data for osilodrostat eller pasireotid vedr. normalisering af kortisol efter 4-ugers behandling.

12 uger
Efter 12 uger havde 37 ud af 48 (77,1 %) patienter opnået normalisering af kortisol i LINC-4. Til sammenligning havde 2 ud af 25 (8 %) opnået normalisering af kortisol i placebogruppen.

I G2304 var andelen af patienter, der opnåede normalisering af kortisol ved 12-ugers behandling, 27,9 % blandt patienter, der startede med at modtage 10 mg pasireotid, og 35,1 % blandt patienter, der startede med at modtage 30 mg pasireotid (se tabel 3).

Det betyder, at der var mellem 42 og 49,2 %-point flere patienter, der opnåede normalisering af kortisol ved behandling med osilodrostat sammenlignet med behandling med pasireotid.

Længst mulig opfølgning
Det længste opfølgningstidspunkt i LINC-4 var 48 uger. På det tidspunkt havde 50 ud af 73 (68,5 %) patienter komplet respons på behandling med osilodrostat. I G2304 er det længste opfølgningstidspunkt 1 år, og 30 % havde på det tidspunkt normalisering af kortisol (se Tabel 5-11).

Adjusted comparison
Den relative effektforskel fra ansøgers *adjusted comparison*-analyse er RR: 1,42 (95 % CI: 0,81; 2,13) efter 4 uger, RR:2,14 (95 % CI: 1,26; 4,64) efter 12 uger og RR:1,16 (95 % CI: 0,89; 1,91) ved længst mulig opfølgning.

Værdien af osilodrostat overfor pasireotid kan ikke kategoriseres for normalisering af kortisol, fordi der mangler komparative data. Ved både 12 uger samt længst mulig opfølgning peger data i retning af, at flere patienter i behandling med osilodrostat opnår normalisering af kortisol end patienter i behandling med pasireotid. Forskellen er større end den MKRF, der er defineret i protokollen. Omvendt er det kun ved uge 12, at der er en statistisk signifikant forskel mellem behandlingerne vurderet ved ansøgers *adjusted comparison*. Selvom manglen på komparative data behæfter konklusionen med usikkerhed, vurderer fagudvalget, at osilodrostat er en bedre behandling til at opnå normalisering af kortisol end pasireotid.

Livskvalitet
Ved uge 12 var livskvaliteten målt ved CushingsQoL steget med 8,6 point (95 % CI: 3,5 ; 13,7) ift. baseline for patienter behandlet med osilodrostat og 6,2 point (95 % CI: 1,7; 10,6) ift. baseline for patienter, der fik placebo. Efter 48 uger var livskvaliteten steget med 12,0 point (95 % CI: 8,2; 15,9) ift. baseline, men på det tidspunkt blev alle patienter behandlet med osilodrostat, og det er derfor ikke muligt at lave en sammenligning med placebo på dette tidspunkt. For pasireotid steg livskvaliteten målt ved CushingsQoL 6,4 (95 % CI: 1,3; 11,6) og 7,0 (95 % CI: 3,0; 10,9) point ift. baseline efter 1 år i G2304 ved

hhv. 10 og 30 mg behandling. Det betyder, at forbedringen i livskvalitet fra baseline var mellem 5,0 og 5,6 point bedre blandt patienter behandlet med osilodrostat sammenlignet med patienter behandlet med pasireotid efter ca. 1 års behandling.

Værdien af osilodrostat overfor pasireotid kan ikke kategoriseres for livskvalitet, fordi der mangler komparative data. Data for pasireotid og osilodrostat peger i retning af, at begge behandlinger øger livskvaliteten, men fagudvalget kan ikke vurdere, om der er en klinisk relevant forskel mellem behandlingerne på det nuværende datagrundlag, hvad angår livskvalitet.

Bivirkninger

Kvantitativ sammenligning
I LINC-4 oplevede 95,8 % af patienterne, der modtog osilodrostat, mindst én behandlingskrævende uønsket hændelse. I G2304 var det 96,7 % af patienterne, der oplevede behandlingskrævende uønskede hændelser.

Nedenfor er hændelsesraterne for de hyppigste uønskede hændelser i studierne opgjort.

Tabel 5-12. Oversigt over uønskede hændelser

	Placebo-kontrolleret periode i LINC-4		Samlet opfølgning i LINC-4	G2304
	Osilodrostat (n = 48)	Placebo (n = 25)	Alle patienter[a] (n = 73)	Pasireotid, uanset dosis (n=150)
Alle bivirkninger	46 (95,8)	23 (92,0)	73 (100)	10 mg: 98,6 % 30 mg: 100 %
Alvorlige bivirkninger	2 (4,2)	1 (4,0)	8 (11)	Grad 3-4: 10 mg: 54,1 % 30 mg: 60,5 %
Bivirkninger, der ledte til ophør	1 (2,1)	0	8 (11)	10 mg: 8,1 % 30 mg: 9,2 %
Mest almindelige bivirkninger i studierne				
Forhøjet blodsukker, antal (%)	Ikke opgjort	Ikke opgjort	Ikke opgjort	72 (48 %)
Nedsat appetit, antal (%)	18 (37,5)	4 (16,0)	33 (45,2)	< 10 %[a]

	Placebo-kontrolleret periode i LINC-4		Samlet opfølgning i LINC-4	G2304
	Osilodrostat (n = 48)	**Placebo (n = 25)**	**Alle patienter[a] (n = 73)**	**Pasireotid, uanset dosis (n=150)**
Ledsmerter, antal (%)	17 (35,4)	2 (8,0)	33 (45,2)	< 10 %[a]
Udmattelse, antal (%)	12 (25,0)	4 (16,0)	28 (38,4)	26 (17)
Kvalme, antal (%)	15 (31,3)	3 (12,0)	27 (37,0)	31 (21)
Hovedpine, antal (%)	7 (14,6)	6 (24,0)	24 (32,9)	28 (19)
Muskelsmerter, antal (%)	11 (22,9)	1 (4,0)	19 (26,0)	< 10 %[a]
Diabetes, antal (%)	Ikke opgjort	Ikke opgjort	Ikke opgjort	32 (21)
Svimmelhed, antal (%)	9 (18,8)	4 (16,0)	19 (26,0)	17 (11)
Adrenal insufficiens, antal (%)	7 (14,6)	0	18 (24,7)	< 10 %[a]
Forøget testosteron i blodet, antal (%)	5 (10,4)	0	18 (24,7)	< 10 %[a]
Diarré, antal (%)	10 (20,8)	0	17 (23,3)	59 (39)
Forhøjet blodtryk, antal (%)	8 (16,7)	7 (28,0)	16 (21,9)	22 (15)
Asteni, antal (%)	11 (22,9)	0	15 (20,5)	< 10 %[a]
Øvre luftvejsinfektion, antal (%)	5 (10,4)	0	15 (20,5)	< 10 %[a]

Inkluderer alle data indtil data cut-off (da den sidste patient afsluttede eller afbrød hovedundersøgelsen); median (interval) osilodrostateksponering var 70,0 (2,0-112,7) uger. A) Indeholder ikke data for placebo-modtagere indsamlet i løbet af den 12-ugers randomiserede periode. Patienter med flere sværhedsgrader for en bivirkning tælles kun under den maksimale grad.

A = Uønskede hændelser med en hyppighed < 10 % er ikke opgivet i studiet.

Deskriptiv gennemgang

Bivirkningsprofilen for osilodrostat er beskrevet i afsnit 5.1.4.

Af EMAs produktresumé fremgår det, at de hyppigste bivirkninger (> 10 % forekomst) ved behandling med pasireotid er diarré, kvalme, mavesmerter og træthed.

Bivirkninger af særlig interesse vedr. pasireotid er beskrevet nedenfor.

QT-forlængelse

Af EMAs produktresumé vedr. pasireotid fremgår det, at pasireotid forlænger QT-intervallet i elektrokardiogram (EKG). Den kliniske betydning af denne forlængelse er ukendt. QT-relaterede hændelser er generelt forbigående og er normalt ikke behandlingskrævende. Der er ikke observeret episoder med Torsades de Pointes i kliniske studier med pasireotid.

Levertoksicitet

Af EMAs produktresumé vedr. pasireotid fremgår det, at forbigående forhøjelse af leverenzymtallet er rapporteret ved brug af pasireotid i kliniske studier. Forhøjelserne er som regel asymptomatiske, svage og reversible ved fortsat behandling.

Diabetes (HbA1C)

Af EMAs produktresumé vedr. pasireotid fremgår det, at hos patienter med Cushings sygdom var forhøjede fastende plasmaglukose (FPG)-niveauer den hyppigst indberettede CTC-grad 3 laboratorieabnormalitet (14,7 % af patienterne) i fase III-studiet G2304 og med ingen indberetninger af grad 4 tilfælde. Stigninger i gennemsnitlig HbA1c var mindre udtalte hos patienter med normalt blodsukker ved indtræden i studiet sammenlignet med prædiabetiske eller diabetiske patienter. De gennemsnitlige FPG-niveauer steg normalt inden for den første måned af behandlingen, mens fald og stabilisering blev observeret i de efterfølgende måneder. Stigninger i FPG og HbA1c var dosisafhængige, og værdierne faldt generelt efter seponering af pasireotid til intramuskulær anvendelse, men forblev over baseline-værdier. Den samlede incidens af hyperglykæmi-relaterede bivirkninger var 75,3 % (alle grader) og 22,7 % (CTC-grad 3). Bivirkningerne hyperglykæmi og diabetes mellitus medførte udtræden af studiet for henholdsvis 3 (2,0 %) og 4 patienter (2,7 %). De stigninger, der ses i FPG og HbA1c ved pasireotid til intramuskulær anvendelse, er reversible efter seponering.

Fagudvalgets konklusion vedr. sikkerhed

Både osilodrostat og pasireotid er forbundet med en høj forekomst af uønskede hændelser. Dette kan i høj grad tillægges sygdommens natur, og også placebogruppen i LINC-4-studiet har en høj forekomst af uønskede hændelser. Samlet set er hændelsesraterne for uønskede hændelser og behandlingskrævende bivirkninger sammenlignelige ved de to behandlinger. Fagudvalget fremhæver dog, at risikoen for at udvikle type 2-diabetes er mindre blandt patienter, der modtager osilodrostat, fordi pasireotid hæmmer insulinsekretionen. Af den årsag vurderer fagudvalget, at osilodrostat samlet set har en mere skånsom bivirkningsprofil sammenlignet med pasireotid.

5.3.5 Fagudvalgets konklusion

Den samlede værdi af osilodrostat sammenlignet med pasireotid til patienter med Cushings syndrom kan ikke kategoriseres, fordi der ikke er data til at udføre en komparativ analyse for nogen af effektmålene. Fagudvalget vurderer, at osilodrostat samlet set er et bedre behandlingsalternativ end pasireotid. Dette er baseret på en deskriptiv sammenligning, der viser, at:

- Flere patienter opnår normalisering af kortisol ved behandling med osilodrostat sammenlignet med pasireotid.
- Effekten på livskvalitet er som minimum tilsvarende ved de to behandlinger.
- Hændelsesraterne for uønskede hændelser generelt er sammenlignelige ved de to behandlinger.
- Bivirkningsprofilen ved behandling med osilodrostat kan være mere skånsom, fordi forekomsten af diabetes forventes lavere ved behandling med osilodrostat.

Fagudvalget bemærker også, at pasireotid kun anvendes til patienter med Cushings sygdom.

6. Andre overvejelser

6.1 Hypokortisolisme

Fagudvalget har i protokollen efterspurgt en oversigt over, hvordan hypokortisolisme er målt og vurderet i de enkelte studier. Oversigten kan ses i tabel 6-1 og indeholder alle studier, som indgår i vurderingen af de tre kliniske spørgsmål.

Tabel 6-1. Oversigt over hypokortisolisme i de kliniske studier

Studienavn	Hypokortisolisme vurderet ud fra	Assays i studiet	Opgjort som bivirkning?
LINC-4	Kropsvægt, BMI, fastende blodglukosekoncentration, blodtryk	Kliniske tests inkluderede: Plasma adrenocorticotropic hormone (ACTH) målt med Immulite 2000 ACTH kit; PIL2KAC-18, Siemens Medical Solutions Diagnostics. Morgenserumkortisol målt ved LC-MS/MS. Serum 11- deoxycortisol målt ved LC-MS/MS). Aftenkortisolkoncentration i spyt målt ved LC-MS/MS.	Ja

Studienavn	Hypokortisolisme vurderet ud fra	Assays i studiet	Opgjort som bivirkning?
		11-deoxycorticosteron målt ved LC-MS/MS.	
Castinetti 2014	Blodtryk, kaliumkoncentration i plasma og glukosetolerance	Ikke rapporteret	Ikke rapporteret
Daniel 2015	Ikke rapporteret	Ikke rapporteret	Ikke rapporteret
G2304	Ikke specifikt opgjort. Ansøger skriver, at blodtryk, BMI, taljemål, fastende serumlipidkoncentration, vægt, knogletæthed, kropsbygning er målt	Kliniske test inkluderede UFC målt ved ultra-performance liquid chromatography-tandem mass spectrometry (LC-MS/MS; Waters Corp.). Serumkortisol i morgenblodprøver blev målt ved UPLC-MS/MS (Waters Corp.). Aftenkortisolkoncentration i spyt målt ved LC-MS/MS, Waters Corp., Milford, MA, USA. Serumkortisol og plasma ACTH blev målt hver måned indtil måned 12. Aftenkortisolkoncentration I spyt blev målt hver måned indtil måned syv og derefter ved måned 9 og 12	Nej

Fagudvalget vurderer, at risikoen for krydsaktivitet og dermed medbestemmelse af kortisol-forstadier for studierne LINC-4 og G2304 er lav, eftersom kortisol er bestemt med analytiske metoder med lav risiko for krydsaktivitet. Dermed vurderer fagudvalget, at forskellene i responsrater i LINC-4 og G2304 ikke kan tilskrives usikkerheder forbundet med målemetoden af kortisol. For Castinetti 2014 og Daniel 2015 kan fagudvalget ikke vurdere, om målemetoden til indsamling af kortisolniveauer har haft betydning, da der ikke er indleveret informationer om metoden fra disse studier.

6.2 Compliance

Fagudvalget har i sin protokol bedt ansøger om at bidrage med en oversigt over håndtering og opbevaring af lægemidlerne (intervention og komparatorer) samt forhold vedrørende indtagelse m.v., i forhold til at vurdere compliance.

Lægemiddel	Holdbarhed	Særlige forholdsregler ved opbevaring	Særlige forholdsregler ved håndtering eller bortskaffelse
Osilodrostat	3 år	Må ikke opbevares ved over 25 °C. Skal opbevares i den originale indpakning for at undgå fugt.	Ingen særlige regler ved bortskaffelse.
Ketoconazol	3 år	Ingen særlige forholdsregler.	Ingen særlige regler ved bortskaffelse.
Metyrapon	3 år. Efter åbning: 2 måneder	Må ikke opbevares ved over 25 °C. Beholderen skal holdes tæt lukket for at undgå fugt.	Ingen særlige regler ved bortskaffelse.
Pasireotid LAR	3 år	Skal opbevares i køleskab ved mellem 2 °C og 8 °C. Må ikke fryses.	Injektionskit skal tempereres ved stuetemperatur i mindst 30 minutter før rekonstituering. Opløsningen skal rystes i 30 sekunder og injiceres med det samme derefter. Administrationen skal foretages af uddannet sundhedspersonale.

LAR: *Long-acting release.*

Samlet set vurderer fagudvalget, at det er en ulempe ved pasireotid, at patienterne skal møde op på sygehuset for at modtage behandling. Dette er i modsætning til de andre behandlinger, der alle er orale formuleringer.

6.3 Behandlingsvarighed

Fagudvalget har ingen erfaringer med osilodrostat. Data peger i retning af, at responsraten er højere ved behandling med osilodrostat sammenlignet med nuværende medicinske behandlinger, samt at responset varer længere. Fagudvalget vil i udgangspunktet altid behandle, så længe effekten vedvarer, og der er balance mellem klinisk effekt og alvorlighed af bivirkninger. Dette er afspejlet i Medicinrådets sundhedsøkonomiske analyse.

Fagudvalget fremhæver, at osilodrostat kan have potentiale til at erstatte adrenalektomi blandt nogle patienter, men at evidensen for brugen af osilodrostat imidlertid ikke er tilstrækkelig belyst til at anse osilodrostat som alternativ til adrenalektomi.

6.4 Efterfølgende behandlingslinjer

Fagudvalget har bedt ansøger om at beskrive, hvorvidt osilodrostat vil komme til at ændre på tilgangen til behandling af de patienter, der i dag bliver behandlet. Ansøger skriver i sin ansøgning, at osilodrostat ikke vil ændre i tilgangen, da førstevalg vil forblive operation med henblik på at fjerne årsagen til den forhøjede kortisol. Osilodrostat skal ses som et alternativ til de eksisterende behandlinger. Fagudvalget er enigt i denne vurdering.

7. Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning.

8. Referencer

1. Dansk endokrinologisk selskab. National behandlingsvejledning: Cushings syndrom [internet]. 2018. Tilgængelig fra: https://endocrinology.dk/nbv/hypofyse-og-binyresygdomme/cushings-syndrom/

2. Scaroni C, Zilio M, Foti M, Boscaro M. Glucose Metabolism Abnormalities in Cushing Syndrome: From Molecular Basis to Clinical Management. Endocr Rev. 2017;38(3):189–219.

3. Canalis E, Mazziotti G, Giustina A, Bilezikian JP. Glucocorticoid-induced osteoporosis: pathophysiology and therapy. Osteoporos Int. 2007;18(10):1319–28.

4. Clayton RN, Jones PW, Reulen RC, Stewart PM, Hassan-Smith ZK, Ntali G, et al. Mortality in patients with Cushing's disease more than 10 years after remission: a multicentre, multinational, retrospective cohort study. Lancet Diabetes Endocrinol. 2016;4(7):569–76.

5. Cain DW, Cidlowski JA. Immune regulation by glucocorticoids. Nat Rev Immunol. 2017;17(4):233–47.

6. Ragnarsson O, Olsson DS, Papakokkinou E, Chantzichristos D, Dahlqvist P, Segerstedt E, et al. Overall and disease-specific mortality in patients with cushing disease: A Swedish nationwide study. Journal of Clinical Endocrinology and Metabolism. 2019;104(6):2375–84.

7. Scaroni C, Zilio M, Foti M, Boscaro M. Glucose Metabolism Abnormalities in Cushing Syndrome: From Molecular Basis to Clinical Management. Endocr Rev. 2017;38(3):189–219.

8. Canalis E, Mazziotti G, Giustina A, Bilezikian JP. Glucocorticoid-induced osteoporosis: pathophysiology and therapy. Osteoporos Int. 2007;18(10):1319–28.

9. Cain DW, Cidlowski JA. Immune regulation by glucocorticoids. Nat Rev Immunol. 2017;17(4):233–47.

10. Lindsay JR, Nansel T, Baid S, Gumowski J, Nieman LK. Long-Term Impaired Quality of Life in Cushing ' s Surgical Remission. 2006;91(2):447–53.

11. European Medicines Agency (EMA). Bilag I Produktresumé - Isturisa. 2020;1–22.

12. European Medicines Agency (EMA). Isturisa - EPAR. 2020;31(November 2019).

13. European Medicines Agency (EMA). Isturisa - EPAR. 2020;31(November 2019).

14. Nieman LK, Biller BMK, Findling JW, Murad MH, Newell-Price J, Savage MO, et al. Treatment of cushing's syndrome: An endocrine society clinical practice

guideline. Journal of Clinical Endocrinology and Metabolism. 2015;100(8):2807–31.

15. European Medicines Agency (EMA). Ketoconazole - EPAR. 2014;44(September).

16. Daniel E, Aylwin S, Mustafa O, Ball S, Munir A, Boelaert K, et al. Effectiveness of metyrapone in treating cushing's syndrome: A retrospective multicenter study in 195 patients. Journal of Clinical Endocrinology and Metabolism. 2015;100(11):4146–54.

17. European Medicines Agency (EMA). Bilag I produktresumé Signifor. 2014;44(0).

18. Gadelha M, Bex M, Feelders RA, Heaney AP, Auchus RJ, Gilis-Januszewska A, et al. Randomized Trial of Osilodrostat for the Treatment of Cushing Disease. Journal of Clinical Endocrinology and Metabolism. 2022;107(7):E2882–95.

19. Pivonello R, Fleseriu M, Newell-Price J, Bertagna X, Findling J, Shimatsu A, et al. Efficacy and safety of osilodrostat in patients with Cushing's disease (LINC 3): a multicentre phase III study with a double-blind, randomised withdrawal phase. Lancet Diabetes Endocrinol. 2020;8(9):748–61.

20. Bertagna X, Pivonello R, Fleseriu M, Zhang Y, Robinson P, Taylor A, et al. LCI699, a Potent 11β-hydroxylase Inhibitor, normalizes urinary cortisol in patients with Cushing's disease: Results from a multicenter, proof-of-concept study. Journal of Clinical Endocrinology and Metabolism. 2014;99(4):1375–83.

21. Fleseriu M, Pivonello R, Young J, Hamrahian AH, Molitch ME, Shimizu C, et al. Osilodrostat, a potent oral 11β-hydroxylase inhibitor: 22-week, prospective, Phase II study in Cushing's disease. Pituitary. 2016;19(2):138–48.

22. Tanaka T, Satoh F, Ujihara M, Midorikawa S, Kaneko T, Takeda T, et al. A multicenter, phase 2 study to evaluate the efficacy and safety of osilodrostat, a new 11β-hydroxylase inhibitor, in Japanese patients with endogenous Cushing's syndrome other than Cushing's disease.

23. Castinetti F, Guignat L, Giraud P, Muller M, Kamenicky P, Drui D, et al. Ketoconazole in Cushing's disease: is it worth a try? J Clin Endocrinol Metab. 2014;99(5):1623–30.

24. Castinetti F, Morange I, Jaquet P, Conte-Devolx B, Brue T. Ketoconazole revisited: A preoperative or postoperative treatment in Cushing's disease. Eur J Endocrinol. 2008;158(1):91–9.

25. CHMP. Isturisa, INN-osilodrostat.

26. Auchus RJ, Belaya Z, Bex M, Feelders RA, Heaney AP, Paul M, et al. Neuroendocrinology and Pituitary OR27-3 Long-Term Results from the Phase III LINC 4 Study: Osilodrostat Maintained Normal Mean Urinary Free Cortisol in Patients with Cushing's Disease, with a Favorable Safety Profile. Tilgængelig fra: https://doi.org/10.1210/jendso/bvac150

27. Daniel E, Aylwin S, Mustafa O, Ball S, Munir A, Boelaert K, et al. Effectiveness of metyrapone in treating cushing's syndrome: A retrospective multicenter study in 195 patients. Journal of Clinical Endocrinology and Metabolism. 2015;100(11):4146–54.

28. Fleseriu M, Petersenn S, Biller BMK, Kadioglu P, De Block C, T'Sjoen G, et al. Long-term efficacy and safety of once-monthly pasireotide in Cushing's disease: A Phase III extension study. Clin Endocrinol (Oxf). 2019;91(6).

29. Lacroix A, Gu F, Gallardo W, Pivonello R, Yu Y, Witek P, et al. Efficacy and safety of once-monthly pasireotide in Cushing's disease: a 12 month clinical trial. Lancet Diabetes Endocrinol. 2018;6(1).

30. Colao A, Petersenn S, Newell-Price J, Findling JW, Gu F, Maldonado M, et al. A 12-Month Phase 3 Study of Pasireotide in Cushing's Disease. New England Journal of Medicine. 2012;366(10).

31. Petersenn S, Salgado LR, Schopohl J, Portocarrero-Ortiz L, Arnaldi G, Lacroix A, et al. Long-term treatment of Cushing's disease with pasireotide: 5-year results from an open-label extension study of a Phase III trial. Endocrine. 2017;57(1).

32. Schopohl J, Gu F, Rubens R, Van Gaal L, Bertherat J, Ligueros-Saylan M, et al. Pasireotide can induce sustained decreases in urinary cortisol and provide clinical benefit in patients with Cushing's disease: results from an open-ended, open-label extension trial. Pituitary. 2015;18(5).

33. Webb SM, Ware JE, Forsythe A, Yang M, Badia X, Nelson LM, et al. Treatment effectiveness of pasireotide on health-related quality of life in patients with Cushing's disease. Eur J Endocrinol. 2014;171(1).

34. Fleseriu M, Iweha C, Salgado L, Mazzuco TL, Campigotto F, Maamari R, et al. Safety and efficacy of subcutaneous pasireotide in patients with Cushing's disease: Results from an open-label, multicenter, single-arm, multinational, expanded-access study. Front Endocrinol (Lausanne). 2019;10(JULY).

35. Pivonello R, Arnaldi G, Scaroni C, Giordano C, Cannavò S, Iacuaniello D, et al. The medical treatment with pasireotide in Cushing's disease: an Italian multicentre experience based on "real-world evidence". Endocrine. 2019;64(3).

36. Boscaro M, Bertherat J, Findling J, Fleseriu M, Atkinson AB, Petersenn S, et al. Extended treatment of Cushing's disease with pasireotide: Results from a 2-year, Phase II study. Pituitary. 2014;17(4).

9. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende hypofyse- og binyresygdomme	
Formand	**Indstillet af**
Claus Larsen Feltoft *Overlæge*	LVS og Dansk Endokrinologisk Selskab
Medlemmer	**Udpeget af**
Eigil Husted Nielsen *Overlæge*	Region Nordjylland
Marie Juul Ørnstrup *Afdelingslæge*	Region Midtjylland
Torben Leo Nielsen *Overlæge*	Region Syddanmark
Har ikke specialet	Region Sjælland
Mikkel Andreassen *Overlæge*	Region Hovedstaden
Torben Laursen *Overlæge, klinisk lektor*	Dansk Selskab for Klinisk farmakologi
Deltager ikke	Dansk Pædiatrisk Selskab
Gitte Stampe Møller *Klinisk farmaceut*	Dansk Selskab for Sygehusapoteksledelse
Lone Muxoll Storkfelt *Sygeplejerske*	Dansk Sygepleje Selskab
Helga Vaarbjerg *Patient/patientrepræsentant*	Danske Patienter
Matilde Kyst Behrens *Patient/patientrepræsentant*	Danske Patienter
Gry Bispelund Knudsen *Patient/patientrepræsentant*	Inviteret af formanden

Medicinrådets sekretariat
Medicinrådet
Dampfærgevej 21-23, 3. sal
2100 København Ø
+45 70 10 36 00
medicinraadet@medicinraadet.dk

10. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	23. november 2022	Godkendt af Medicinrådet.

11. Bilag

11.1 Bilag 1: Cochrane – risiko for bias

Vurdering af risiko for bias ved Cochrane risk of bias tool 2.0.

Tabel 11-1. Vurdering af risiko for bias, Gadelha et al., 2022, LINC-4, NCT02697734

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	**Lav**	Patienterne er randomiseret via interactiv-respons technology.
Effekt af tildeling til intervention	**1 – 12 uger: Lav** **12 – 48 uger: Høj**	I de første 12 uger var studiet dobbeltblindet. Efter 12 uger blev bindingen ophævet, og studiet var herefter single-armet.
Manglende data for effektmål	**Lav**	
Risiko for bias ved indsamlingen af data	**Lav**	
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Lav**	
Overordnet risiko for bias	**Lav**	

Tabel 11-2. Vurdering af risiko for bias, Fleseriu et al., 2019, G2304, NCT01374906

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	**Lav**	Randomisering til to doser af det samme lægemiddel
Effekt af tildeling til intervention	**Lav**	Dobbeltblinding
Manglende data for effektmål	**Lav**	
Risiko for bias ved indsamlingen af data	**Lav**	
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Lav**	
Overordnet risiko for bias	**Lav**	

Application for the assessment of Isturisa® (osilodrostat) for endogenous Cushing's Syndrome

Submitted on 22-12-2021
Update on: 14-09-2022

Contents

Submitted documents:

- Excel spreadsheet with cost-analysis and budget impact analysis
- Cost-analysis report

General information

This application form should be submitted to the Danish Medicines Council (Medicinrådet) for the assessment of new medicines and new indications. The purpose of the form is to provide an overview of the basic information, literature search, study, and analysis results that will serve as the basis for the assessment. It indicates the minimum required information needed for the assessment.

The assessment of the pharmaceutical will be based on the outcomes defined in the protocol. Results for all critical and important outcomes (kritiske og vigtige effektmål) must be addressed in the application. The results of less important outcomes (mindre vigtige effektmål) do not need to be addressed. For all the data provided, a reference is mandatory.

During the completion of this form, elements should not be removed from the document. All sections should be filled in (if a section is not applicable, state "not applicable" and explain why). Table examples are provided in the form. Layout may deviate from the template to accommodate data; however, all requested information must be stated. We accept submission of appendices. Audits of literature searches and data analyses will occur.

In order to minimize translation errors between the application and the assessment report, submission in Danish is preferred.

If confidential data are submitted, highlight the data in yellow and write the expected publication date in a comment. If confidential data are submitted in an appendix, the document must in addition be watermarked as "confidential."

The application will be published simultaneously with the final assessment and recommendation report on the Danish Medicines Council's web page (www.medicinraadet.dk). Any data that will be considered in the assessment report will be published with the final application.

Checklist before submitting the application form:

- Are all relevant fields in the application form filled in?
- Are references indicated for all data?
- Is the application explicit and self-explanatory?
- Does the application meet the general requirements defined in the Process and Methods Guide (version 2.0) of the Danish Medicines Council for new medicines and new indications?
- Does the application meet the specific requirements in the protocol?
- Are deviation(s) from the protocol (if any) described?
- Are deviation(s) from the protocol (if any) justified?

1. Basic information

Kontaktoplysninger	
Navn	**Joakim Aberg**
Titel	General Manager, Nordics & Baltics
Ansvarsområde	Market Access Nordics
Telefonnummer	+46 730 37 1030
E-mail	aberg.j@recordati.com
Navn	Susanne Schuurman
Titel	Market Access Consultant
Ansvarsområde	Market Access
Telefonnummer	+46 8-519 345 05
E-mail	susanne.schuurman@arexadvisor.com

Overview of the pharmaceutical	
Proprietary name	Isturisa®
Generic name	osilodrostat
Marketing authorization holder in Denmark	Recordati AB
ATC code	H02CA02
Pharmacotherapeutic group	Steroidogenesis inhibitor
Active substance(s)	osilodrostat
Pharmaceutical form(s)	Tablet
Mechanism of action	Osilodrostat, is a steroidogenesis inhibitor of 11β-hydroxylase (CYP11B1), the enzyme responsible for the final step in cortisol synthesis in the adrenal glands. Osilodrostat also dose-dependently inhibits aldosterone synthase (CYP11B2), which leads to reduced aldosterone synthesis.
Dosage regimen	Osilodrostat is manufactured as a phosphate salt and is available in film-coated tablets of 1 mg, 5 mg and 10 mg for oral administration. The recommended starting dose of Osilodrostat is 2 mg twice daily (bid); for patients of Asian ancestry a lower starting dose of 1 mg twice daily (bid) may be required. The dose can be gradually titrated (initially by increments of 1 or 2 mg twice daily) based on individual response and tolerability, until normal cortisol levels are achieved. The usual maintenance dose in clinical studies varied between 2 and 7 mg twice daily. The maximum recommended dose of osilodrostat is 30 mg twice daily. (1)
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Treatment of endogenous Cushing's Syndrome in adults

Overview of the pharmaceutical	
Other approved therapeutic indications	None
Will dispensing be restricted to hospitals?	Yes, hospital only
Combination therapy and/or co-medication	No
Packaging – types, sizes/number of units, and concentrations	Pack of 60 coated tablets of Ist 1mg, Ist 5mg, Ist 10mg
Orphan drug designation	Yes Received an orphan drug status in October 2014 and confirmed by the EMA Committee on Orphan Medicinal Products (COMP) in November 2019 due to Significant Benefit over all existing authorised products. (2)

2. Abbrevations

Abbreviation	Definition
ACC	Adrenal carcinoma
ACTH	Adrenocorticotropic hormone
AE	Adverse event
AESI	Adverse events of special interest
BDI	Beck Depression Inventory
BDI-II	Beck Depression Inventory-II
BID	Twice daily
BIM	Budget impact model
BLA	Bilateral adrenalectomy
CD	Cushing's disease
CI	Confidence interval
CR	Complete response
CS	Endogenous Cushing’s syndrome
CushingQoL	Cushing Quality of Life
EMA	European Medicines Agency
EOT	End of treatment
FAS	Full analysis set
GH	Growth hormone
HbA1C	Glycated hemoglobin
HDL	High-density lipoprotein
HR	Hazard ratio
HRQoL	Health-related quality of life
IM	Intramuscular
ITT	Intention-to-treat
LAR	Long-acting release
LLN	Lower limit of normal
LOCF	Last observed carried forward
MID	Minimal important difference
MRI	Magnetic resonance imaging
mUFC	Mean urinary free cortisol
NFPA	Non-functioning pituitary adenoma
ORR	Overall response rate
PRO	Patient-reported outcome
QoL	Quality of life
RT	Radiotherapy
RW	Randomized withdrawal
SAE	Serious adverse event
s.c.	Subcutaneous
SD	Standard deviation
SLR	Systematic literature review
SMR	Standardized mortality ratio
TSS	Transsphenoidal surgery
UFC	Urinary free cortisol

Abbreviation	Definition
ULN	Upper limit of normal

3. Summary

This application is a response to the protocol (*Medicinrådets protokol for vurdering vedrørende osilodrostat til behandling af Cushings syndrom*) issued by the Medicinrådet on 13 juli 2021. The aim is to seek reimbursement for osilodrostat in adults with a pathologically defined or clinically defined diagnosis of Cushing's Syndrome (CS) with persistent or recurrent disease, or with de novo disease who are not considered candidates for pituitary surgery as per approved regulatory label. (1) The protocol asks for data on complete response (at week 4, 12 and longest follow up), quality of life using the CushingsQoL tool, adverse events requiring additional treatment and a qualitative overview of adverse events. Treatments identified relevant in the protocol include ketoconazole, metyrapone and pasireotide. A total of 12 unique studies from 16 publications were identified in the literature search and one additional study was included upon the request of the expert committee.

As there are no randomized trials comparing efficacy of other agents used in CS and no other placebo-controlled trials to assess mean urinary free cortisol (mUFC) response, it was not possible to perform an indirect treatment comparison of osilodrostat versus other active agents, even via placebo. Hence, at this time a narrative analysis of the different treatments is presented for this assessment. The only treatment approved to lower mUFC levels is pasireotide but the Phase III trials compared different pasireotide doses, with no placebo arm. Using available patient level data, two indirect treatment comparisons using propensity score weighting on complete response of osilodrostat and pasireotide has been included (covering LINC-3 and LINC-4).

Complete response

The naïve comparison, including the pivotal or largest studies, showed that the osilodrostat arm in LINC-4 at week 12 and for all patients at the longest follow up at week 72 and at the end of treatment (EOT) (77.1%, 61.5% and 72.4%, respectively) has higher complete response (CR) rates compared to ketoconazole (48.5% at variable timepoint), metyrapone (43% at variable timepoint) and pasireotide (28-35% and 30-37.5%). It should be noted that the response rates from ketoconazole and metyrapone mainly come from retrospective studies, where there is a chance of overestimated results due to selection bias compared to when it would have been reviewed in a randomized clinical trial (RCT). Despite small differences in the patient population and trial design, an indirect comparison between pasireotide and osilodrostat was feasible and showed realistic results with osilodrostat having better and sustained efficacy than pasireotide. The propensity weighted analysis based on LINC-3 showed significantly more patients on osildrostat achieved CR versus pasireotide LAR (73.7% versus 24.3% at 12 weeks, OR: 8.14 [95% CI: 3.20 to 20.72], 62.8% versus 44.6% at longest follow-up, RR: 1.65 [95% CI: 1.07 to 3.01] respectively). The proponsity weighted analysis based on LINC-4 showed consistent outcomes with more patients on osilodrostat achieved CR versus pasireotide LAR (77.1% versus 24.3% at 12 weeks, OR: 5.98 [95% CI: 2.12 to 16.88]; 72.9% versus 44.6% at longest follow-up, OR: 1.58 [95% CI: 0.58 to 4.35) and versus pasireotide SC (77.1% versus 15.9% at 12 weeks, OR: 14.19 [95% CI: 5.03 to 40.06]; 72.9% versus 15.9% at longest follow-up, OR: 11.43 [95% CI: 4.14 to 31.55]). The matching adjusted indirect treatment comparison (MAIC) based on LINC-4 data in addition showed a better CR for patients on osilodrostat versus those on metyrapone in the PROMPT study, with 83% versus 47% at week 12, respectively, RR 1.62 (95% CI: 1.12 to 1.9); 88% versus 49% at week 36, respectively, RR: 1.82 (95% CI: 1.37 to 1.98).

Quality of life and patient reported outcomes

The quality of life (QoL) using the CushingQoL tool was reported for osilodrostat, metyrapone and pasireotide. Osilodrostat achieved a mean absolute change from baseline of 12.0 and 14.0 points at week 48 in LINC-4 and LINC-3, respectively. Reviewing against the minimal important difference (MID) of 10.1 point difference required in the protocol, we state that treatment with osilodrostat improves the patient's QoL. The MID was not achieved with metyrapone and pasireotide s.c., however pasireotide LAR showed a 11.1 change at month 12 using the CushingQoL tool. This clinically significant QoL improvement with osilodrostat was seen from week 12 and maintained throughout the study.

Additional patient reported outcomes for osilodrostat incluced Beck Depression Inventory (BDI) II, EQ-5D-5L and EQ-5D VAS. For all endpoints clinically significant improvement with osilodrostat was reached in LINC-4 trial.

Adverse events

The adverse events (AEs) of osilodrostat are overall well tolerated and comparing to other treatments a lower percentage of patients required additional treatment due to an AE. Osilodrostat's AEs are generally manageable with dose reduction/interruption and/or concomitant medication. Serious AEs which have a high impact on the patients measured with ketoconazole (hepatoxicity), metyrapone (hypertension) and pasireotide (hyperglycaemia) do not occur with osilodrostat treatment. Additionally, ketoconazole showed an extensive number of clinically relevant drug-drug interactions.

The current treatment landscape for CS is heterogenous, there is not one clearly defined Standard of Care (SoC) for the medical treatment of CS. Due to high risk of adverse events and limited efficacy, there is a significant need for the availability of a new long-term therapeutic option that can effectively normalize persistent hypercortisolism and sustain biochemical control. The addition of osilodrostat as a new efficacious and well-tolerated therapy to the management of CS will allow to address this unmet need. Based on the assessment it can be concluded that osilodrostat has a better efficacy, improved QoL and a better safety profile than ketoconazole, metyrapone and pasireotide. No escape was experienced by patients on osilodrostat, which is a benefit compared to the comparators. Additionally, osilodrostat treatment led to clinically relevant improvements in cardiovascular and metabolic parameters associated with persistent hypercortisolism in CS.

4. Literature search

The objective of the clinical systematic literature review (SLR) was to identify and summarize the relevant clinical evidence (including randomized controlled trials and non-randomized controlled trials) related to the treatment of patients with CS as required for request for reimbursement submission to the Danish Medicines Council (DMC). The inclusion and exclusion criteria can be found in section 8.1.

The review included searches of the following electronic databases as standard evidence sources for clinical data used in HTAs:

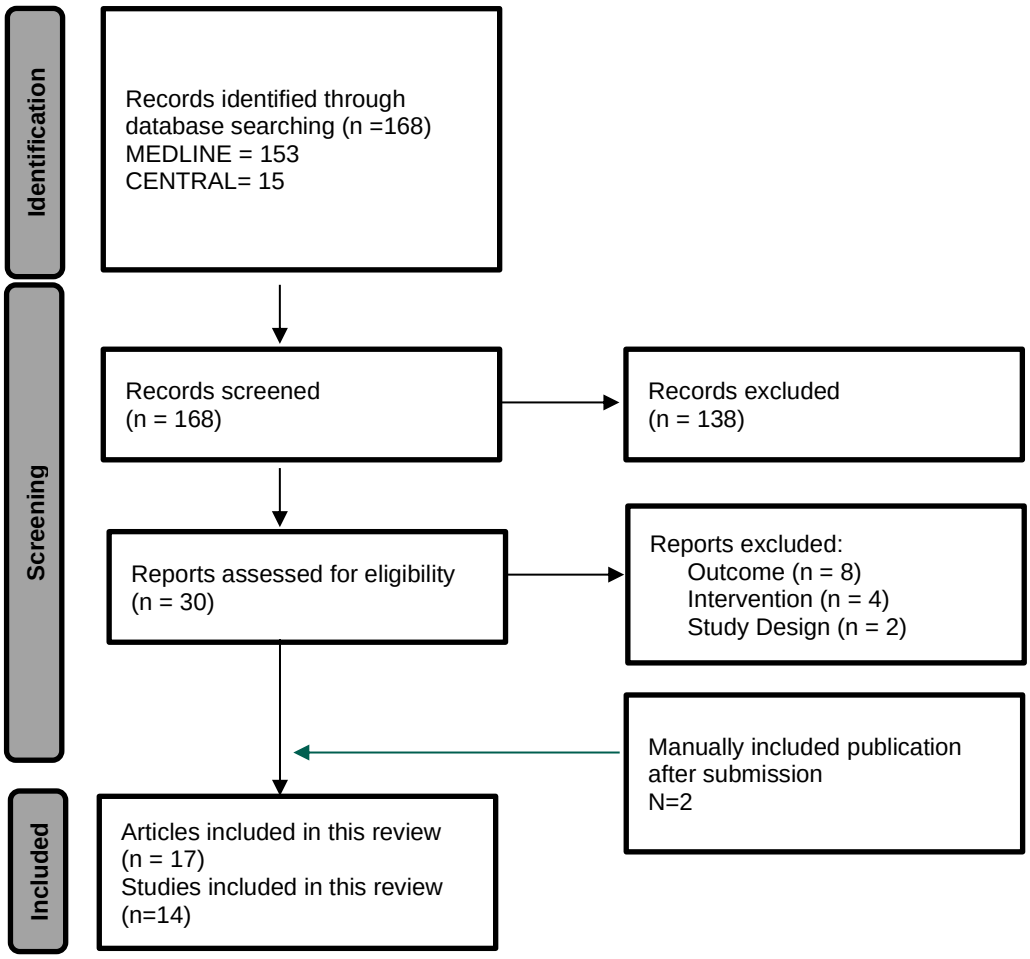
- MEDLINE® In-Process (using PubMed.com)
- The Cochrane Library (using Wiley.com), including the following:
  - Cochrane Central Register of Controlled Trials (CENTRAL)

A systematic literature search was performed according to the DMC protocol. Database were searched for this dossier on 13 July 2021. The searches followed the search strings provided in the protocol and covered an unlimited time period. A total of 164 potentially relevant titles or abstracts were identified for the review and screened based on the information reported in their titles and/or abstracts. Of these, 138 records were excluded at the primary screening stage as they were not relevant to the research question. Out of 30 included articles, 14 articles were excluded due to the following reasons: outcome (n=8), intervention (n=4), and study design (n=2). A total of 16 records were included and assessed in full for further evaluation. As some studies were assosciated with secondary publications, these were combined, therefore this resulted in 12 unique studies from 16 publications. The details for the flow of studies are presented in Figure 1 using a PRISMA flow diagram.

In addition to the hits identified in PubMed and Cochrane Library, two additional studies have been included in the other considerations section, namely LINC-4 (osilodrostat) and the non-peer reviewed PROMPT (metyrapone):

- LINC-4 is an additional Phase 3 trial assessing the efficacy and safety of osilodrostat in patients with CD, the study confirms efficacy and safety results from the LINC-3 trial.On request by the expert commmittee, this study has been included in the core dossier.
- PROMPT is the first prospective Phase 3 study assessing the efficacy and safety of metyrapone, currently results are available in 2 conference abstracts presented at ENDO 2021 adn ECE 2021. Given the lack of other prospective studies for metyrapone, it is considered relevant to be included in this assessment. This study has been included in the appendix and MAIC analysis versus osilodrostat for question 2.

Figure 1 PRISMA flow diagram of clinical studies



4.1 Relevant studies

Three clinical questions developed by the DMC for the assessment of osilodrostat include:

1. What is the value of osilodrostat compared to **ketoconazole** in adult patients with endogenous Cushings's syndrome?
2. What is the value of osilodrostat compared to **metyrapone** in adult patients with endogenous Cushings's syndrome?
3. What is the value of osilodrostat compared to **pasireotide** in adult patients with endogenous Cushings's syndrome?

Sixteen relevant publications were identified from the literature search covering 12 studies. One additional study was included upon the request of the expert committee (LINC4). Table 1 below lists each publication included in the assessment as well as the respective trial and its relevance for the different clinical questions.

Table 1 Relevant studies included in the assessment

Reference (title, author, journal. year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question
Randomized Trial of Osilodrostat for the Treatment of Cushing Disease Gadelha M, Bex M, Feelders RA, Heaney AP, Auchus RJ, Gilis-Januszewska A, Witek P, Belaya Z, Yu Y, Liao Z, Chen Ku CH. The Journal of Clinical Endocrinology & Metabolism. 2022	LINC-4	NCT02697734	October 3, 2016 to December 31, 2020	1, 2, 3
Efficacy and safety of osilodrostat in patients with Cushing's disease (LINC 3): a multicentre phase III study with a doubleblind, randomised withdrawal phase. Pivonello R, Fleseriu M, Newell-Price J, Bertagna X, Findling J, Shimatsu A, Gu F, Auchus R, Leelawattana R, Lee EJ, Kim JH. The Lancet Diabetes & Endocrinology. 2020	LINC-3	NCT02180217	Nov 12, 2014 to March 22, 2017	1,2,3
Osilodrostat, a potent oral 11β-hydroxylase inhibitor: 22-week, prospective, Phase II study in Cushing's disease. Fleseriu M, Pivonello R, Young J, Hamrahian AH, Molitch ME, Shimizu C, Tanaka T, Shimatsu A, White T, Hilliard A, Tian C, Sauter N, Biller BM, Bertagna X. Pituitary. 2016	LINC-2	NCT01331239	7 January and 26 July 2013	1,2,3
A multicenter, phase 2 study to evaluate the efficacy and safety of osilodrostat, a new 11β-hydroxylase inhibitor, in Japanese patients with endogenous Cushing's syndrome other than Cushing's disease. Tanaka T, Satoh F, Ujihara M, Midorikawa S, Kaneko T, Takeda T, Suzuki A, Sato M, Shimatsu A. Endocr J. 2020	C1201	NCT02468193	Ended October 29, 2018).	1,2,3
LCI699, a potent 11β-hydroxylase inhibitor, normalizes urinary cortisol in patients with Cushing's disease: results from a multicenter, proof-of-concept study. Bertagna X, Pivonello R, Fleseriu M, Zhang Y, Robinson P, Taylor A, Watson CE, Maldonado M, Hamrahian AH, Boscaro M, Biller BM J Clin Endocrinol Metab. 2014	LINC1 (core study); LINC 2 (extension study)	NCT01331239	NR	1,2,3

Reference (title, author, journal. year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question
Ketoconazole in Cushing's disease: is it worth a try? Castinetti F, Guignat L, Giraud P, Muller M, Kamenicky P, Drui D, Caron P, Luca F, Donadille B, Vantyghem MC, Bihan H, Delemer B, Raverot G, Motte E, Philippon M, Morange I, Conte-Devolx B, Quinquis L, Martinie M, Vezzosi D, Le Bras M, Baudry C, Christin-Maitre S, Goichot B, Chanson P, Young J, Chabre O, Tabarin A, Bertherat J, Brue T. J Clin Endocrinol Metab. 2014	NR	NR	1995 and 2012.	1
Ketoconazole revisited: a preoperative or postoperative treatment in Cushing's disease. Castinetti F, Morange I, Jaquet P, Conte-Devolx B, Brue T. Eur J Endocrinol. 2008	NR	NR	1995 and 2005	1
Effectiveness of Metyrapone in Treating Cushing's Syndrome: A Retrospective Multicenter Study in 195 Patients. Daniel E, Aylwin S, Mustafa O, Ball S, Munir A, Boelaert K, Chortis V, Cuthbertson DJ, Daousi C, Rajeev SP, Davis J, Cheer K, Drake W, Gunganah K, Grossman A, Gurnell M, Powlson AS, Karavitaki N, Huguet I, Kearney T, Mohit K, Meeran K, Hill N, Rees A, Lansdown AJ, Trainer PJ, Minder AE, Newell-Price J. J Clin Endocrinol Metab. 2015	NR	NR	NR	2
Prospective, single arm, open-label, multicenter, international study to assess the effects of metyrapone in patients with endogenous Cushing's syndrome during a 12-week treatment period followed by an extension period of 24 weeks. HRA Pharma. Clinicaltrials.gov. 2022.	PROMPT	NCT02297945	2015 and 2020	2
Long-term efficacy and safety of once-monthly pasireotide in Cushing's disease: A Phase III extension study. Fleseriu M, Petersenn S, Biller BMK, Kadioglu P, De Block C, T'Sjoen G, Vantyghem MC, Tauchmanova L, Wojna J, Roughton M, Lacroix A, Newell-Price J. Clin Endocrinol (Oxf) 2019	G2304	NCT01374906	NR	3

Reference (title, author, journal. year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question
Efficacy and safety of once-monthly pasireotide in Cushing's disease: a 12 month clinical trial. Lacroix A, Gu F, Gallardo W, Pivonello R, Yu Y, Witek P, Boscaro M, Salvatori R, Yamada M, Tauchmanova L, Roughton M, Ravichandran S, Petersenn S, Biller BMK, Newell-Price J; Pasireotide G2304 Study Group Lancet Diabetes Endocrinol. 2018	G2304	NCT01374906	Dec 28, 2011 to Dec 9, 2014	3
A 12-month phase 3 study of pasireotide in Cushing's disease. Colao A, Petersenn S, Newell-Price J, Findling JW, Gu F, Maldonado M, Schoenherr U, Mills D, Salgado LR, Biller BM. N Engl J Med. 2012	B2305	NCT00434148	NR	3
Long-term treatment of Cushing's disease with pasireotide: 5-year results from an open-label extension study of a Phase III trial. Petersenn S, Salgado LR, Schopohl J, Portocarrero-Ortiz L, Arnaldi G, Lacroix A, Scaroni C, Ravichandran S, Kandra A, Biller BMK Endocrine. 2017	B2305	NCT00434148	NR	3
Pasireotide can induce sustained decreases in urinary cortisol and provide clinical benefit in patients with Cushing's disease: results from an open-ended, open-label extension trial. Schopohl J, Gu F, Rubens R, Van Gaal L, Bertherat J, Ligueros-Saylan M, Trovato A, Hughes G, Salgado LR, Boscaro M, Pivonello R; Pituitary. 2015	B2305	NCT00434148	Ended 25 March 2011	3
Treatment effectiveness of pasireotide on health-related quality of life in patients with Cushing's disease. Webb SM, Ware JE, Forsythe A, Yang M, Badia X, Nelson LM, Signorovitch JE, McLeod L, Maldonado M, Zgliczynski W, de Block C, Portocarrero-Ortiz L, Gadelha M. Eur J Endocrinol. 2014	B2305	NCT00434148	NR	3
Safety and Efficacy of Subcutaneous Pasireotide in Patients With Cushing's Disease: Results From an Open-Label, Multicenter, Single-Arm, Multinational. Expanded-Access Study. Fleseriu M, Iweha C, Salgado L, Mazzuco TL, Campigotto F, Maamari R, Limumpornpetch P Front Endocrinol (Lausanne). 2019	SEASCAPE	NCT01582061	August 16, 2011 and January 26, 2017	3

Reference (title, author, journal. year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question
The medical treatment with pasireotide in Cushing's disease: an Italian multicentre experience based on "real-world evidence". Pivonello R, Arnaldi G, Scaroni C, Giordano C, Cannavò S, Iacuaniello D, Trementino L, Zilio M, Guarnotta V, Albani A, Cozzolino A, Michetti G, Boscaro M, Colao A Endocrine. 2019	NR	NR	NR	3
Extended treatment of Cushing's disease with pasireotide: results from a 2-year, Phase II study. Boscaro M, Bertherat J, Findling J, Fleseriu M, Atkinson AB, Petersenn S, Schopohl J, Snyder P, Hughes G, Trovato A, Hu K, Maldonado M, Biller BM. Pituitary. 2014	CSOM230 B2208	NCT00088608	NR	3

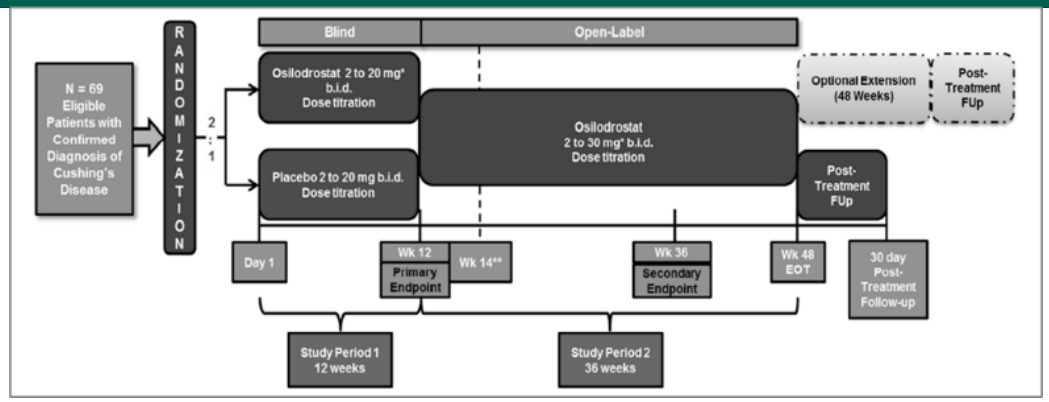
4.2 Main characteristics of included studies for intervention

Studies that included relevant endpoints within relevant patient populations identified in the literature for the intervention, osilodrostat are described in the following sections. The literature search identified four studies for osilodrostat: LINC-3, LINC-2, LINC-1, C1201. After submission the LINC-4 study has been published and is included in this dossier as main study.

4.2.1 LINC-4 study characteristics

Table 2 Study characteristics: LINC-4 (Gadelha 2022) (3)

Main study and patient characteristics (LINC-4)	
Trial name	LINC-4
NCT number	NCT02697734
Objective	The LINC-4 trial was designed to demonstrate the superiority of osilodrostat compared to placebo in achieving a complete response (mUFC ≤ ULN) at Week 12, to evaluate the safety of osilodrostat compared to placebo, and to evaluate the long-term safety and efficacy of osilodrostat.
Publications – title, author, journal. year	Gadelha M, Bex M, Feelders RA, Heaney AP, Auchus RJ, Gilis-Januszewska A, Witek P, Belaya Z, Yu Y, Liao Z, Chen Ku CH. Randomized trial of osilodrostat for the treatment of Cushing's disease. The Journal of Clinical Endocrinology & Metabolism. 2022 Mar 23.
Study type and design	LINC-4 is a Phase III, global, multi-center, randomized, double-blind, 48-week study with an initial 12-week placebo-controlled period; the trial was designed to demonstrate the superiority of osilodrostat compared to placebo in achieving a complete response (mUFC ≤ ULN) at Week 12, to evaluate the safety of osilodrostat compared to placebo, and to evaluate the long-term safety and efficacy of osilodrostat (Figure 12).(127) LINC-4 comprised a Core Phase of 48 weeks with two periods: • Study Period 1 (Weeks 1–12): double-blind and placebo-controlled • Study Period 2 (Weeks 13–48): single arm, open-label treatment. • Optional Extension phase (Weeks 48–96). **LINC-4 Study Design**

Main study and patient characteristics (LINC-4)	
	 *Key: * If needed, the dose may also be titrated to below the 2 mg b.i.d starting dose (e.g. 1mg b.i.d, 1 mg q.d. or 1 mg q.o.d; **The first UFC and lab results available to the investigator will be from samples collected prior to the Week 14 visit*
Follow-up time	At Week 48, patients had the option to enter an optional open-label Extension phase. During the optional extension phase the dose of osilodrostat was maintained at the established effective dose unless a change was required based on mUFC results collected at Week 48, and if applicable, at Weeks 60, 72, and 84. Patients benefitting from study treatment had the option of entering a separate long-term safety follow-up study (Study LCI699C2X01B) once they completed the optional extension phase. The optional extension phase ended when all eligible patients transitioned into the long-term safety follow-up study or were discontinued from the study.
Population (inclusion and exclusion criteria)	**Inclusion Criteria:** • Confirmed CD that is persistent or recurrent as evidenced by all the following criteria being met (i.e., a, b and c): 1. mUFC > 1.3 x ULN (Mean of three 24-hour urine samples collected preferably on 3 consecutive days, during screening after washout of prior medical therapy for CD (if applicable), confirmed by the central laboratory and available before Day 1), with ≥2 of the individual UFC values being > 1.3 x ULN. 2. Morning plasma ACTH above Lower Limit of Normal 3. Confirmation (based on medical history) of pituitary source of excess ACTH as defined by any one or more of the following three criteria: i. Histopathologic confirmation of an ACTH-staining adenoma in patients who have had prior pituitary surgery. OR ii. MRI confirmation of pituitary adenoma > 6 mm OR iii. Bilateral inferior petrosal sinus sampling (BIPSS) with either CRH or DDAVP stimulation for patients with a tumor ≤ 6mm. The criteria for a confirmatory BIPSS test are any of the following: Pre-dose central to peripheral ACTH gradient > 2; Post-dose central to peripheral ACTH gradient > 3 after either CRH or DDAVP stimulation

	• Patients that received glucocorticoid replacement therapy must have discontinued such therapy for at least seven days or 5 half-lives prior to screening, whichever is longer. • Patients with de novo CD can be included only if they are not considered candidates for surgery (e.g., poor surgical candidates due to co-morbidities, inoperable tumors, patients who refuse to have surgical treatment, or surgical treatment is not available). **Exclusion Criteria:** • Patients with pseudo-Cushing's syndrome. This may be diagnosed by a normal late night salivary cortisol value collected during the screening period and after washout of prior CD medication. • Patients with risk factors for QTc prolongation or Torsade de Pointes, including: • Patients with a baseline QTcF > 450 ms for males and QTcF > 460 ms for females; personal or family history of long QT syndrome; concomitant medications known to prolong the QT interval; patients with hypokalemia, hypocalcaemia, or hypomagnesaemia, if not corrected before pre-dose Day 1. • Patients likely to require adrenalectomy, pituitary surgery, or radiation therapy during the placebo-controlled period (Weeks 1-12) for the treatment of severe hypercortisolism or pituitary tumor growth causing compression of the optic chiasm. • Patients with compression of the optic chiasm due to a macroadenoma or patients at high risk of compression of the optic chiasm (tumor within 2 mm of optic chiasm). • Patients who have a known inherited syndrome as the cause for hormone over secretion (i.e. Carney Complex, McCune-Albright syndrome, MEN-1, AIP). • Patients with Cushing's syndrome due to ectopic ACTH secretion or ACTH independent (adrenal) Cushing's syndrome. • Pregnant or nursing (lactating) women. • Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 1 week after completion of dosing.
Intervention	**Study period 1:** The initial study drug dose was 2 mg BID. Independent endocrinologists determined dose adjustments, based on effcacy and tolerability, once mUFC results from the week-2, -5, and -8 visits became available for individual patients. Thus, first dose increases occurred approximately after 3 weeks. Dose could be increased (2-5-10-20 mg twice daily dose-escalation sequence) if mUFC (mean of 2 samples collected immediately before the study visit) exceeded the ULN (reference range, 11-138 nmol/24 hours [4-50 µg/24 hours]).. **Study period 2**: Allowing for further dose titration as needed by the investigator. All patients on doses of ≥2 mg BID at the Week 12 visit received open-label osilodrostat at a starting dose of 2 mg BID at the beginning of Period 2, regardless of treatment assignment in Period 1.

Main study and patient characteristics (LINC-4)

Patients on <2 mg BID at the Week 12 visit continued the same dose they were on at the end of Period 1, regardless of treatment assignment during Period 1

Optional extension phase: During the optional extension phase, the dose of osilodrostat was maintained at the established effective dose unless a change was required based on mUFC results collected at Week 48, and if applicable, at Weeks 60, 72, and 84.

Baseline characteristics

FAS population			
Patient Characteristics, n (%)	**Osilodrostat N=48**	**Placebo N=25**	**All Patients N=73**
Age, years			
Mean (SD)	42.3 (13.82)	38.9 (12.33)	41.2 (13.35)
Median (range)	41.0 (21.0–67.0)	37.0 (19.0–63.0)	39.0 (19.0–67.0)
Sex - n (%)			
Female	43 (89.6)	18 (72.0)	61 (83.6)
Male	5 (10.4)	7 (28.0)	12 (16.4)
Race - n (%)			
Caucasian	34 (70.8)	15 (60.0)	49 (67.1)
Asian	9 (18.8)	8 (32.0)	17 (23.3)
Black or African American	2 (4.2)	0	2 (2.7)
Unknown	2 (4.2)	1 (4.0)	3 (4.1)
American Indian or Alaska Native	1 (2.1)	0	1 (1.4)
Other	0	1 (4.0)	1 (1.4)
Weight, kg			
Mean (SD)	78.8 (17.46)	77.3 (16.90)	78.3 (17.17)
Median (range)	80.1 (46.9–113.7)	74.0 (53.5–114.5)	77.0 (46.9–114.5)
Time (months) to first osilodrostat dose since diagnosis			
Median (range)	69.9 (6.0–257.7)	65.0 (11.2–215.9)	67.4 (6.0–257.7)

CD status - n (%)			
De novo	3 (6.3)	0	3 (4.1)
Persistent/recurrent	45 (93.8)	25 (100)	70 (95.9)
Any previous surgery, n (%)			
Yes	41 (85.4)	23 (92.0)	64 (87.7)
No	7 (14.6)	2 (8.0)	9 (12.3)
Any previous treatments for Cushing's disease: n (%)			
Yes	26 (54.2)	19 (76.0)	45 (61.6)
No	22 (45.8)	6 (4.0)	28 (38.4)
Any previous pituitary irradiation: n (%)			
Yes	6 (12.5)	3 (12.0)	9 (12.3)
No	42 (87.5)	22 (88.0)	64 (87.7)
Baseline mUFC, nmol/day			
Mean (SD)	421.3 (291.3) 3.1xULN	451.5 (535.1) 3.3xULN	431.7 (388.6) 3.1xULN
Median (interquartile range)	342.2 (252.6-519.9) 2.5xULN	297.6 (211.2-518.8) 2.2xULN	340.3 (221.3-518.8) 2.5xULN

Abbreviations: CD, Cushing's disease; FAS: full analysis set; mUFC, mean urinary free cortisol; SD, standard deviation.

*Key: * Pituitary adenomas <10mm in size are defined as microadenomas, ≥10mm in size are defined as macroadenomas.*

Note: Data cut-off is 25 February 2020.

Primary and secondary endpoints

Primary endpoint: The proportion of randomized patients with a complete response, i.e. mUFC ≤ ULN, at Week 12.

Key secondary endpoint: The proportion of patients with mUFC ≤ ULN at Week 36 for combined randomized patients who received osilodrostat treatment.

Secondary endpoints:

- To assess the proportion of patients with a complete response (mUFC ≤ ULN) or a partial response (mUFC decrease ≥50.0% from baseline and >ULN) at Week 12, Week 36, and Week 48.
- To assess the change in mUFC during the Core and Extension periods.
- To compare the time-to-first control of mUFC during the placebo-controlled period (Weeks 1-12) between the randomized treatment arms.
- To assess the time-to-escape during osilodrostat treatment up to Week 48.

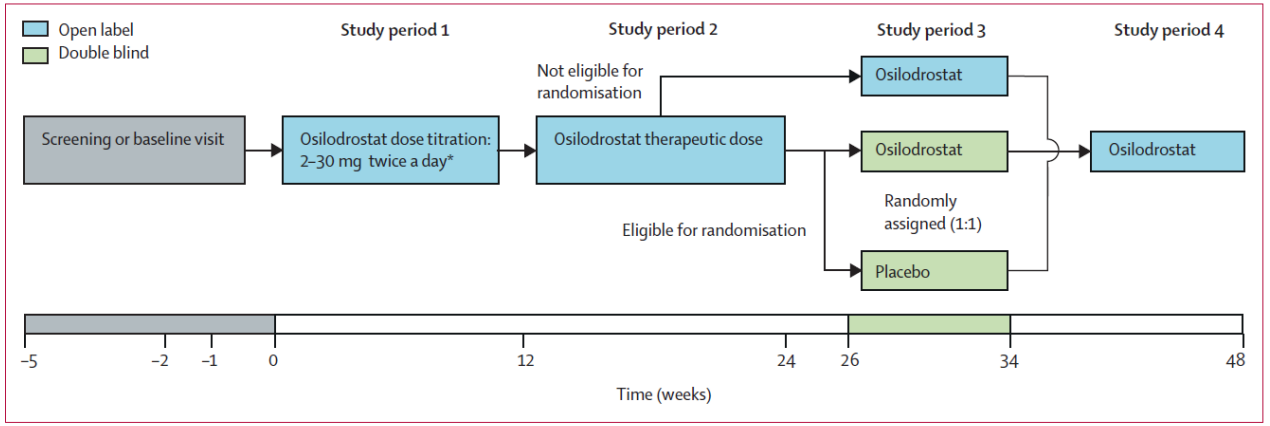
Main study and patient characteristics (LINC-4)	
	• To assess cardiovascular and metabolic related parameters associated with CD (fasting plasma glucose, HbA1c, fasting lipid profile, blood pressure, weight and waist circumference) by assessing actual and percent change from baseline and shift table at Weeks 12, 36, and 48. • To assess the change from baseline at Weeks 12, 36, and 48 in physical features of CD • To assess the change from baseline in BMD by DXA scan at the lumbar spine and total hip at Week 48. • To determine the safety and tolerability of osilodrostat in the study population. • To assess the change from baseline in HRQoL, as measured by the CushingQoL, BDI-II, and EQ-5D-5L, by randomized treatment arm and overall. • To evaluate pharmacokinetic exposure of osilodrostat in the study population. • To assess the change from baseline in serum, salivary and hair cortisol levels
Method of analysis	• Full Analysis Set (FAS): comprised all randomized patients who received at least one dose of study drug (osilodrostat or placebo). FAS is the default analysis set for efficacy. The randomization was stratified by history of pituitary irradiation (yes/no) • Safety Analysis Set (SAS): Comprised all patients who received at least one dose of study drug (osilodrostat or placebo). Patients were analyzed according to the study drug received, where treatment received was defined as the randomized/assigned treatment if the patient took at least one dose of that treatment or the first treatment received if the randomized/assigned treatment was never received • Per-Protocol Set (PPS): Comprised a subset of the patients in the FAS who were compliant (e.g. did not have any protocol deviations that would lead to exclusion from PPS) with the requirements of the Clinical Study Protocol
Subgroup analyses	None

4.2.2 LINC-3 study characteristics

Table 3 Study characteristics: LINC-3 (Pivonello 2020)(4)

Main study and patient characteristics (Pivonello 2020)	
Trial name	LINC-3; C2301
NCT number	NCT02180217
Objective(s)	**Primary:** To compare the complete response rate at the end of the 8-week period of randomized withdrawal (Week 34) between patients randomized to continued osilodrostat therapy versus those receiving placebo. **Secondary:** To assess the complete response rate at the end of individual dose-titration and treatment with osilodrostat in the initial single-arm open-label period (Week 24) **Other secondary:**

Main study and patient characteristics (Pivonello 2020)	
	• To compare the time-to-last control of mUFC during the RW Period between patients randomized to continued osilodrostat therapy and placebo • To assess the complete, partial and overall response rate at Week 12, Week 24, Week 48 and at scheduled timepoints during the Extension Period and the last available assessment • To assess the change in mUFC during the Core and Extension Periods of the stud • To assess the change in cardiovascular-related parameters associated with Cushing's Disease during the Core and Extension Periods of the study • To assess the change in PROs (HRQoL) during the Core and Extension Periods of the study using CushingQoL, BDI-II and EQ 5D-5L • Safety
Publications – title, author, journal. year	**Efficacy and safety of osilodrostat in patients with Cushing's disease (LINC 3): a multicentre phase III study with a double blind, randomised withdrawal phase.** Pivonello R, Fleseriu M, Newell-Price J, Bertagna X, Findling J, Shimatsu A, Gu F, Auchus R, Leelawattana R, Lee EJ, Kim JH. The Lancet Diabetes & Endocrinology. 2020
Study type and design	Phase lll, multi-center, double-blind randomized withdrawal phase, following a 24 week open-label, single-arm dose titration and treatment period which evaluated the efficacy and safety for the treatment of patients with Cushing's disease. **Four study periods (1–4) and an optional extension period:** **Study Period 1** (Week 1 to Week 12; dose-titration period): all patients received open-label osilodrostat 2 mg BID with dose adjustments every 2 weeks up to week 12 based on efficacy and tolerability. **Study Period 2** (Week 13 to Week 24; dose-titration and treatment period): during this study period, the efficacy and safety of osilodrostat were assessed at the therapeutic dose determined during study period 1. Of note, patients with mUFC > ULN had their osilodrostat dose increased as tolerated and the maximum dose of 30 mg BID had not yet been reached. These patients were followed for long-term efficacy and were not considered responders for the key secondary endpoint, hence were not randomized in Study Period 3. **Study Period 3** (Week 26 to Week 34; randomized withdrawal period): Patients were eligible to enter the randomized withdrawal phase at week 26 if they had mUFC ≤ULN at week 24 without a dose increase after week 12; patients were randomized (1:1) in a double-blind manner to continue osilodrostat at the same therapeutic dose or receive matching placebo for 8 weeks without further dose increases. Patients not eligible for randomization received open label osilodrostat until the end of the Core Period (Week 48) unless there was a reason to discontinue from the study prematurely. **Study Period 4** (Week 34 to Week 48): After week 34 all patients received open-label osilodrostat until week 48; dosing could be adjusted based on the mUFC levels during this treatment period.

Main study and patient characteristics (Pivonello 2020)	
	***Extension** phase (optional) (Week 48 to Week 72)*  *Key: *Based on efficacy and tolerability* *Abbreviations: UFC, urinary free cortisol; ULN, upper limit of normal.* *Note: Patients were eligible for randomization if they had mean 24-h UFC concentration of less than or equal to the ULN at week 24 and no dose up-titration of osilodrostat during weeks 13–24.*
Follow-up time	Patients who continued to receive clinical benefit (as assessed by the study investigator) and who wished to enter the extension period, had to be re-consented at Week 48. Patients who entered the extension period did so without interruption of study drug or scheduled assessments. The optional extension period will end after all patients have completed Week 72 or discontinued prior to Week 72.
Population (inclusion and exclusion criteria)	**Key inclusion Criteria:** • Male or female patients aged 18 - 75 years • Patients with confirmed persistent or recurrent Cushing's disease (mUFC≥1.5x ULN and morning plasma ACTH above the LLN (lower limit of normal)) after primary pituitary surgery and/or irradiation, and also de novo patients with Cushing's disease who were not eligible for surgery or who refuse to undergo surgery • Patients with a history of prior pituitary surgery must be at least 30 days post-surgery to be eligible for inclusion in this study. • Patients that received glucocorticoid replacement therapy post-operatively must have discontinued such therapy for at least one week, or 5 half-lives, whichever is longer, prior to screening • Patients with de novo Cushing's disease can be included only if they are not considered candidates for surgery

Main study and patient characteristics (Pivonello 2020)	
	• Patients with a history of pituitary irradiation can be included, provided that at least 2 years (stereotactic radiosurgery) or 3 years (conventional radiation) have elapsed from the time of last radiation treatment to the time of enrollment into this study. *Note: Patients were permitted to wash out current drug therapy to meet entry criteria if they had a known diagnosis of Cushing's disease.* **Key exclusion Criteria:** • Patients who had a known inherited syndrome as the cause for hormone over secretion • Patients with CS due to ectopic ACTH secretion or ACTH-independent (adrenal) CS • Pregnant or nursing (lactating) women • Patients who had undergone major surgery within 1 month before screening • Hypertensive patients with uncontrolled blood pressure defined as systolic blood pressure (SBP) >180 and/or diastolic blood pressure (DBP) >100 • Diabetic patients with poorly controlled diabetes as evidenced by glycosylated hemoglobin (HbA1c) >9 .0% • Patients with a history of congestive heart failure (New York Heart Association Class III or IV), unstable angina, sustained ventricular tachycardia, clinically significant bradycardia, advanced heart block, acute MI less than one year before study entry, or clinically significant impairment in cardiovascular function • Patients with moderate to severe renal impairment • Patients with liver disease • History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there was evidence of local recurrence or metastases • Patients with risk factors for QTc prolongation or Torsade de Pointes • Patients with compression of the optic chiasm due to a macroadenoma or patients at high risk of compression of the optic chiasm • Patients who had had stereotactic radiosurgery in the past 2 years, conventional radiotherapy in the past 3 years or pituitary surgery in the past 29 days.
Intervention	Osilodrostat **Study period 1:** The dosing regimen was up-titrated as follows: 2 mg BID, 5 mg BID, 10 mg BID, 20 mg BID, and 30 mg BID. The up titration continued until mUFC ≤ ULN. The maximum dose of osilodrostat was 30 mg BID. Dose was increased if mUFC (mean of three 24-hour samples) exceeded ULN. Throughout the study, osilodrostat dose was reduced if mUFC was below LLN or if mUFC was in the lower part of the normal range in patients with symptoms of hypocortisolism or adrenal insufficiency. Of note, at Week 0 and Week 2, dose increases were not permitted. (n=137) **Study period 2**: Dose was determined in period 1 and no changes were made. **Study period 3**: Same therapeutic dose (n=36, randomized and n=66, not randomized but continues treatment with osilodrostat)

Main study and patient characteristics (Pivonello 2020)

Study period 4: Dose could be adjusted based on the mUFC levels during this treatment period.

Extension phase (optional): Dose could be adjusted based on the mUFC levels during this treatment period.

Baseline characteristics

Patient Characteristics, n (%)	Randomized to osilodrostat N=36	Randomized to placebo N=35	Not Randomized N=66	All Patients N=137
Age				
Mean (SD)	44.3 (11.27)	42.0 (13.47)	39.0 (13.38)	41.2 (12.98)
Median (range)	41.0	40.0	37.5	40.0 (19.0-70.0)
Age category (years) - n (%)				
18-<65	34 (94.4)	34 (97.1)	62 (93.9)	130 (94.9)
65-≤ 75	2 (5.6)	1 (2.9)	4 (6.1)	7 (5.1)
Sex - n (%)				
Female	30 (83.3)	22 (62.9)	54 (81.8)	106 (77.4)
Male	6 (16.7)	13 (37.1)	12 (18.2)	31 (22.6)
Race - n (%)				
Caucasian	27 (75.0)	23 (65.7)	39 (59.1)	89 (65.0)
Black	0	3 (8.6)	1 (1.5)	4 (2.9)
Asian	7 (19.4)	7 (20.0)	25 (37.9)	39 (28.5)
Other	2 (5.6)	2 (5.7)	1 (1.5)	5 (3.6)
Body mass index (kg/m2)				
Mean (SD)	29.6 (7.35)	30.9 (8.37)	30.4 (7.73)	30.3 (7.76)
Median	28.5	29.0	28.8	28.8
Time (months) to first osilodrostat dose since diagnosis				
Mean (SD)	71.4 (63.54)	88.3 (67.46)	46.5 (43.26)	63.7 (58.20)
Median	53.6	76.8	34.7	47.2
CD status - n (%)				
De novo (no previous surgery)	4 (11.1)	2 (5.7)	11 (16.7)	17 (12.4)
Persistent/recurrent (with previous surgery)	32 (88.9)	33 (94.3)	55 (83.3)	120 (87.6)
Any previous treatments for Cushing's disease: n (%)				

Main study and patient characteristics (Pivonello 2020)					
	Yes	35 (97.2)	33 (94.3)	63 (95.5)	131 (95.6)
	No	1 (2.8)	2 (5.7)	3 (4.5)	6 (4.4)
	Any previous pituitary irradiation: n (%)				
	Yes	6 (16.7)	5 (14.3)	11 (16.7)	22 (16.1)
	No	30 (83.3)	30 (85.7)	55 (83.3)	115 (83.9)
	Baseline mUFC, nmol/24h				
	Mean (SD)	890.0 (1275.66)	560.0 (548.84)	1,305.8 (2012.21)	1,006.0 (1,589.86)
	Median	457.0	357.9	556.9	476.4

Primary and secondary endpoints	**Primary endpoint:** Proportion of randomized patients in each arm with: mUFC ≤ ULN at the end of 8 weeks of RW (Week 34), and were neither discontinued, nor had osilodrostat dose increase above the level at Week 26 during the RW period **Key secondary endpoint:** Proportion of enrolled patients with mUFC ≤ ULN at Week 24 and had no dose increase above the level established at Week 12 between Week 13 and Week 24 **Other secondary endpoints:** • To compare the time-to-last control of mUFC during the RW Period between patients randomized to continued osilodrostat therapy and placebo • To assess the complete, partial and overall response rate at Week 12, Week 24, Week 48 and at scheduled timepoints during the Extension Period and the last available assessment • To assess the change in mUFC during the Core and Extension Periods of the study • To assess the change in cardiovascular-related parameters associated with CD during the Core and Extension Periods of the study • To assess the change in PROs (HRQoL) during the Core and Extension Periods of the study using CushingQoL, BDI-II and EQ 5D-5L • Safety
Method of analysis	Analysis was by intention-to-treat (IIT) for all patients who received at least one dose of osilodrostat (full analysis set; key secondary endpoint) or randomized treatment (randomized analysis set; primary endpoint) and safety was assessed in all enrolled patients who received at least one dose of osilodrostat (safety analysis set) and had at least one post-baseline safety assessment.
Subgroup analyses	None

Abbreviations: ACTH, adrenocorticotropic hormone; BID, twice daily; CD, Cushing's disease; CS, Cushing's syndrome; HRQoL, health related quality of life; LLN=lower limit of normal; RW, randomized week; ULN, pper limit of normal; UFC=urinary free cortisol

4.2.3 LINC-2 study characteristics

Table 4 Study characteristics: LINC-2 (Fleseriu, 2016) (5)

Main study and patient characteristics (Fleseriu, 2016)	
Trial name	LINC-2; C2201 (part II)
NCT number	NCT01331239

Objective(s)	**Primary**: To assess the effects of 10 weeks' treatment of osilodrostat on 24-hour UFC in patients with Cushing's Disease (same objective as in LINC-1)
	
	Secondary: (Follow-up and Expansion cohorts):
	
	• To assess the effects of 10 weeks' treatment of osilodrostat on 24-hour UFC in patients with Cushing's Disease
	• To assess the 10-week and 22-week safety and tolerability of multiple doses of osilodrostat
	• To assess the effect of osilodrostat on steroid hormones of the HPA-axis in plasma, urine and saliva
	• To assess the effects of osilodrostat on improving the metabolic abnormalities (hypertension, dyslipidemia, obesity, insulin sensitivity, glycosylated hemoglobin [HbA1c] and fasting plasma glucose [FPG]) of Cushing's disease
	• To assess the steady state pharmacokinetics of osilodrostat in patients with Cushing's Disease
	• To assess the effect of 22-weeks of treatment with osilodrostat monotherapy on 24-hour UFC in patients with Cushing's Disease. The proportion of patients controlled or partially controlled was determined as follows:
	  ◦ Controlled UFC: defined as a mUFC level≤ ULN
	  ◦ Partially controlled UFC: defined as a mUFC level >ULN but with ≥ 50.0% reduction from baseline
	• To assess escape. Escape is defined as loss of UFC control (i.e. UFC >ULN) on at least 2 consecutive visits at the highest tolerated dose after previously attaining UFC normalization
	
	Objectives of the extensions-1 and -2 (optional beyond the 22 weeks) were to provide long-term efficacy and safety data.

Publications – title, author, journal. year	**Osilodrostat, a potent oral 11β-hydroxylase inhibitor: 22-week, prospective, Phase II study in Cushing's disease.** Fleseriu M, Pivonello R, Young J, Hamrahian AH, Molitch ME, Shimizu C, Tanaka T, Shimatsu A, White T, Hilliard A, Tian C, Sauter N, Biller BM, Bertagna X. Pituitary. 2016
Study type and design	The LINC-2 study was a 22-week, prospective, open-label, multicenter, phase II study that enrolled patients (aged 18–75 years) with a confirmed diagnosis of CD. Patients were enrolled in two cohorts: • The '**follow-up cohort'** comprised patients who completed LINC 1 and

- The '**expansion cohort'** which comprised newly enrolled patients who were naïve to osilodrostat.

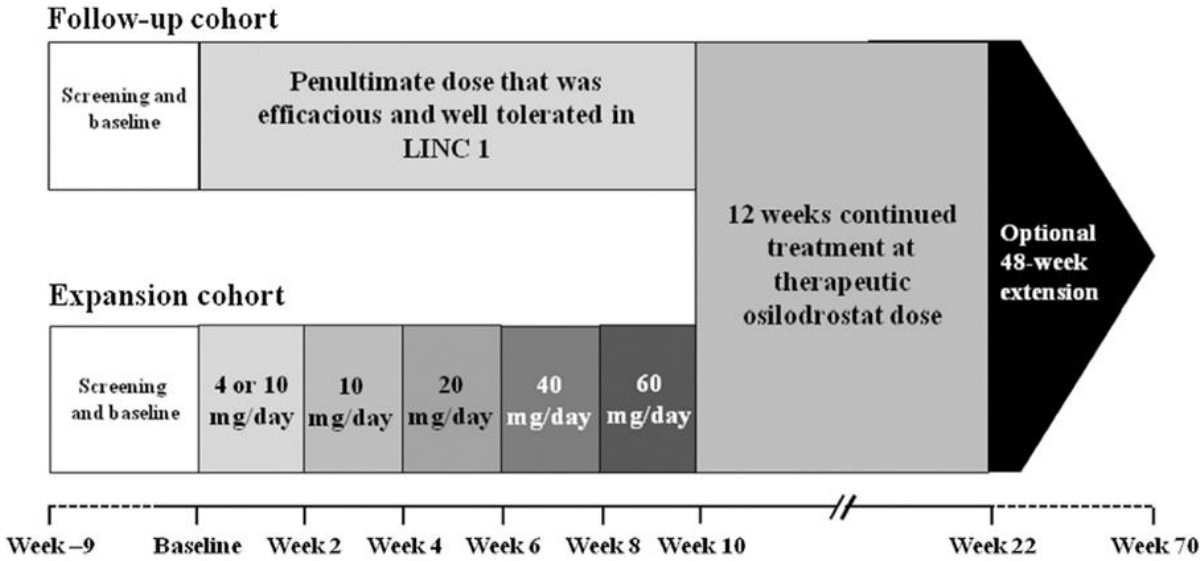
Extension phase (optional)

At the End of Week 22, patients were evaluated for clinical benefit and had the option to enter the 12-month long term Extension Phase at the Investigators discretion provided they did not meet discontinuation criteria. This is not part of the Fleseriu, 2016 article, but is described.

The optional extension phase consists of two extensions:

Long-term extension 1
At Day 154 (Week 22), patients had the option to enter the 12-month extension phase at the Investigators discretion, provided they did not meet any discontinuation criteria. Dosing titration during the extension 1 was based on efficacy (UFC control) and safety. Patients were to come for monthly visits for the first 6 months (Day 154- Day 322) and then every 3 months from month 6 through 12 (Day 322 - Day 490) of long-term extension 1 (extension-1).

Long term extension 2
At Day 490, patients had the option to enter a second long-term extension phase (extension-2) at the Investigator's discretion, provided they did not meet any of the study discontinuation criteria. Dose adjustment during extension-2 was based on efficacy (UFC control) and safety. Patients were to visit every 3 months during the first 18 months of extension-2 (approximately 3 years into the study), and every 6 months thereafter. This additional long-term extension (extension-2) was planned to provide long-term safety and efficacy data of osilodrostat in patients with Cushing's disease.

Main study and patient characteristics (Fleseriu, 2016)	
	 *Note: Patients in the Follow-up cohort could re-enter the study if their current UFC level was above the upper limit of normal (ULN; i.e.>1 x ULN). Patients were off osilodrostat treatment for 15–19 months before enrolment in LINC-2 (administrative time between the end of LINC 1 and initiation of LINC-2)* *Note: An amendment to the protocol was conducted to allow the total treatment duration with osilodrostat to extend to 22 weeks. This amendment led to the expansion of the LINC-1 trial into LINC-2. In addition, at Day 154 visit or End of Treatment Core visit (Week 22), two optional long-term extension phases (Extension-1 and Extension-2) were planned to evaluate long-term safety and efficacy data of* osilodrostat *in patients with CD. The study duration was subsequently extended several times*
Follow-up time	19 months (optional extension)
Population (inclusion and exclusion criteria)	The eligibility criteria for LINC-2 are the same as LINC-1. In addition, patients should complete the 22-week study and if they responded to osilodrostat or were considered by the investigator to be receiving clinical benefit could enter the extension phase. **Inclusion criteria:** • Patients could be included once they had given written informed consent and had confirmed CD and were willing to complete the prescribed washout periods prior to baseline efficacy assessments • Male or female patients aged 18 – 75 years • Patients must have confirmed CD (including de novo patients)

Exclusion criteria:

- Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of enrollment, whichever is longer; or longer if required by local regulations, and for any other limitation of participation in an investigational trial based on local regulations
- History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases
- Patients who have been treated with mitotane during the last 6 months prior to Visit 1
- Patients who have a known inherited syndrome as the cause for hormone over secretion (i.e. Carney Complex, McCune-Albright syndrome, MEN-1, AIP)
- Patients with CS due to ectopic ACTH secretion or adrenal CS
- Patients with pseudo-Cushing's syndrome
- Patients with renal impairment

Intervention

Osilodrostat

Expansion cohort: Patients in the Expansion cohort started osilodrostat treatment at Day 1 with 2 mg BID (if baseline UFC ≤ 3xULN) or 5 mg BID (if baseline UFC >3xULN). The dose was then escalated every 2 weeks according to the escalation sequence 10, 20, 40, and 60 mg/day until UFC was ≤ULN.

Follow-up cohort: Patients in the Follow-up cohort started at the penultimate osilodrostat dose that was efficacious and well tolerated for them. The dose was up titrated from the penultimate dose according to the escalation sequence 10, 20, 40, and 60 mg/day until UFC was ≤ULN. This titration was continued up to Week 10 as needed based on efficacy and tolerability.

If UFC normalized before Week 10 in either cohort, dose was maintained at the effective level until Week 10; if UFC normalized but subsequently increased to >ULN, dose escalation was resumed.

Extension phase (optional): Patients continued on the same dose of osilodrostat as at Week 22; however, dose adjustments were permitted during the extension (min/max, 1 mg once daily/30 mg BID). (n=16 in long-term extension-1 and n=13 in long-term extension-2)

Baseline characteristics

Factor	Expansion Cohort N=15	Follow-up Cohort N=4	All Patients N=19
Mean age ±SD, years	37.5±9.0	34.3±5.5	36.8±8.4
Female:male, n	11:4	3:1	14:5
Race, n (%)			
Caucasian	11 (73.3)	4 (100.0)	15 (78.9)
Other	4 (26.7)	0	4 (21.1)
Mean (SD) BMI (kg/m^2)	30.6 (7.46)	31.3 (5.5)	30.7 (7.0)

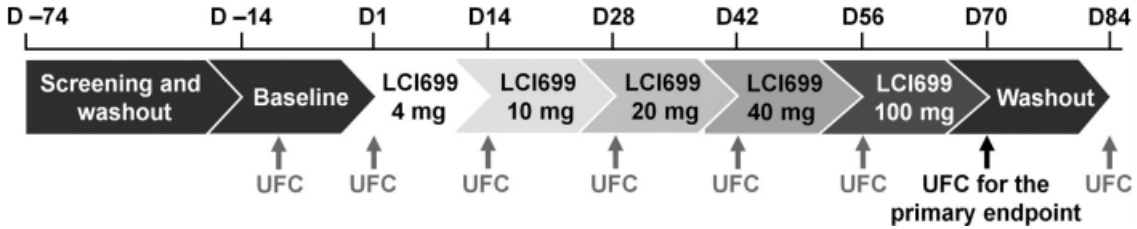
Main study and patient characteristics (Fleseriu, 2016)				
	Median time since diagnosis (range), months	63.4 (12–155.2)	82.5 (57.6–100.3)	70.2 (12.2–155.2)
	Previous treatment for CD	12 (80.0)	4 (100)	16 (84.2)
	Previous surgery, n (%)	13 (86.7)	4 (100.0)	17 (89.5)
	Mean baseline UFC ± SD, nmol/24 hours*	1630±3043	398±176[†]	1371±2734
Primary and secondary endpoints	Objectives of the extensions-1 and -2 were to provide long-term efficacy (response rate of [partially] controlled UFC) and safety data.			
Method of analysis	The analysis sets were as follows: • Full Analysis Set (FAS): all patients who re-entered the study in the Follow-up cohort, and who were newly enrolled in the study in the Expansion cohort • Safety Analysis Set (SAS): all patients that received at least 1 dose of osilodrostat in each patient cohort • Pharmacokinetic Analysis Set (PAS): all patients with at least 1 dose of osilodrostat and at least 1 post-dose pharmacokinetic assessment			
Subgroup analyses	NA			

Abbreviations: ACTH, adrenocorticotropic hormone; BID, twice daily; CD, Cushing's disease; CS, Cushing's syndrome; HRQoL, health-related quality of life; LLN=lower limit of normal; ULN, upper limit of normal; UFC=urinary free cortisol

4.2.4 LINC-1 study characteristics

Table 5 Study characteristics: LINC-1 (Bertagna, 2014) (6)

Main study and patient characteristics (Bertagna, 2014)	
Trial name	LINC-1; C2201 (part I)
NCT number	NCT01331239

Main study and patient characteristics (Bertagna, 2014)	
Objective	**Primary:** To assess the effects of 10 weeks' treatment of osilodrostat on 24-hour UFC in patients with Cushing's Disease **Secondary:** • To assess the safety and tolerability of multiple doses of osilodrostat in patients with Cushing's Disease • To assess the effect of osilodrostat on steroid hormones of the HPA-axis in plasma, urine and saliva • To assess the effects of osilodrostat on improving the metabolic abnormalities (hypertension, dyslipidemia, obesity, insulin sensitivity) of Cushing's Disease • To determine steady-state through plasma concentrations of osilodrostat
Publications – title, author, journal. year	**LCI699, a potent 11β-hydroxylase inhibitor, normalizes urinary cortisol in patients with Cushing's disease: results from a multicenter, proof-of-concept study.** Bertagna X, Pivonello R, Fleseriu M, Zhang Y, Robinson P, Taylor A, Watson CE, Maldonado M, Hamrahian AH, Boscaro M, Biller BM. J Clin Endocrinol Metab. 2014
Study type and design	A proof-of-concept, single-arm, open-label, multicenter study, designed to assess the efficacy, safety and tolerability of 10 weeks (70 days) of sequentially increasing doses of osilodrostat treatment in patients with Cushing's disease LINC-1 comprised of the following periods: • A **screening period** of up to 60 days (to allow an adequate washout period for any medications that modified cortisol levels) • A 10–14-day **baseline period** • A 10-week **treatment period** (Days 1–70); and • A 14-day **washout period** (Days 71–84) followed by the end of study evaluation 
Follow-up time	12 weeks (see LINC-2)

Main study and patient characteristics (Bertagna, 2014)	
Population (inclusion and exclusion criteria)	**Inclusion criteria:** • Patients could be included once they had given written informed consent and had confirmed CD and were willing to complete the prescribed washout periods prior to baseline efficacy assessments • Male or female patients aged 18 – 75 years • Patients must have confirmed Cushing's disease (including de novo patients) **Exclusion criteria:** • Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of enrollment, whichever is longer; or longer if required by local regulations, and for any other limitation of participation in an investigational trial based on local regulations • History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases • Patients who have been treated with mitotane during the last 6 months prior to Visit 1 • Patients who have a known inherited syndrome as the cause for hormone over-secretion (i.e. Carney Complex, McCune-Albright syndrome, MEN-1, AIP) • Patients with Cushing's syndrome due to ectopic ACTH secretion or adrenal Cushing's syndrome • Patients with pseudo-Cushing's syndrome • Patients who had undergone major surgery within 1 month before screening • Patients who had poorly controlled diabetes mellitus *Patients with moderate-to-severe Cushing's disease were enrolled.*
Intervention	Osilodrostat; 2 mg BID starting dose for the first 2 weeks. The dose was escalated every 14 days to 5, 10, 20 and 50 mg bid until UFC normalized, whereupon the dose was maintained until treatment ended (day 70). If UFC normalized during the escalation period, the dose was maintained at the effective level until the end of active treatment (Day 70). If a patient's UFC had normalized but subsequently increased to above the ULN, dose escalation was resumed.

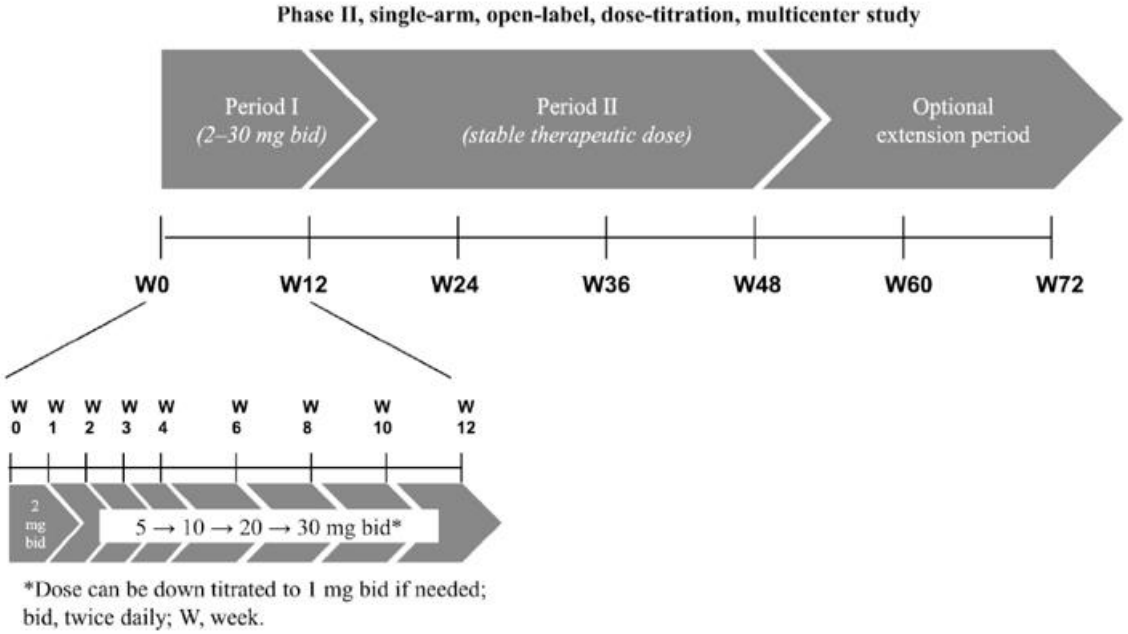
Main study and patient characteristics (Bertagna, 2014)	
Baseline characteristics	Patient Demographics and Baseline Characteristics (SAS) **Patient demographics** / **All patients (N=12)** Mean (SD) age, years: 39 (10.3) Female, n (%): 8 (66.7) Weight, mean (SD), kg: 95.6 (30.95) Height, mean (SD) cm: 167 (7.7) BMI, mean (SD), kg/m^2: 33.8 (8.54) *Abbreviations: SAS, safety analysis set; SD, standard deviation.*
Primary and secondary endpoints	**Primary** The primary endpoint was UFC ≤ULN or a ≥50% decrease from baseline at day 70. *Mean UFC level from at least two 24-hour urine samples collected at baseline and within the 10th week of treatment was used. Otherwise, UFC was assessed from a single 24-hour urine sample taken on the penultimate day of each 14-day treatment period. Responders were classed as patients whose mean UFC level from three 24-hour urine samples collected at Week 10 was ≤ ULN (as defined by the local laboratories) or represented a ≥50.0% decrease from baseline.*
Method of analysis	Patient analysis sets were as follows: • Primary variable: All patients with evaluable UFC data (at least two 24-hour measurements for both baseline and Week 10) were included in the analysis of the primary variable • Safety analysis set (SAS): All patients that received at least one dose of study drug • PK/PD data analysis: Comprised all patients with evaluable PK/PD data
Subgroup analyses	NA

Abbreviations: ACTH, adrenocorticotropic hormone; BID, twice daily; CD, Cushing's disease; CS, Cushing's syndrome; HRQoL, health-related quality of life; LLN=lower limit of normal; ULN, upper limit of normal; UFC=urinary free cortisol

4.2.5 C1201 study characteristics

Table 6 Study characteristics: C1201 (Tanaka, 2020) (7)

Main study and patient characteristics (Tanaka 2020)	
Trial name	C1201
NCT number	NCT02468193
Objective	**Primary:** To assess the percentage change from baseline in the mUFC at the individual patient level at Week-12 **Secondary:** • To assess the percentage change from baseline in the mUFC at the individual patient level at Week 24 and Week 48 • To assess the absolute and percentage change from baseline in mUFC at Week 12, Week 24 and Week 48 • To assess the complete, partial. and overall response rate at Week 12, Week 24 and Week 48 • To assess the absolute and percentage change from baseline in morning serum cortisol at the individual patient level at Week 12, Week 24 and Week 48 • To assess the absolute and percentage change from baseline in steroid hormones at the individual patient level at Week 12, Week 24 and Week 48 • To assess the change from baseline in cardiovascular-related metabolic parameters associated with Cushing's syndrome at Week 12, Week 24 and Week 48 • To assess the general safety of osilodrostat • To assess the change from baseline in Patient-Reported Outcomes (HRQoL) at individual patient level at Week 12, Week 24 and Week 48 using the CushingQoL and Beck Depression Inventory-II instruments • To evaluate osilodrostat PK in patients with CS
Publications – title, author, journal. year	**A multicenter, phase 2 study to evaluate the efficacy and safety of osilodrostat, a new 11β-hydroxylase inhibitor, in Japanese patients with endogenous Cushing's syndrome other than Cushing's disease.** Tanaka T, Satoh F, Ujihara M, Midorikawa S, Kaneko T, Takeda T, Suzuki A, Sato M, Shimatsu A. Endocr J. 2020
Study type and design	Phase II, single-arm, open-label, dose titration, multi-center study to assess osilodrostat in Japanese patients with all types of endogenous Cushing's syndrome except Cushing's disease caused by adrenal tumor/hyperplasia or ectopic adrenocorticotropic hormone syndrome. The study comprised three distinct study periods: • **Study Period I** (Week 0 [Day 1]) to Week-12): In this study period, the aim was to achieve a stable therapeutic dose of osilodrostat. • **Study Period II** (After Week-12 to Week-48): In this period, the aim was to assess efficacy and long-term safety, on the stable therapeutic dose of osilodrostat achieved in Study Period I. During this period, only patients who tolerated and agreed to continue osilodrostat treatment continued the study.

Main study and patient characteristics (Tanaka 2020)	
	• **Extension phase (optional)** (After Week 48): Patients who entered the extension period were to be continued to be treated with the study drug without interruption to be assessed for efficacy and safety. Patients who continued to benefit from study treatment as assessed by the study investigator and who completed Week 72 were to be invited to participate in a separate long-term safety follow-up study. The optional extension period ended after all patients had completed Week 72 or had discontinued early.  *Dose can be down titrated to 1 mg bid if needed; bid, twice daily; W, week.
Follow-up time	Optional **extension period** (After Week-48): Patients were re-consented at Week-48 to participate in the extension period. Patients who entered the extension period were to be continued to be treated with the study drug without interruption to be assessed for efficacy and safety. • **Post-treatment Follow-up**: All patients had 30 days safety follow-up after the last dose of study treatment
Population (inclusion and exclusion criteria)	**Inclusion criteria:**

Main study and patient characteristics (Tanaka 2020)	
	• Patients with confirmed Cushing's Syndrome [i.e. ectopic corticotropin syndrome, adrenal adenoma, adrenal carcinoma, ACTH-Independent Macronodular Adrenal Hyperplasia (AIMAH), or Primary Pigmented Nodular Adrenal Dysplasia (PPNAD)] • Patients who were expected to remain in stable condition for at least 5 months • For patients on medical treatment for hypercortisolism due to Cushing's syndrome, the washout periods were completed prior to baseline efficacy assessments • Patients (both genders) aged 18–85 years **Exclusion criteria:** • Patients with Cushing's Disease • History of hypersensitivity to osilodrostat or to drugs of similar chemical classes • History of malignancy of any organ system (with the exception of: a) malignancy causing ectopic corticotropin syndrome, or b) localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases • Patients receiving treatment for malignancy (e.g., cytotoxic chemotherapy, molecular targeting drugs, somatostatin analogue) within 4 weeks or ≤ 5 x half-life of the agent (whichever was longer) before first dose of osilodrostat • Patients with risk factors for QTc prolongation or Torsades de Pointes
Intervention	Osilodrostat; 2 mg BID starting dose, with titration up to a maximum of 30 mg bid **Study period I**: The titration schedule was 2 mg bid, 5 mg bid, 10 mg bid, 20 mg bid, and 30 mg bid. The maximum dose was 30 mg BID. • **Study period II**: The stable therapeutic dose of osilodrostat achieved in Study Period I • **Optional Extension Period**
Baseline characteristics	

Patient demographics	**All patients (N=9)**
Median (range) age, years	46.0 (20–75)
≥65 years, n (%)	3 (33.3)
Female, n (%)	7 (77.8)
Weight, median (range), kg	59.30 (47.0–106.5)
Height, median (range), cm	156.00 (145.0–170.0)
BMI, median (range), kg/m^2	23.876 (19.31–38.19)
Type of disease, n (%)	
AIMAH	1 (11.1)
Adrenal adenoma	5 (55.6)

Main study and patient characteristics (Tanaka 2020)		
	Ectopic corticotropin syndrome	3 (33.3)
	Previous treatment, n (%)*	
	Surgery	1 (11.1)
	Medication†	5 (55.6)
	Radiotherapy	0 (0.0)
	Median mUFC	841.80
Primary and secondary endpoints	**Primary endpoint:** • The percentage change from baseline in the mUFC at the individual patient level at Week-12 **Secondary endpoints:** • The percentage change from baseline in the mUFC at the individual patient level at Week-24 and Week-48 • The absolute and percentage change from baseline in mUFC at Week-12, Week-24 and Week-48 • The complete, partial. and overall response rate at Week-12, Week-24 and Week-48 • The absolute and percentage change from baseline in morning serum cortisol at the individual patient level at Week-12, Week-24 and Week-48 • The absolute and percentage change from baseline in steroid hormones at the individual patient level at Week-12, Week-24 and Week-48 • The change from baseline in cardiovascular-related metabolic parameters associated with Cushing's Syndrome at Week-12, Week-24 and Week-48 • The general safety of osilodrostat • The change from baseline in Patient-Reported Outcomes (HRQoL) at individual patient level at Week-12, Week-24 and Week-48 using the CushingQoL and Beck Depression Inventory-II instruments • Osilodrosat PK in patients with Cushing's Syndrome	
Method of analysis	The analysis sets were as follows: • Full Analysis Set (FAS): Comprises all enrolled patients who received at least one dose of osilodrostat • Safety Analysis Set (SAS): Comprises all patients who received at least one dose of osilodrostat and had at least one valid post-baseline safety assessment • Pharmacokinetic Analysis Set (PAS): Comprises all patients who received at least one dose of osilodrostat and had at least one evaluable PK concentration at any visit (post-first-dose)	

Main study and patient characteristics (Tanaka 2020)	
	Due to the limited sample size and patients enrolled with various disease types, no statistical hypothesis was set up for this study. Given the small sample size, data were primarily described on an individual basis or by disease type (ectopic corticotropin syndrome, adrenal adenoma, adrenal carcinoma, AIMAH, and PPNAD)
Subgroup analyses	NA

Abbreviations: ACTH, adrenocorticotropic hormone; BID, twice daily; CD, Cushing's disease; CS, Cushing's syndrome; HRQoL, health-related quality of life; LLN=lower limit of normal; ULN, upper limit of normal; UFC=urinary free cortisol

4.3 Main characteristics of included studies for comparators

This section will provide an overview for the relevant studies identified in the SLR for the comparators: ketoconazole (Castinetti 2014 (8), Castinetti 2008 (9)), metyrapone (Daniel 2015 (10)) and pasireotide (G2304 (11), B2305 (12), SEASCAPE (13), B2208 (14), " Italian real-world evidence study" (15)).

4.3.1 Castinetti et al 2014 study characteristics

Table 7 Study characteristics (Castinetti 2014) (8)

Main study and patient characteristics (Castinetti 2014)	
Trial name	Castinetti 2014
NCT number	NA
Objective	To evaluate efficacy and tolerance, particularly hepatic tolerance, to clarify whether this drug should still be considered in therapeutic algorithms of hypercortisolism.
Publications – title, author, journal. year	**Ketoconazole in Cushing's disease: is it worth a try?** Castinetti F, Guignat L, Giraud P, Muller M, Kamenicky P, Drui D, Caron P, Luca F, Donadille B, Vantyghem MC, Bihan H, Delemer B, Raverot G, Motte E, Philippon M, Morange I, Conte-Devolx B, Quinquis L, Martinie M, Vezzosi D, Le Bras M, Baudry C, Christin-Maitre S, Goichot B, Chanson P, Young J, Chabre O, Tabarin A, Bertherat J, Brue T. J Clin Endocrinol Metab. 2014
Study type and design	Retrospective, multicenter (France), cohort study (year 1995-2012) reviewing data from patients treated by ketoconazole as a single agent for Cushing's Disease The studied population was divided in three groups: • Pre-surgical

<table>
<tr><th colspan="2">Main study and patient characteristics (Castinetti 2014)</th></tr>
<tr><td></td><td>• Primary treatment (treatment naïve)
• Second-line treatment (treatment after either a non successful operation or radiotherapy)</td></tr>
<tr><td>Follow-up time</td><td>Up to 135 months</td></tr>
<tr><td>Population (inclusion and exclusion criteria)</td><td>Inclusion:
• Treatment of ketoconazole as only treatment for active Cushing’s disease
• Diagnosis of Cushing based on current guidelines
Exclusion:
• Not applicable due to retrospective study design</td></tr>
<tr><td>Intervention</td><td>Ketoconazole; 200mg p.o., 2-3 times daily
Starting dose 400-600mg/day, max dose 1200mg/day
• Ketoconazole dose was increased by 200 mg/day every 7 to 28 days until normalization was achieved.</td></tr>
<tr><td>Baseline characteristics</td><td>N=200
<table><tr><th>Patient demographics</th><th>All patients (N=200)</th></tr><tr><td>Median ± SD (range) age, years</td><td>41.9 ±15.8 (8 – 87)</td></tr><tr><td>Male, n (%)</td><td>44 (22)</td></tr><tr><td>Female, n (%)</td><td>156 (78)</td></tr><tr><td>Type of disease, n (%)</td><td></td></tr><tr><td>Microadenoma</td><td>156 (78)</td></tr><tr><td>Macroadenoma</td><td>106 (53.4)</td></tr><tr><td>Lack of obvious adenoma</td><td>36 (18.2)</td></tr><tr><td>Previous treatment, n (%)</td><td></td></tr><tr><td>Transsphenoidal surgery, n (%)</td><td>144 (72)</td></tr><tr><td>Radiotherapy, n (%)</td><td>47 (23.6)</td></tr><tr><td>Second surgery, n (%)</td><td>16 (8)</td></tr><tr><td>Mean baseline UFC ± SD, nmol/24 hours (range)</td><td>4.1±5.3 x ULN (1.1-40)</td></tr></table></td></tr>
<tr><td>Primary and secondary endpoints</td><td>• UFC level at the final assessment
• Controlled, partial and non-responder rate at the final assessment
• Assessment of clinical signs of hypercortisolism including blood pressure, plasma potassium and glucose tolerance at the final assessment</td></tr>
</table>

Main study and patient characteristics (Castinetti 2014)	
	• Assessment of liver status including aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), and gamma-glutamyl transpeptidase • Adverse events • Discontinuation rate at final assessment including reason discontinuation *Patients were considered:* - *Controlled if they had normal 24-hour UFC at 2 consecutive evaluations.* - *Partial control was defined as a decrease in UFC of more than 50% without normalization.* - *Not controlled was defined by a decrease in UFC of less than 50% and/or immediate clinical or biological intolerance leading to ketoconazole discontinuation.* *Improvement in hypertension was defined as a decrease of at least 10 mm Hg of systolic and/or diastolic blood pressure in patients with hypertension.* *Improved glycemic control was defined as 1 or more of the following: a decrease of insulin dose (>10% of the total dose), a decrease in the number of antidiabetic drugs, and an improvement of hemoglobin A1c (>0.5% when available) without addition of other antidiabetic drugs* *Final assessment could vary from patient to patient.* *For each patient final UFC, final dose, length of ketoconazole treatment, length of follow-up period, and reason for withdrawal were recorded.*
Method of analysis	NR
Subgroup analyses	NA

Abbreviations: ACTH, adrenocorticotropic hormone; BID, twice daily; CD, Cushing's disease; CS, Cushing's syndrome; HRQoL, health-related quality of life; LLN=lower limit of normal; ULN, upper limit of normal; UFC=urinary free cortisol

In additon to the available studies for ketoconazole, is should be noted that the EMA reported in the special warnings of the smpc the need for monitoring of liver function in all patients receiving ketoxonazole. Close follow-up of patients is required due to the risk of serious hepatic toxicity. (16)

4.3.2 Castinetti et al 2008 study characteristics

Table 8 Study characteristics (Castinetti 2008) (9)

Main study and patient characteristics (Castinetti 2008)	
Trial name	Castinetti 2008
NCT number	NA
Objective	To analyze the long-term hormonal effects and tolerance of ketoconazole in patients with Cushing's disease
Publications – title, author, journal. year	**Ketoconazole revisited: a preoperative or postoperative treatment in Cushing's disease.** Castinetti F, Morange I, Jaquet P, Conte-Devolx B, Brue T. Eur J Endocrinol. 2008
Study type and design	Retrospective, single centre (France), cohort study (year 1995-2005) reviewing data from patients treated by ketoconazole as a single agent for Cushing's Disease The studied population was divided in two groups: • No pituitary surgery group - those who were not treated surgically before ketoconazole • After pituitary surgery group – those who had ketoconazole as an adjunctive treatment
Follow-up time	Between 6 to 72 months (mean of 23 months)
Population (inclusion and exclusion criteria)	**Inclusion:** • Treatment of ketoconazole as only treatment for active Cushing's disease **Exclusion:** • Not applicable due to retrospective study design
Intervention	Ketoconazole Starting dose was 200–400 mg/day, max dose1200 mg/day The dose of ketoconazole was increased by 200 mg per day every 10–15 days until biochemical remission
Baseline characteristics	N= 38

Patient demographics	No pituitary surgery group (N=16)	After pituitary surgery group (N=)	All patients (N=33)*
Median (range) age, years	44 (24-73)	42 (18-66)	

Main study and patient characteristics (Castinetti 2008)				
	Male, n	2	3	
	Female, n	14	14	
	Previous treatment, n (%)			
	Transsphenoidal surgery, n			17
	Unsuccessful pituitary surgery			15
	Mean baseline UFC, nmol/24 hours (range)	1792 (275-16700)	2124 (248-12500)	
	**The 5 patients with immediate cessation of treatment because of intolerance have been excluded*			
Primary and secondary endpoints	• UFC level • Controlled and non controlled rate • Assessment of clinical signs of hypercortisolism, weight, blood pressure • Assessment of blood glucose • Assessment of liver status including aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), and gamma-glutamyl transpeptidase *Note:* *Patients were considered controlled if they had normal 24-hour UFC at 2 consecutive evaluations.* *Final assessment could vary from patient to patient.* *For each patient final UFC, final dose, length of ketoconazole treatment, length of the follow-up period were recorded.*			
Method of analysis	NR			
Subgroup analyses	NA			

4.3.3 Daniel et al 2015 study characteristics

Table 9 Study characteristics Daniel et al 2015 (10)

Main study and patient characteristics (Daniel et al 2015)	
Trial name	Daniel et al. 2015
NCT number	NA
Objective	To assess the effectiveness of metyrapone therapy in a contemporary series of patients with CS, by performing a retrospective study of patients treated in the United Kingdom.
Publications – title, author, journal. year	**Effectiveness of Metyrapone in Treating Cushing's Syndrome: A Retrospective Multicenter Study in 195 Patients.**

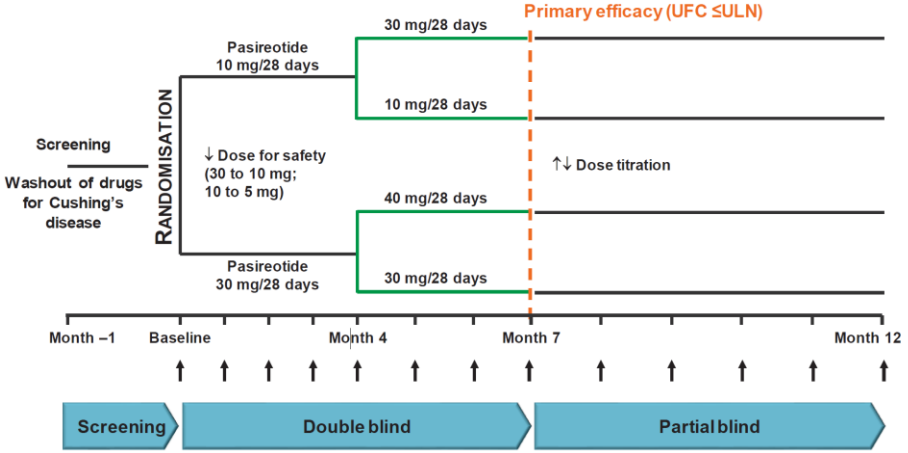
Main study and patient characteristics (Daniel et al 2015)	
	Daniel E, Aylwin S, Mustafa O, Ball S, Munir A, Boelaert K, Chortis V, Cuthbertson DJ, Daousi C, Rajeev SP, Davis J, Cheer K, Drake W, Gunganah K, Grossman A, Gurnell M, Powlson AS, Karavitaki N, Huguet I, Kearney T, Mohit K, Meeran K, Hill N, Rees A, Lansdown AJ, Trainer PJ, Minder AE, Newell-Price J. J Clin Endocrinol Metab. 2015
Study type and design	Multicenter, retrospective study was performed across 13 University hospital centers in England and Wales, members of the United Kingdom Endocrine Neoplasia Collaboration. Patients treated with metyrapone were identified through pharmacy records and electronic databases. Patients with a diagnosis of CS and treated with metyrapone between 1997 and 2013 were included.
Follow-up time	NA
Population (inclusion and exclusion criteria)	Patients with a diagnosis of Cushing's Syndrome
Intervention	Metyrapone, Patients were treated either with a dose titration regimen, i.e. metyrapone dose was up-titrated according to response to achieve a biochemical target for cortisol, or a block-and-replace regimen, where the dose of metyrapone was quickly up-titrated to achieve blockade of cortisol synthesis and a replacement dose of glucocorticoid was added to provide background physiological levels. Table 3 of the Daniels et al article shows the different total daily dosage of metyrapone for patients treated with a dose titration regimen.
Baseline characteristics	A total of 195 patients were treated with metyrapone across the 13 centers. Most patients had CD (115 patients, of which 37 with macroadenoma) with the remainder having ectopic ACTH syndrome (EAS) (37), adrenocortical carcinoma (ACC) (10), and benign adrenal disease (30 adrenal adenoma [AA], ACTH-independent macronodular adrenal hyperplasia [2] and primary pigmented nodular adrenal hyperplasia [1]) 31 patients received metyrapone as secondary treatment after either surgery (21) or pituitary radiotherapy (17): 21/31 as monotherapy and 10/31 as combination therapy There was a female predominance in all causes of CS except EAS (female patients:74% CD, 49% EAS, 86% AA, and 80% ACC). At initiation of treatment, there was a wide age distribution, with 76% of patients aged 30–69 years (age range 1–81, median age 48, average age 49.6 ± 15.7 y), and 32% of patients (n = 63) were women in the reproductive ages 18–45. (N=195) Comorbidities at presentation included hypertension (64.6%) and diabetes mellitus (35.3%) (N=195)
Primary and secondary endpoints	Biochemical targets for treatment (eucortisolemia) were defined as a mean CDC value of 150–300 nmol/L (10.9 µg/dL), which has been shown to equate to a normal cortisol production rate as assessed by stable isotopic methodology (11), a UFC level below the upper limit of normal (ULN) for the assay used or a 9 AM serum cortisol within target. Although 9 AM serum cortisol is occasionally being used as a sole test for evaluating patients' response to treatment, there is currently no standardized agreement for what values of this test represent appropriate control. Two different levels of

Main study and patient characteristics (Daniel et al 2015)	
	target 9 AM cortisol weretherefore assessed: 1) below the ULN for the assay used, or less than 600 nmol/L (21.7 µg/dL) if the ULN was higher than this value; and 2) a recommended value of 331 nmol (12.0 µg/dL) (12). Cortisol levels were reported in nmol/L and divided by 27.59 to calculate the equivalent value in µg/dL. There was a wide range of UFC assays used with variable reference range of normal values; therefore, UFC values were converted to multiples of the ULN for the assay and this value was used for statistical comparisons
Method of analysis	NR
Subgroup analyses	NA

4.3.4 G2304 study characteristics

Table 10 Study characteristics: G2304 trial (11, 17)

Main study characteristics (G2304 trial)	
Trial name	G2304
NCT number	NCT01374906
Objective	To describe results of the first Phase 3 trial of long-acting pasireotide in patients with Cushing's disease.
Publications – title, author, journal. year	**Efficacy and safety of once-monthly pasireotide in Cushing's disease: a 12 month clinical trial.** Lacroix A, Gu F, Gallardo W, Pivonello R, Yu Y, Witek P, Boscaro M, Salvatori R, Yamada M, Tauchmanova L, Roughton M, Ravichandran S, Petersenn S, Biller BMK, Newell-Price J; Pasireotide G2304 Study Group. Lancet Diabetes Endocrinol. 2018 **Long-term efficacy and safety of once-monthly pasireotide in Cushing's disease: A Phase III extension study.** Fleseriu M, Petersenn S, Biller BMK, Kadioglu P, De Block C, T'Sjoen G, Vantyghem MC, Tauchmanova L, Wojna J, Roughton M, Lacroix A, Newell-Price J. Clin Endocrinol (Oxf). 2019

Main study characteristics (G2304 trial)	
Study type and design	Study G2304 is a global, multi-center, randomized, double-blind, Phase 3 study evaluating the efficacy and safety of pasireotide LAR in patients with CD. The study is divided into a core phase and an extension phase.  In the core phase, patients first underwent a 30-day screening period, after which there was randomization 1:1 into a starting dose of either 10 mg or 30 mg pasireotide LAR once every 28 days for 4 months. Doses could be titrated at Months 4, 7, and 9 depending on the patient's mUFC levels. The total duration of treatment in the core phase was 12 months. Patients who completed the core phase, showed acceptable tolerability to treatment, achieved/maintained ≤1.0 x ULN at Month 12, or were deemed to have received clinical benefit by the investigator, and met additional extension phase inclusion criteria were able to continue treatment in the extension phase based on ending treatment dosage.
Follow-up time	Core study: Up to 12 months Extension study: Up to 36 months
Population (inclusion and exclusion criteria)	**Inclusion criteria:** A confirmed pituitary source of Cushing's disease was defined as: • Magnetic resonance imaging (MRI) confirmation of a pituitary adenoma >6 mm with positive dynamic test (eg, corticotrophin-releasing hormone [CRH] or high-dose dexamethasone test); or • Inferior petrosal sinus sampling gradient ≥3 after CRH/desmopressin stimulation or ≥2 at baseline for patients with a pituitary adenoma ≤6 mm; or

Main study characteristics (G2304 trial)	
	• Histopathology confirming an adrenocorticotropic hormone (ACTH)-staining adenoma (in patients who had prior pituitary surgery) **Exclusion criteria:** Patients who were candidates for surgery; pituitary irradiation within 10 years, previous pasireotide therapy, or mitotane therapy within 6 months; compression of the optic chiasm causing any visual field defect requiring surgical intervention; poorly controlled diabetes on antidiabetic medication (defined as glycated haemoglobin [HbA1c] >8%); symptomatic cholelithiasis at study entry; liver disease such as cirrhosis, chronic active hepatitis, or chronic persistent hepatitis, or patients with alanine aminotransferase and/or aspartate aminotransferase >2x the upper limit of normal (ULN) or serum bilirubin >1·5xULN; risk factors for torsades de pointes, congestive heart failure, unstable angina, 4 sustained ventricular tachycardia, ventricular fibrillation, advanced heart block, or a history of acute myocardial infarction within 1 year of study entry.
Intervention	Pasireotide, suspension for intramuscular injection, once every 28 days Starting dose 10 or 30 mg Max dose 40 mg Four dose levels available
Baseline characteristics	

Factor	**10 mg group N=74**	**30 mg group N=76**	**All Patients N=150**
Mean age, (SD) years	38,3 (12,5)	38,6 (13,0)	38,5 (12,7)
Female sex – n (%)	58 (78)	60 (79)	118 (79)
Pituitary adenoma – n (%)			
Microadenoma	34 (46)	34 (45)	68 (45)
Macroadenoma	20 (27)	29 (38)	49 (33)
Mean time since diagnosis (range), months	22,3 (9,5–53,7)	22,4 (5,0–64,3)	22,3 (6,6–62,5)
Mean baseline UFC, nmol/24 hours	2,8 (1,5)	2,9 (2,0)	2,8 (1,8)
Previous treatment – n (%)			
Surgery	59 (80)	64 (84)	123 (82)
Medical therapy	32 (43)	30 (39)	62 (41)
Cushing's disease status - n (%)			
Persistent or recurrent	59 (80)	64 (84)	123 (82)
De novo*	15 (20)	12 (16)	27 (18)

**27 (18%) patients did not have pituitary surgery before study entry for the following reasons: 15 (10%) refused surgery, 11 (7%) were poor candidates for surgery, and one (1%) could not access a surgical facility*

Main study characteristics (G2304 trial)	
Primary and secondary endpoints	Primary objective – percentage of patients that attained a mUFC concentration of less than or equal to the ULN at month 7, regardless of dose titration. Key secondary objective – percentage of patients that attained a mUFC concentration of less than or equal to the ULN at month 7 and without dose uptitration at month 4
Method of analysis	Efficacy analyses using the intention-to-treat principle (based on randomised dose).
Subgroup analyses	NA

4.3.5 B2305 study characteristics

Table 11 Study characteristics: B2305 trial (12, 18-20)

Main study characteristics (B2305 trial)	
Trial name	B2305 trial
NCT number	NCT00434148
Objective	To evaluate the safety and efficacy of two different doses of Pasireotide in patients with de novo or recurrent/persistent Cushing's Disease.
Publications – title, author, journal. year	**A 12-month phase 3 study of pasireotide in Cushing's disease.** Colao A, Petersenn S, Newell-Price J, et al.; A 12-month phase 3 study of pasireotide in Cushing's disease. N Engl J Med 2012 **Long-term treatment of Cushing's disease with pasireotide: 5-year results from an open-label extension study of a Phase III trial.** Petersenn S, Salgado LR, Schopohl J, Portocarrero-Ortiz L, Arnaldi G, Lacroix A, Scaroni C, Ravichandran S, Kandra A, Biller BMK. Endocrine. 2017 **Pasireotide can induce sustained decreases in urinary cortisol and provide clinical benefit in patients with Cushing's disease: results from an open-ended, open-label extension trial.** Schopohl J, Gu F, Rubens R, Van Gaal L, Bertherat J, Ligueros-Saylan M, Trovato A, Hughes G, Salgado LR, Boscaro M, Pivonello R. Pituitary. 2015

Main study characteristics (B2305 trial)	
	Treatment effectiveness of pasireotide on health-related quality of life in patients with Cushing's disease. Webb SM, Ware JE, Forsythe A, Yang M, Badia X, Nelson LM, Signorovitch JE, McLeod L, Maldonado M, Zgliczynski W, de Block C, Portocarrero-Ortiz L, Gadelha M. Eur J Endocrinol. 2014
Study type and design	Multicenter, randomized, double-blind
Follow-up time	Core study: Up to 12 months Extension study: Up to 76.6 months
Population (inclusion and exclusion criteria)	**Inclusion criteria:** Patients (aged ≥18 years) with a confirmed diagnosis of persistent/recurrent or de novo (if not surgical candidates) Cushing's disease, defined as: mean 24-hour urinary free cortisol (UFC), calculated from four 24-hour urine samples collected within 2 weeks, ≥1.5x the upper limit of normal (ULN) and morning plasma adrenocorticotropic hormone (ACTH) ≥5ng/L (≥1.1nmol/L). A pituitary source of the Cushing's syndrome was confirmed by at least one of the following: pituitary macroadenoma on magnetic resonance imaging (MRI), bilateral inferior petrosal sinus sampling central-to-peripheral ACTH gradient >2 basally, or >3 after corticotropin releasing hormone stimulation in patients with a microadenoma, or histopathology confirming an ACTH staining adenoma. For patients on medical treatment for Cushing's disease, the following washout periods must have been completed before baseline efficacy assessments were performed: • Inhibitors of steroidogenesis (ketoconazole, metyrapone): 1 week • Dopamine agonists (bromocriptine, cabergoline): 4 weeks • Rosiglitazone: 1 week • Octreotide LAR and Lanreotide Autogel: 8 weeks • Lanreotide SR: 4 weeks • Octreotide (immediate release formulation): 1 week **Exclusion criteria:** Pituitary irradiation within the last 10 years; mitotane within the last 6 months; optic chiasm compression causing any visual-field defect; Cushing's syndrome due to non-pituitary sources or an inherited syndrome; glucocorticoid-remediable aldosteronism; uncontrolled hypothyroidism; symptomatic cholelithiasis; HbA1C >8%; abnormal coagulation; significantly impaired cardiovascular function; QTc >480ms; liver disease; Karnofsky performance status <60; an immunocompromised state.

Main study characteristics (B2305 trial)

Intervention

Pasireotide, subcutaneous injection, twice daily

Starting dose 600 µg (82 patients) or 900 µg (80 patients) per injection

Max dose 1200 µg per injection

Baseline characteristics

Factor	600 µg group N=82	900 µg group N=80	All Patients N=162
Mean age, years	41	40	40
Female sex – n (%)	62 (76)	64 (80)	126 (78)
Race, n (%)			
Caucasian	65 (79)	62 (78)	127 (78)
Asian	10 (12)	10 (12)	20 (12)
Mean time since diagnosis (range), months	53.4 (0.1–341.8)	54.7 (0.1–372.1)	54.0 (0.1–372.1)
Previous medication treatment, n (%)	36 (44)	42 (52)	78 (48)
Previous surgery, n (%)	64 (78)	64 (80)	128 (79)
Previous pituitary irradiation, n (%)	3 (4)	4 (5)	7 (4)
Mean baseline UFC ± range, nmol/24 hours	1156 (220-22,944)	782 (195-6123)	970 (195-22,944)
Severity of hypercortisolism - n (%)			
Mild	12 (15)	14 (18)	26 (16)
Moderate	26 (32)	40 (50)	66 (41)
Severe	28 (34)	13 (16)	41 (25)
Very severe	11 (13)	9 (11)	20 (12)

Primary and secondary endpoints

Primary endpoint: number of UFC ≤ ULN responders at month 6 without a prior dose increase

Secondary endpoints:

- a urinary free cortisol level at or below the upper limit of the normal range at months 3, 6, and 12, regardless of dose adjustment;
- partial control of hypercortisolism (a urinary free cortisol level above the upper limit of the normal range but reduced by ≥50% from baseline);
- levels of plasma corticotropin, urinary free cortisol, and serum and salivary cortisol over time;
- changes in clinical signs and symptoms;
- quality of life;

Main study characteristics (B2305 trial)	
	• safety.
Method of analysis	Intention-to-treat population at all time points for efficacy and safety analysis.
Subgroup analyses	*NA*

4.3.6 SEASCAPE study characteristics

Table 12 Study characteristics SEASCAPE (13)

Main study characteristics (SEASCAPE)	
Trial name	SEASCAPE
NCT number	NCT01582061
Objective	To describe safety and efficacy results of an international. real-world study of pasireotide subcutaneous in a large population of patients with Cushing's disease in clinical practice.
Publications – title, author, journal. year	**Safety and efficacy of subcutaneous pasireotide in patients with Cushing's disease: results from an open-label, multicenter, single-arm, multinational. expanded-access study** Fleseriu M, Iweha C, Salgado L, Mazzuco TL, Campigotto F, Maamari R, Limumpornpetch P. *Frontiers in endocrinology,* 10, p. 436. 2019
Study type and design	An Open-label, Multi-center international. Expanded Access Study of Pasireotide s.c. in Patients With Cushing's Disease Non-RCT single arm
Follow-up time	Patients received treatment until pasireotide s.c. was approved for commercial use and reimbursed in each respective country or until December 31, 2015 (December 31, 2016 for sites in South Korea and Brazil), whichever occurred first.
Population (inclusion and exclusion criteria)	**Inclusion**: Adult patients (>18 years old) with persistent or recurrent Cushing's disease, or de novo patients not considered candidates for surgery, were recruited. Patients must have had active disease, as evidenced by: mean of three 24 h UFC samples collected during a 3-week screening period above the upper limit of normal (ULN; 137.95 nmol/24 h), which was determined from a central laboratory reference; morning plasma ACTH within or above the normal range; and confirmed pituitary source of the disease. For

Main study characteristics (SEASCAPE)	
	patients on previous medical treatment for Cushing's disease, the following washout periods were required prior to screening assessments: mitotane, 6 months; long-acting octreotide, lanreotide Autogel, 8 weeks; dopamine agonists (bromocriptine, cabergoline), mifepristone, lanreotide sustained release, 4 weeks; steroidogenesis inhibitors (ketoconazole, metyrapone, rosiglitazone), octreotide immediate release, 1 week **Exclusion**: Patients were excluded from the study if they had any of the following criteria: prior exposure to pasireotide sc; radiotherapy <4 weeks before screening; tumor compressing the optic chiasm, causing visual field defects; symptomatic cholelithiasis; diabetes with poorly controlled blood glucose levels (glycated hemoglobin [HbA1c] >8%); QTcF >450ms at screening and any other clinically significant impairment of cardiovascular function; pregnancy.
Intervention	After a 21-day screening period, enrolled patients in EU countries received pasireotide sc starting doses of 900 µg bid; the study protocol was amended in 2013 (patient enrollment began in 2011) so that all EU patients received starting doses of 600 µg bid to align with the recommendation by the Committee for Medicinal Products for Human Use and the European Medicines Agency that the starting dose of pasireotide sc should be 600 µg bid (21). Patients in non-EU countries received starting doses of 900 µg bid (600 µg bid in patients with impaired glucose metabolism). The dose could be increased (after >2 months' treatment if UFC was not controlled) or decreased (for sustained UFC normalization/tolerability issues) in 300 µg increments or decrements to a maximum of 900 µg bid or a minimum of 300µg bid.
Baseline characteristics	

	Pasireotide 600 µg bid *N* = 49	Pasireotide 900 µg bid *N* = 55	All patients *N* = 104
Mean age, years (SD)	45.5 (13.1)	39.9 (12.6)	42.5 (13.1)
Female, *n* (%)	37 (75.5)	47 (85.5)	84 (80.8)
Race, *n* (%)			
Caucasian	39 (79.6)	36 (65.5)	75 (72.1)
Black or African American	3 (6.1)	2 (3.6)	5 (4.8)
Asian	6 (12.2)	15 (27.3)	21 (20.2)
Other	1 (2.0)	2 (3.6)	3 (2.9)
Median time from diagnosis to first pasireotide dose, months(range)	60.3 (0.7–309.0)	34.3 (1.0–298.0)	39.7 (0.7–309.0)
Cushing's disease status, *n* (%)			
De novo	8 (16.3)	5 (9.1)	13 (12.5)
Persistent/recurrent	41 (83.7)	50 (90.9)	91 (87.5)
Previous pituitary surgery, *n* (%)			
Yes	38 (77.6)	46 (83.6)	84 (80.8)

Main study characteristics (SEASCAPE)				
	No	3 (6.1)	4 (7.3)	7 (6.7)
	Missing	8 (16.3)	5 (9.1)	13 (12.5)
	Median time from previous surgery to first pasireotide dose,months (range)	44.8 (4.1–306.1)	30.5 (1.9–294.1)	38.1 (1.9–306.1)
	Prior pituitary irradiation, *n* (%)			
	Yes	12 (24.5)	15 (27.3)	27 (26.0)
	No	37 (75.5)	40 (72.7)	77 (74.0)
	Median time from last pituitary irradiation to first pasireotide dose, months (range)	56.9 (8.5–169.9)	29.0 (3.1–205.8)	33.3 (3.1–205.8)
Primary and secondary endpoints	The primary objective of the study was to document the safety of pasireotide s.c.; the primary endpoint was the proportion of patients with drug-related grade 3/4 AEs or drug-related SAEs. Key secondary endpoints, which were assessed at weeks 12, 24, and 48, included: proportion of patients with mUFC≤ULN; proportion of patients achieving at least 50% reduction from baseline in mUFC; changes from baseline in clinical signs and symptoms; and changes from baseline in health-related QoL (HRQoL).			
Method of analysis	The analysis populations were defined as follows: Safety assessments were performed on all patients who received at least one dose of pasireotide s.c. and had at least one post-baseline safety assessment and are summarized descriptively. Secondary efficacy assessments were performed on all patients who received at least one dose of pasireotide s.c. and are summarized descriptively with corresponding two-sided 95% exact confidence intervals (CIs) for weeks 12, 24, and 48.			
Subgroup analyses	Diabetic vs non-diabetic patients Shift in fasting plasma glucose, fasting plasma glucose and HbA1c levels from baseline to last post-baseline value according to diabetic status.			

4.3.7 B2208 study characteristics

Table 13 Study characteristics B2208 study (14)

Main study characteristics (B2208)	
Trial name	CSOM230B2208
NCT number	NCT00088608

Main study characteristics (B2208)	
Objective	The objective of this study was to evaluate the efficacy and safety of extended treatment with pasireotide.
Publications – title, author, journal. year	**Extended treatment of Cushing's disease with pasireotide: results from a 2-year, Phase II study.** Boscaro M, Bertherat J, Findling J, Fleseriu M, Atkinson AB, Petersenn S, Schopohl J, Snyder P, Hughes G, Trovato A, Hu K, Maldonado M, Biller BM. *Pituitary.* 2014
Study type and design	Open-ended, single-arm extension study and a planned extension to the 15-day core study
Follow-up time	Core study: 15 days Extension study: 6 months
Population (inclusion and exclusion criteria)	**Inclusion:** <u>Core study:</u> • Eligible patients were at least 18 yr of age and had clinically and biochemically confirmed ACTH-dependent Cushing's disease within 2 months of study entry. Patients were required to have a Karnofsky performance status of at least 60 and either have de novo Cushing's disease and be candidates for pituitary surgery or have persistent or recurrent Cushing's disease after surgery without having received any prior pituitary irradiation. <u>Extension phase:</u> • Patients with Cushing's disease (aged≥18 years) who had completed the 15-day, proof-of-concept, Phase II core study were eligible to enter this extension phase if they had normal 24-h UFC levels at the end of the core study and/or, in the opinion of the investigator, obtained significant clinical benefit with pasireotide. • Patients were included if they did not experience any unacceptable AEs or tolerability issues during the original 15-day treatment period. Female patients of childbearing potential who had not undergone clinically documented total hysterectomy and/or ovariectomy, or tubal ligation, had to agree to use barrier contraception throughout the course of the extension study and for 1 month after the study had ended. **Exclusion:** <u>Core study:</u> • Key exclusion criteria included Cushing's syndrome due to ectopic ACTH secretion, hypercortisolism secondary to adrenal tumors or nodular (primary) bilateral adrenal hyperplasia, a known inherited syndrome as a cause forACTHhypersecretion (e.g. Carney complex,MEN-1), and McCune-Albright syndrome. Patients who were not euthyroid, had received octreotide LAR or any other long-acting somatostatin analogue within 8 wk of study entry, had poorly

Main study characteristics (B2208)	
	controlled diabetes mellitus (presence of ketoacidosis or a glycosylated hemoglobin level >10%), liver disease, or active gallbladder disease were also ineligible. Extension phase: • Patients could not enrol in the extension study if they experienced any of the following during the core study: development of poorly controlled diabetes mellitus (as indicated by ketoacidosis or HbA1c >10%); persistent alanine aminotransferase/aspartate aminotransferase or alkaline phosphatase levels >2.5 x ULN; serum creatinine >2.0 x ULN and/or serum bilirubin >2 x ULN; abnormal coagulation (prothrombin time and partial thromboplastin time elevated by 30% above normal limits) or white blood cell (<3.0 x 10^9/L), hemoglobin (<12.0 g/dL for females, <13.0 g/dL for males) or platelet count (<100 x 10^9/L); or any other unacceptable AEs or tolerability problems.
Intervention	Patients self-administered pasireotide 600 µg sc twice daily (bid) for 15 d at 09:00 and 21:00 h. Dose adjustments were permitted for patients unable to tolerate the protocol-specified dosage. Patients who achieved normalized UFC levels at the end of the core study continued at a dose of 600 µg sc bid. If UFC levels increased, the pasireotide dose could be increased to 900 µg sc bid. The dose of pasireotide could be reduced by 150 µg per injection at any time if the investigator believed that a drug-related AE was present. One patient had a dose decrease to 450 µg sc bid and subsequent increase back to 600 µg. Seven patients had a dose increase to pasireotide 900 µg sc bid at some point before month 6.
Baseline characteristics	Of 38 patients who completed 15 days' pasireotide therapy, 19 entered this extension phase, 17 women and two men, all Caucasian, mean age 43 years (range 22–73, standard deviation [SD]: 11.6).
Primary and secondary endpoints	**Outcomes for core study:** • Primary outcome: Normalization of mean UFC levels after 15 day treatment* • Changes in plasma ACTH and serum cortisol • Safety assessments **Outcomes of the extended study:** • Primary outcome: The proportion of patients with normalized UFC levels after 6 months of treatment (normal UFC range: 55–276 nmol/24 h;20–100 µg/24 h). • Mean percentage change from core baseline in body weight, systolic BP and diastolic BP. Improvement in HB1AC and fasting plasma glucose, Electrocardiogram intervals

Main study characteristics (B2208)	
	• Secondary objectives included assessment of the safety and tolerability of multiple doses of pasireotide and trough plasma concentrations of pasireotide after chronic dosing.
Method of analysis	The analysis populations were defined as follows: the intention-to-treat (ITT) and safety populations consisted of patients who received at least one pasireotide dose in the extension period. The primary efficacy population consisted of those ITT patients whose mean UFC at core baseline, based on at least two UFC samples, was (ULN). No formal statistical comparisons were performed for this study because of the small sample size.
Subgroup analyses	NA

4.3.8 'Italian pasireotide real-world evidence' study characteristics

Table 14 Study characteristics: Italian pasireotide real-world evidence study (15)

Main study characteristics (Italian real-world evidence study)	
Trial name	NR
NCT number	NR
Objective	The objective of this study was to evaluate the efficacy and safety of pasireotide treatment according to the real-world evidence
Publications – title, author, journal. year	**The medical treatment with pasireotide in Cushing's disease: an Italian multicentre experience based on "real-world evidence".** Pivonello R, Arnaldi G, Scaroni C, Giordano C, Cannavò S, Iacuaniello D, Trementino L, Zilio M, Guarnotta V, Albani A, Cozzolino A, Michetti G, Boscaro M, Colao A. *Endocrine*. 2019
Study type and design	Real-world evidence-study
Follow-up time	24 weeks Converted from months (6 months) to weeks

Main study characteristics (Italian real-world evidence study)	
Population (inclusion and exclusion criteria)	**Inclusion:** Confirmation of a diagnosis of CD in active phase of disease, based on the presence of average (mean of two or three determinations performed in different days along one week) UC > ULN and/or late night salivary cortisol (LNSC) > ULN and/or increase in midnight serum cortisol (> 1.8 µg/dl), together with lack of suppression (≥ 1.8 µg/dl) in serum cortisol after low-dose (overnight 1-mg and/or 2-days 2-mg dexamethasone) suppression test and a clinical picture suggestive of CD. The diagnosis of CD needed to be confirmed by one of the following evidence: histological confirmation of corticotroph pituitary tumour at a previous surgery for patients who already had surgery before starting pasireotide or the presence of a pituitary macroadenoma or large (maximal diameter > 5 mm) microadenoma, or positive gradient at the inferior petrosal sinus sampling, performed anytime before starting pasireotide treatment. **Exclusion:** Pituitary or adrenal surgery performed less than three months before entering the study, pituitary radiotherapy performed less than three years for stereotactic radiotherapy and less than five years for conventional radiotherapy before entering the study, history of intolerance to somatostatin analogues, risk conditions for prolonged QT syndrome, uncontrolled DM, with glycated haemoglobin (HbA1c) > 9%, severe liver or renal insufficiency and pregnancy.
Intervention	Pasireotide Initial dose: 600 µg sc bid twice daily Patients with persistently increased UC received an up-titration of the drug dose to 900 µg bid. In case of occurrence of adrenal insufficiency, diagnosed on the basis of clinical or hormonal picture, as well as in case of drug intolerance during the first period of treatment, pasireotide was reduced to 450 or 300 µg bid. During the following period of treatment, clinical and hormonal evaluation was performed every three months and pasireotide dose was adjusted on the basis of UC levels and/or clinical picture, as well as drug intolerance, according to the physician judgement, considering 300 µg bid as the minimal dose and 900 µg bid as the maximal dose.
Baseline characteristics	

Characteristics	**Patients no. (%)**
Females	21 (80.8)
Males	5 (19.2)
Age - years	
Mean	47
Range	21-71
Time since diagnosis – years	
Mean	7.5
Range	0–17

Main study characteristics (Italian real-world evidence study)	

Previous treatment	
Pituitary Surgery	21 (80.8)
Adrenalectomy	2 (7.7)
Medication	16 (61.5)
Pituitary irradiation	8 (30.8)
Urinary Cortisol - ULN	
Mean	1.55
Median	1.39
Range	0.48–2.71

Primary and secondary endpoints

- Disease responsiveness, in terms of normalization or significant decrease of UC levels after six months of treatment
- Proportion of patients who normalized UC after three months of treatment, Change in plasma ACTH and morning serum cortisol after three and six months, change in clinical and metabolic parameters after three and six months, Change in tumor size after six months of treatment;
- Clinical parameters included the measurement of weight, body mass index (BMI), waist circumference, blood pressure and heart rate;
- Metabolic evaluation included the measurement of fasting plasma glucose (FPG), HbA1c, total cholesterol (Total-C), lowdensity lipoprotein-cholesterol (LDL-C) and high density lipoprotein-cholesterol (HDL-C), triglycerides (TG) and liver enzymes;
- Hormonal evaluation included UC, plasma ACTH and serum cortisol levels;
- Safety and tolerability.

Method of analysis

The efficacy analysis was performed considering the totality of patients entering the study and starting pasireotide treatment, and particularly the 32 patients with any degree of disease, and the 31 patients with very mild to moderate disease, which is the main focus of the current study, as well as the 28 patients with very mild to moderate disease, and increase UC at baseline, according to an “intention-to-treat” and a “per-protocol” approaches.

Subgroup analyses

NA

5. Clinical questions

5.1 Clinical question 1: What is the value of osilodrostat compared to ketoconazole in adult patients with endogenous Cushing's syndrome?

Population
Adult patients with endogenous Cushing's syndrome.
Intervention
Osilodrostat (starting dose 2 mg twice daily, then individual dosing on background of response and tolerability).
Comparator
Ketoconazole start dose 200mg x 2-3 daily, maximum 1600mg
Outcomes

- Proportion of patients with complete response at Week 4
- Proportion of patients with complete response at Week 12
- Proportion of patients with complete response at longest follow up
- Quality of Life (CushingQoL)
- Proportion of patients with adverse events requiring treatment

5.1.1 Presentation of relevant studies

This paragraph provides an overview of the relevant studies used to answer clinical question 1. The present review identified 7 full-texts studies addressing the clinical question defined above.

Study characteristics

In addition to the baseline characteristics described in the table overview of the respective studies, a summary of the study characteristics is presented in Table 15. For more details per individual study, please refer to section 4.2 and 4.3 where the main characteristics of the studies are described.

Patients in LINC-3 were CD patients only, which the EMA considered of relevance to provide marketing authorisation osilodrostat for the indication of endogenous Cushing's Syndrome. The LINC-3 trial design only included CD patients, because it reflects the most homogenous population and sensitive to osilodrostat. Cushing's Disease, which refers specifically to the form of the disease that results from a pituitary corticotroph adenoma, represents the most common form of endogenous CS, corresponding to approximately 70% of CS patients. Therefore, this target population is considered of relevance for the assessment of endogenous CS. In addition, if other etiologies would have been included in the overall study population, conclusions on the safety and efficacy of osilodrostat would have been challenging to be drawn based on a small subgroup. EMA stated in their scientific advice report that using CD as target population is supported as this will reflect the most homogenous and available population. The inclusion/eligibility criteria are acceptable and in line with clinical practice. (21)

Table 15 Study characteristics for question 1

Study name (Trial name / NCT)	Intervention/ comparator	Number screened Number enrolled Number randomized	Study setting Study country	Study design Blinding Study phase	Duration of study (weeks)
Gadelha, 2022 (3) LINC-4	Osilodrostat Placebo	Screened: 119 Enrolled: 74 Randomized: 73	Multi-centre Belgium, Brazil, Canada, China, Costa Rica, Poland, Portugal, Russia,, Spain, Switzerland, Thailand, Turkey, United States	RCT Double blind Phase III	Overall study: 48 weeks RCT phase: initial 12 weeks Extension phase (optional): up to week 96
Pivonello, 2020 (4) (LINC3/ NCT02180217/EUCTR2013-004766-34-NL)	Osilodrostat/LCI699 (Period 1 +2) Osilodrostat/LCI699 (Period 3-RCT) Placebo (Period 3-RCT) Osilodrostat/LCI699 (Overall patients)	Screened: 202 Enrolled: 137 Randomized: 71	Multi-centre international Argentina, Austria, Bulgaria, Canada, China, Colombia, France, Germany, India, Italy, Japan, Korea, Netherlands, Russian Federation, Spain, Thailand, Turkey, UK, and US	RCT Double blind Phase III	Overall study: 48 weeks RCT phase: 8 weeks Extension phase (optional): 72 Weeks
Fleseriu, 2016 (5) (LINC-2/NCT01331239)	Osilodrostat	Screened: 19 Enrolled: 19 Randomized: NA	Multi-centre NR	Prospective Open label Phase II	22 weeks Extension phase (optional): 83 weeks (converted from 19 months reported in study; calculated as 19X30.5/7)
Tanaka, 2020 (7) (C1201/ NCT02468193)	Osilodrostat	Screened: 9 Enrolled:9 Randomized: NA	Multi-centre Japan	Single arm Open label Phase II	Core study: 48 weeks Extension phase (optional): 24 weeks
Bertagna, 2014 (6) (LINC1 (core study); (LINC 2 (extension study)/ NCT01331239)	Osilodrostat/LCI699 Osilodrostat/LCI699	Screened: NR Enrolled: 12 Randomized: NA	Multi-centre international Italy, France and US	nRCT single arm NR Phase II	Core study: 10 weeks Extension phase: 22 weeks
Castinetti, 2008 (9) (NR)	Ketoconazole	Screened: NR Enrolled: 38 Randomized: NA	Single centre France	Retrospective observational NA NA	Mean follow-up: 92 weeks (24 – 288) Originally data reported in the study as mean follow-up of 23 months (6–72). (conversion used was 4 weeks=1 month)
Castinetti, 2014 (8) (French Retrospective Study on Ketoconazole Outcome (FReSKO)/NR)	Ketoconazole	Screened: NR Enrolled: 200 Randomized: NA	Multi-centre France	Retrospective observational NA NA	NR

Abbreviations: NA, not applicable; NR, not reported; RCT, randomized controlled trial; nRCT, non-randomized controlled trial

Table 16 Patient characteristics for question 1

Study name	Intervention/ comparator	Mean age (years) Male, n (%)	Type of CS, n (%)	Weight Mean BMI (kg/m2)	Prior treatment, n (%) Surgery Medications Radiation	Comorbidities, n (%)	Mean mUFC (SD)
Gadelha, 2022 (3) LINC-4	Osilodrostat	41.0 5 (10.4)	Microadenoma: 30 (62.5) Macroadenoma: 17 (35.4) Missing 1 (2.1)	78.8 NR	41 (85.4) 26 (54.2) 6 (12.5)	NR	421.3 (291.3)
	Placebo	37.0 7 (28.0)	Microadenoma: 20 (80.0) Macroadenoma: 4 (16.0) Missing 1 (4.0)	77.3 NR	23 (92.0) 19 (76.0) 3 (12.0)	NR	451.5 (535.1)
	All patients	41.2 12 (16.4)	Microadenoma: 50 (68.5) Macroadenoma: 21 (28.8) Missing 3 (2.7)	78.3 NR	64 (87.7) 45 (61.6) 9 (12.3)	NR	431.7 (388.6)
Pivonello, 2020 (4) LINC-3	Osilodrostat (Period 1+2)	NR 31 (22.6)	Pituitary adenoma: 137 (100)	NR 30.3	102 (74.5) 120 (87.6) 22 (16.1)	NR	NR
	Osilodrostat (Period 3-RCT)	NR 6 (16.6)	Pituitary adenoma: 36 (100)	NR NR	26 (72.2) 32 (88.9) 6 (16.7)	NR	890.0 (1275.66)
	Placebo (Period 3-RCT)	NR 13 (37.1)	Pituitary adenoma: 35 (100)	NR NR	24 (68.6) 33 (94.3) 5 (14.3)	NR	560.0 (548.84)
	Osilodrostat (Overall patients)	NR 31 (22.6)	Pituitary adenoma: 137 (100)	NR 30.3	102 (74.5) 120 (87.6) 22 (16.1)	NR	1,006.0 (1,589.86)
Fleseriu, 2016 (5) LINC-2	Osilodrostat	36,8 5 (26.3)	NR	NR NR	17 (89.5)NR NR	NR	1371 (2734)
Tanaka, 2020 (7) C1201	Osilodrostat	NR 2 (22.2)	Adrenal adenoma: 5 (55.5%) Ectopic CS: 3 (33.3) Other: 1 (11.1)	NR NR	5 (55.6) 1 (11.1) 0 (0)	NR	NR
Bertagna, 2014 (6) LINC-1	Osilodrostat	39 4 (33.3)	Pituitary adenoma: 12 (100)	85.1 33.8	1 (8.3) 12 (100) 0 (0)	Hypertension: 3 (NR)	4.7-fold above the ULN (SEM 1.3)

	Osilodrostat (expansion cohort + follow up cohort)	36.8 5 (26.3)	NR	NR NR	NR 17 (89.5) NR	NR	NR
	Osilodrostat (expansion cohort)	37.5 4 (26.7)	NR	NR NR	NR 13 (86.7) NR	NR	NR
	Osilodrostat (follow up cohort)	34.3 1 (25)	NR	NR NR	NR 4 (100) NR	NR	NR
Castinetti, 2008 (9)	Ketoconazole	NR 5 (15.15)	Pituitary adenoma: 38 (100)	NR NR	NR 17 (51.51) NR	Diabetes: 5 (15.15)	NR
Castinetti, 2014 (8)	Ketoconazole	NR 44 (22)	Pituitary adenoma: 142 (71)	NR NR	NR 144 (72) 47 (23.6)	Hypertension: 116 (66.7) Hypokalaemia: 39 (22.4) Diabetes: 55 (31.8)	4.1 (5.3) x ULN

Abbreviations: CS, Cushing's syndrome; NA, not applicable; NR, not reported; UFC, urinary free cortisol;

Data sources include the main publications and available DATA ON FILE

5.1.2 Results per study

5.1.2.1 LINC-4

Efficacy

The mUFC was measured during several timepoints throughout the study, complete response was defined as mean 24-h UFC concentration of ≤ULN.

LINC-4 met its primary endpoint; mUFC ≤ULN at Week 12 was significantly (p<0.0001) different between the two groups (Table 17). The complete response rate was higher with osilodrostat compared with placebo (77.1% vs 8.0%; RR 9.64, 95% CI: 2.53, 36.73) (3) and these findings were consistent irrespective of randomised stratum. Un-stratified analysis of the primary endpoint by FAS were in favour of osilodrostat as were stratified and un-stratified analyses on the PPS (p<0.0001 for all).

The key secondary endpoint was also met, with 59/73 patients having mUFC ≤ULN at week 36 (which is 24 weeks after open-label osilodrostat), this results in a complete response rate of 80.8% (95% CI: 69.9-89.1) (3)

Table 17 LINC-4 Proportion of Complete Responders at Week 12 by Treatment Group and strata at randomisation (FAS)

		CMH exact test	
	Complete Responder/N (%)	**Odds ratio (95% CI)**	**2-sided p-value**
All Patients			
Osilodrostat	37/48 (77.1)	Osilodrostat vs. Placebo 43.4 (7.06, 343.19)	<.001
Placebo	2/25 (8.0)		
Stratum 1: History of pituitary radiation			
Osilodrostat	5/6 (83.3)	Osilodrostat vs. Placebo 10.0 (0.20, 704.49)	Na/
Placebo	1/3 (33.3)		
Stratum 2: No history of pituitary radiation			
Osilodrostat	32/42 (76.2)	Osilodrostat vs. Placebo 67.2 (8.12, 2861.80)	n/a
Placebo	1/22 (4.5)		

Abbreviations: CI, confidence interval; CMH: Cochran-Mantel-Haenszel; FAS: full analysis set; n/a, not applicable

Note: A Complete responder: a patient who had mUFC ≤ ULN at the end of Period 1 (Week 12). Non-responders: All other patients, including patients who discontinued prior to Week 12, or who did not have a valid mUFC assessment at Week 12.

Note: Data cut-off is 25 February 2020

Source: LINC-4 DATA ON FILE (22)

Complete response

Patients switching from placebo to osilodrostat after week 12 experienced rapid and high rates of sustained complete response. No data was collected during the trial at week 4, therefore data from week 5 has been included for this assessment. The benefit of osilodrostat was maintained in all patients during the open-label treatment, including those who were initially randomized to placebo, with a complete response of 80.8% (59/73) at week 36. (3) During the optional extension phase more than 70% of the overall patient population are considered complete responders at end of treatment. (22)

Table 18 Propotion of responders at selected timepoints (FAS)

Visit	Osilodrostat N=48	Placebo* N=25	All patients N=73
Week 5			
Complete responder: n/N (%)	28/48 (58.3)	4/25 (16.0)	32/73 (43.8)**
Week 12 (End of randomized period)			
Complete responder: n/N (%) CI:	37/48 (77.1) (62.7, 88.0)	2/25 (8.0) (1.0, 26.0)	39/73 (53.4)
Week 14			
Complete responder: n/N (%)	24/48 (50.0)	8/25 (32.0)	32/73 (43.8)
Week 26			
Complete responder: n/N (%)	38/48 (79.2)	22/25 (88.0)	60/73 (82.2)
Week 36			
Complete responder: n/N (%) Ci:	38/48 (79.2) (65.0, 89.5)	21/25 (84.0) (63.9, 95.5)	59/73 (80.8) (69.9, 89.1)
Week 48			
Complete responder: n/N (%) CI:	34/48 (70.8) (55.9, 83.0)	16/25 (64.0) (42.5, 82.0)	50/73 (68.5) (56.6, 78.9)
Week 60 (optional extension phase)			
Complete responder: n/N (%)	25/44 (56.8)	16/24 (66.7)	41/68 (60.3)
Week 72 (optional extension phase)			
Complete responder: n/N (%)	25/41 (61.0)	15/24 (62.5)	40/65 (61.5)
EOT (optional extension phase)			
Complete responder: n/N (%)	28/38 (73.7)	14/20 (70.0)	42/58 (72.4)

*Key: * Patients randomized to placebo in Period 1 switched to osilodrostat after week 12. ** calculated for the purpose of this submission*

Available CIs have been included in the table overview

Abbreviations: CI: confidence interval; EOT: end of treatment; FAS: full analysis set; mUFC: mean urinary free cortisol; NA: not applicable; RW: Randomized Withdrawal.

Notes: Patients who discontinued prior to the data cutoff date were included in the analysis for all scheduled visits. If a patient has a missing mean UFC at a visit, they are counted as non-responders. Complete responder: mean UFC $\leq$1.0 x ULN, Non-responder: neither a complete nor partial responder If a patient has a missing mean UFC at a visit, they are counted as non-responders. 2-sided 95% CI for proportions are based on the exact (Clopper-Pearson) method.

Note: Data cut-off is 31 December 2020 (which is also study completion date)

Source: LINC-4 DATA ON FILE (22) and week 12 data from Gadelha et al. 2022 (3)

Cardiovascular and metabolic related parameters

Improvements in cardiovascular-related metabolic parameters associated with CD were observed at Week 48. The improvement was evident amongst all patients treated with osilodrostat, in both the placebo-controlled period (Baseline to Week 12) and the open-label treatment period (Week 12 to 48). The only exception was triglycerides, which had not improved in the osilodrostat arm (relative to placebo). (3) At the end of the optional extension phase, there was an improvement in most cardiovascular-related metabolic parameters associated with CD. (22)

Bone mineral density

Bone mineral density of femoral neck, L1-L4 lumbar spine and total hip increased from baseline at Week 48. The highest change was in femoral neck (percentage change from baseline: 2.2%). (22)

Physical features

The study showed that osilodrostat treatment was associated with an improvement in at least one physical feature of CS in all patiens during osilodrostat treatment. (3) At Week 48, approximately half of the patients had a favorable shift from baseline in the reduction of supraclavicular and dorsal fat pad. More than a quarter of patients had a favorable shift from baseline for facial rubor, striae, proximal muscle wasting (atrophy), and central obesity. Less than 10% patients had a worsening of physical features of CD. (3) At the EOT extension visit, most phycisal features of CD had either improved or not changed compared with baseline. (22)

Dosages

Median (IQR) dose during the placebo-controlled period was 6.9 (4.0–10.7) mg/day for osilodrostat and 9.3 (6.2–12.2) mg/day for matching placebo; a similar proportion of patients received the highest dose (20 mg bid osilodrostat: n=5, 10.4%; matching placebo: n=3, 12.0%). Median (IQR) osilodrostat dose from baseline to data cut-off was 5.0 (3.8–9.2) mg/day. For patients initially randomized to placebo, overall median (IQR) osilodrostat dose was 6.0 (3.7–9.7) mg/day. During the entire study period (up to data cut-off), three patients received the maximum dose of 30 mg bid. (3)

Quality of Life and Patient Reported Outcomes

The PRO results in LINC-4 showed a trend of improvement over time in all measurements, EQ-5D-5L, EQ-5D VAS, Cushing's QoL and BDI-II.

The study showed an improvement with Cushing's Qol versus baseline in all patients is above the 10.0 MID at week 48. The results remain > MID, with an absolute change of 10.3 at as last observed value in the open label extension (n=70). Results of the instruments up to Week 48, with a MID> 10.0 (as defined by the DMC as clinical relevant endpoint) are visible in (Table 19).

Table 19 Mean change in CushingQol score by randomized treatment group and overall score

	Randomized to osilodrostat (n = 48)		Randomized to placebo (n = 25)[a]		All patients (N = 73)	
	Mean value (SD)	Actual change (95% CI)	Mean value (SD)	Actual change (95% CI)	Mean value (SD)	Actual change (95% CI)
Baseline	49.1 (19.6)	–	56.9 (19.0)	–	51.8 (19.6)	–
Week 12	56.1 (22.1)	6.2 (1.7, 10.6)	65.6 (17.6)	8.6 (3.5, 13.7)	–	–
Week 48	62.8 (22.2)	11.7 (6.6, 16.7)	69.9 (16.9)	12.8 (6.5, 19.1)	65.3 (20.7)	12.0 (8.2, 15.9)

A: at week 48, patients randomized to placebo had received 12 weeks of placebo followed by 36 weeks of osilodrostat treatment.
Source: Gadelha et al. 2022 (3)

- BDI-II mean (all patients, n=73) total derived score was 10.9 (SD: 9.58) at baseline, which reduced by 46.8% to 5.8 (SD: 7.0) at Week 48. (3) This result is above the MID of a 17.5% reduction in scores. (23)
- The mean EQ-5D-5L utility index scores were 0.851 (SD: 0.1418) at baseline in all patients (n=73), and 0.899 (SD: 0.1393) at Week 48. The changes indicate a trend of improvement in EQ-5D scores, which exceeded the minimum range for MID (0.037) for EQ-5D-5L. (24). The mean EQ-5D VAS score was 72.4 (SD: 17.59) at baseline (n=71) and 81.4 (SD: 14.03) at Week 48. (22) The last observed value during the open label period was 78.9 (SD: 17.04). (22)

Over the longer period of exposure to osilodrostat up to EOT Extension, the mean scores for Cushing's QoL scores, Beck's depression Inventory-II, and EQ-5D-5L scores showed an improvement over baseline, in the all patients group (osilodrostat arm, placebo arm, all patients) (22):

- • Cushing's QoL scores overall indicated an improvement over time:
  - The mean Standardized Psychosocial issues score improved from 52.2 (SD: 20.71) at baseline to 69.0 (SD: 21.55) at EOT Extension.

- The mean Standardized HRQL score improved from 51.8 (SD: 19.62) at baseline to 69.0 (SD: 20.91) at EOT Extension.
- The mean Standardized Physical problems score improved from 50.6 (SD: 22.62) to 68.7 (SD: 22.54) at EOT Extension.

- The BDI-II mean Total derived score was 10.9 (SD: 9.58) at baseline, which reduced to 6.2 (SD: 7.12) at EOT Extension, indicating improvement, exceeding the MID score difference.
- The mean EQ-5D-5L utility index scores improved from 0.851 (SD: 0.1418) at baseline, to 0.903 (SD: 0.1355) at EOT Extension, which exceeded the minimum range for MID (0.037). The mean EQ-5D VAS score also improved from 72.4 (SD: 17.59) at baseline to 81.2 (SD: 14.99) at EOT Extension, exceeding the MID score difference at 7.

The LINC-4 study confirmed the benefit of osilodrostat in improving the quality of life and reported outcomes of patients with CD. The assessment by the different scales shows improvements in the average QoL of the patients included in the study for an exposure period of 48 weeks and up to 96 weeks during extension period.

Safety

During the placebo-controlled period, the most common AEs included decreased appetite, arthralgia and nausea. Grade 3/4 AEs occurred in 20.8% and 20.0% of osilodrostat and placebo recipients, respectively; hypertension was most common (8.3% osilodrostat vs 16.0% placebo). Only 1 patient discontinued because of an AE (arthralgia). (3)

For the entire study duration, all patients experienced at least one AE, and grade 3/4 AEs occurred in 38.4% of patients. Eight patients (11.0%) discontinued because of AEs. No deaths were reported. (3)

During the 12-week placebo-controlled period, 14.6% (n = 7) of osilodrostat and 0% of placebo recipients experienced any AE that was categorized in accordance with the protocol as potentially related to hypocortisolism, compared with 27.4% (n = 20; grade 3/4, n = 2/0; adrenal insufficiency, n = 18; acute adrenocortical insufficiency, n = 1; steroid-withdrawal syndrome, n = 1) of all patients up to data cutoff. Overall, dose was temporarily interrupted in 15, adjusted in 6, and discontinued in 2 patients. Thirteen patients received concomitant glucocorticoids to manage the AE. AEs of arrhythmogenic potential and QT prolongation occurred in 3 patients overall, all of which resolved. (3)

At data cutoff, the number of female patients with testosterone levels > ULN had reduced to 22/61 (36.1%); during the entire study, increased testosterone was reported as an AE in 18/61 females (29.5%). AEs of hirsutism occurred in 7 females (9.6%; grade 1/2), all of which were suspected to be related to the study drug. (3)

In Table 20, an overview of the adverse events according to the LINC-4 publication is presented.

Table 20 Summary of adverse events during the placebo-controlled period and overall Core study period

	Placebo-controlled period		Overall period
	Osilodrostat (n = 48)	**Placebo (n = 25)**	**All patients[a] (n = 73)**
Any AE	46 (95.8%)	23 (92.0%)	73 (100%)
Serious AE	2 (4.2%)	1 (4.0%)	8 (11%)
AE leading to discontinuation	1 (2.1%)	0	8 (11%)
Most common study emergent AEs (occurring in >20% of patients overall)			
Decreased appetite	18 (37.5%)	4 (16.0%)	33 (45.2%)
Arthralgia	17 (35.4%)	2 (8.0%)	33 (45.2%)
Fatigue	12 (25.0%	4 (16.0%)	28 (38.4%)
Nausea	15 (31.3%)	3 (12.0%)	27 (37.0%)
Headache	7 (14.6%)	6 (24.0%)	24 (32.9%)
Myalgia	11 (22.9%)	1 (4.0%)	19 (26.0%)
Dizziness	9 (18.8%)	4 (16.0%)	19 (26.0%)
Adrenal insufficiency	7 (14.6%)	0	18 (24.7%)

Increased blood testosterone	5 (10.4%)	0	18 (24.7%)
Diarrhea	10 (20.8%)	0	17 (23.3%)
Hypertension	8 (16.7%)	7 (28.0%)	16 (21.9%)
Asthenia	11 (22.9%)	0	15 (20.5%)
Upper respiratory tract infection	5 (10.4%)	0	15 (20.5%)

Abbreviations: AE, adverse event.

Includes all data until data cutoff (occurred when the last patient completed or discontinued the core study); median (range) osilodrostat exposure was 70.0 (2.0–112.7) weeks. [a]Excludes data collected for placebo recipients collected during the 12-week randomized period. Patiens with multiple severity grades for an AE is only counted under the maximum grade.

Source: Gadelha et al. 2022 (3)

Detailed information regarding AEs requiring additional treatment was not available in the identified publications and have therefore been extracted from the clinical study report (CSR).

Table 21 LINC-4 AEs requiring additional therapy (safety set)

	Osilodrostat (Osilodrostat arm) N = 48		Osilodrostat (Placebo arm) N = 25		All patients N = 73	
Category	**All grades n (%)**	**Grade ≥3 n (%)**	**All grades n (%)**	**Grade ≥3 n (%)**	**All grades n (%)**	**Grade ≥3 n (%)**
AEs requiring additional therapy	46 (95.8)	18 (37.5)	21 (84.0)	4 (16.0)	67 (91.8)	22 (30.1)

Abbreviations: AE, adverse event. Source: LINC-4 DATA ON FILE (22)

Overall, LINC-4 showed a favorable safety profile for osilodrostat.
The proportion of patients who experienced any AE potentially related to hypocortisolism was lower in this trial (27%) than in LINC 3 (51%), possibly resulting from the slower dose-escalation schedule (every 3 vs 2 weeks). (3)

Escape

No patient randomized to osilodrostat experienced an escape event up to end of optional extension phase. (22)

5.1.2.2 LINC-3

Efficacy

LINC-3 was the osilodrostat's pivotal study and used to gain marketing authorization.

The mUFC was measured during several timepoints throughout the study, complete response was defined as mean 24-h UFC concentration of ≤ULN. Based on the DMC protocol week 12 (end of dose titration period prior to randomization phase) and week 72 (open-label follow-up phase) are included in this section. However, only using these timepoints would not show the results during the randomization phase. We, therefore, find it important that the measurements from week 34 (end of randomization period) and week 24 are included. No measurements are available for week 4, hence not included.

The LINC-3 study showed that osilodrostat is efficient in lowering the mUFC and reduction in mUFC levels with osilodrostat was maintained over time (Table 22) in the full analysis set (ie, all enrolled participants who received at least one dose of osilodrostat). The first 12 weeks of the study consisted of an intra-patient dose-titration period. Most patients who responded to osilodrostat had a very short time to response. Patients responded to osilodrostat treatment with an overall responder rate of 85.4% at Week 8, with 68.6% of patients (117/137) being complete responders and 16.8% (23/137) being partial responders.

At the end of the individual dose-titration period (Week 12 – end of Study Period 1), the overall response rate was maintained at 85.4% (117/137), with 71.5% of patients (98/137) achieving a complete response and 13.9% (19/137) achieving a partial response.

At the end of the RW Period (Week 34) using the randomized treatment and strata (RAS) population, the complete response rate for patients on osilodrostat was higher (86.1%; 95% CI: 70.50, 95.33) compared to those on placebo (29.4%; 95% CI: 15.10, 47.48) with an estimated odds ratio of 13.71 (95% CI: 3.73, 53.44 in favor of osilodrostat). The RAS population includes all randomized patients who have received at least one dose of the drug.

More importantly, regardless of the dose increase between Week 12 and Week 24 overall response was achieved in 82.5% (113/137) of the patients at Week 24 versus 52.6% without dose increase. This shows the expected treatment effect in clinical practice.

Table 22 Proportion of mUFC complete responders at Selected Timepoints by Treatment Group (FAS)

Visit	Randomized to osilodrostat during RW N=36	Randomized to placebo during RW* N=35	Non-randomized N=66	All patients N=137
Week 12 (End of dose-titration)				
Complete responder: n/N` (%) 95% CI	31/36 (86.1) (70.50, 95.33)	32/35 (91.4) (76.94, 98.20)	35/66 (53.0) (40.34, 65.44)	98/137 (71.5) (63.20, 78.91)
Week 24				
Complete responder: n/N` (%) 95% CI	36/36 (100) (90.26, 100.00)	34/35 (97.1)[1] (85.08, 99.93)	23/66 (34.8) (23.53, 47.58)	93/137 (67.9) (59.37, 75.60)
Week 26 (start of RW period)**				
Complete responder: n/N` (%)	33/36 (91.7) (77.53, 98.25)	29/35 (82.9) (66.35 ,93.44)	27/66 (40.9) (28.95, 53.71)	89/137 (65.0) (56.35,72.91)
Week 34 (End of RW Period)**				
Complete responder: n/N` (%)	33/36 (91.7) (77.53, 98.25)	6/11 (54.5) (23.38 ,83.25)	31/66 (47.0) (34.56, 59.66)	70/113 (69.1) (52.33, 70.92)
Week 48 (End of Core Period)				
Complete responder: n/N` (%) 95% CI	32/36 (88.9) (73.94, 96.89)	27/35 (77.1) (59.86, 89.58)	32/66 (48.5) (35.99, 61.12)	91/137 (66.4) (57.86, 74.26)
Week 72 * **				
Complete responder: n/N` (%) 95% CI	29/35 (82.9) (66.35, 93.44)	25/30 (83.3) (65.28, 94.36)	32/41 (78.0) (62.39, 89.44)	86/106 (81.1) (72.38, 88.8)

*Key: * For patients randomized*

Abbreviations: CI: confidence interval; FAS: full analysis set; mUFC: mean urinary free cortisol; NA: not applicable; RW: Randomized Withdrawal.

Notes: 95% CIs is based on Clopper-Pearson method (exact method); N` is the number of patients used in the analysis. It is the number of patients in the Full analysis set for visits in the core phase (up to Week 48); Beyond Week 48: Patients who declined to enter optional extension periods or are ongoing at the cutoff date for the data base lock were included in the analysis up to their last available scheduled visit. Patients discontinued prior to the data cutoff date will be included as a non-responder up to the furthest scheduled visit they could have completed if they did not discontinue earlier.

*Source: Pivonello et al 2020 (4), **LINC-3 Data on File (25) and Fleseriu et al 2021 abstract (26)*

Significantly more patients receiving osilodrostat maintained normal mUFC compared with those that switched to placebo at the end of the 8-week randomised withdrawal period. Most enrolled patients (132 (96%) of 137) had a mean 24-hours UFC concentration of ≤ULN at least once during the study; median time to first complete response was 41 days (IQR 27.0–56.0). Excluding patients who were randomly assigned to placebo, 64 (66%) of 97 patients who had a complete response during the study period maintained a complete response for at least 6 months. At week 12 (following the dose titration phase), 71.5% of the patients having received osilodrostat were complete responders. At week 34 there was a significant difference in response between those being randomized to osilodrostat and placebo; complete responders in the osilodrostat group was 86.1% and 29.4% in the group being randomized to placebo. Among the enrolled patients, 106 (77%) entered the extension open-label phase with, 81.1% of the patients being complete responders at week 72, showing a sustained cortisol normalisation. Combining the patients randomized to osilodrostat (n=35) and those receiving open-label osilodrostat (n=41), 80.2% (61/76) achieved complete response at week 72.

Cardiovascular-related Metabolic Parameters

Treatment with osilodrostat led to an improvement in most cardiovascular-related metabolic parameters associated with hypercortisolism (including bodyweight, BMI, fasting plasma glucose, systolic and diastolic blood pressure, and total and LDL cholesterol) with improvements seen as early as Week 12. These improvements were maintained over time. By Week 48, osilodrostat treatment led to an improvement in all cardiovascular-related metabolic parameters associated with CD, except for triglycerides and HDL cholesterol where the worst results were seen in the non-randomized group. (4)

Physical features of CD

The physical features of CD were assessed clinically for severity at defined time points rated on a semi-quantitative scale as follow: 0=absent; 1=mild; 2=moderate; and 3=severe. Physical features of CD were also documented by photography. At the end of the Core period (Week 48), 83/97 (85.6%) patients with an assessment (change from baseline in physical features of CD captured by a semi-quantitative Likert scale) had improvements in at least one physical feature in CD, including facial rubor, striae, supraclavicular fat pad, proximal muscle wasting, central obesity, ecchymoses and hirsutism for female only). Approximately half of the patients had a favourable shift from baseline in at least one physical feature in CD including facial rubor, dorsal fat pad, central (abdominal) obesity, and supraclavicular fat pad, whereas approximately one third had a favourable shift from baseline for ecchymosis (bruising), proximal muscle wasting (atrophy), striae and hirsutism (in female patients only). The improvements were seen in some patients as early as Week 12 and were progressive up to the end of the Core Period. Patients who were randomized to placebo had fewer improvements in physical features than patients who were always taking osilodrostat during the study. The observed favourable improvements in physical features of CD were maintained at the end of study. (25)

Quality of Life

Osilodrostat reduces the mUFC which leads to improvement of the cardiovascular and metabolic parameters and treatment with osilodrostat leads to improvement in the quality of life (QoL), as measured by disease specific and generic instruments and improvement on the depression score.

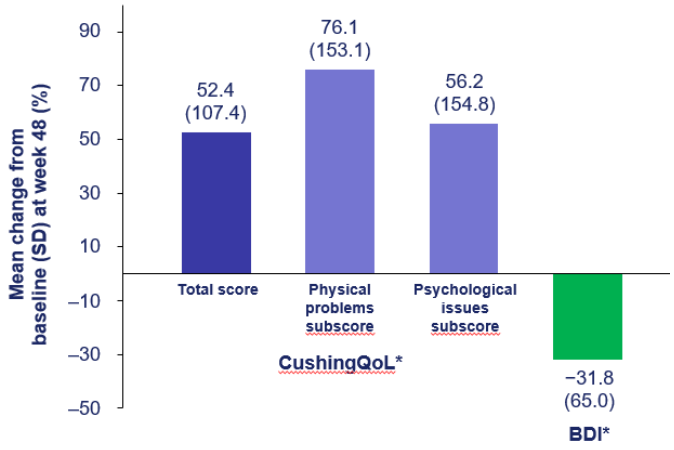
Three PRO questionnaires were used to assess the impact of osilodrostat treatment on patients' Health-Related QoL (HRQoL) and symptom burden. For the purpose of this application the results based on the CushingQoL Questionnaire are described at week 48, i.e. the end of the core study.

From Week 12, osilodrostat led to clinically meaningful improvements in CushingQoL score, despite the impairments associated with extended duration of hypercortisolism at baseline. Improvements above the minimal important difference (MID) were measured for the QoL in Cushing (Cushing QoL total score, and respective subscales: physical and psychological issues). The actual change from baseline in all patients (N=137, FAS population) is 14.1 (95% CI 10.9 to 17.3) at week 48. (4) The percentage change from baseline in this population is 52.4% (95% CI 32.2 to 72.7) (4). Showing that the MID of 10.1 point change from baseline has been reached at this timepoint. An overview of the HRQoL at Week 48 can be seen in

Figure 2.

It should be noted that the normalization in mUFC also leads to improvement in depression, as shown by the improvement on the BDI above the MID. This outcome is of high importance for these patients, where depression is a very frequent comorbidity in CS patients.

Figure 2 Mean change in HRQoL scores including CushingQoL



Abbreviations: BDI, Beck Depression Inventory; HRQoL, health-related quality of life; MID, minimal important difference; SD, standard deviation.

*Key: *Changes in CushingQoL and BDI scores indicate a clinically relevant improvement; †Corresponding to a minimum 10.1-point change from baseline; ‡Corresponding to a 17.5% reduction in scores from baseline*

Improvements in HRQoL (CushingQoL) were observed early on, and were sustained, clinically relevant, and usually more pronounced in patients randomized to osilodrostat. Osilodrostat improved the HRQoL in both the physical and psychological domains relevant to CS (CushingQoL subscales).

Safety

In LINC-3, the most common AEs related to the drug were adrenal insufficiency (27.0%), nausea (27.0%), fatigue (21.2%) and glucocorticoid deficiency. These AEs were mainly grade 1/2 and successfully managed by dose reduction/interruption and corticosteroid supplementation. The most common events include nausea (45.3%), headache (36.5%), fatigue (32.8%), adrenal insufficiency (29.2%) and vomiting (24.8%).

Detailed information regarding AEs requiring additional treatment was not available in the identified publications and have therefore been extracted from the clinical study report (CSR). At time of the cut-off date, 130 patients (94.9%) had AEs requiring additional therapy. In 93.4% of patients, the AEs were suspected to be study drug related. Grade 3/4 AEs were suspected to be drug related in 22.2% of the patients. This led to drug discontinuation in 5.1% of the patients, dose interruption and/or change in 19% of the patients and requirement of additional therapy in 19% of the patients. Most commonly reported (in >15% of patients) AEs suspected to be study drug related were adrenal insufficiency and nausea (27.0%, each), fatigue (21.2%), glucocorticoid deficiency (20.4%) and blood corticotrophin increased (15.3%).

During the RW period, 16 patients (44.4%) in the osilodrostat group and 15 patients (42.9%) in the placebo group had AEs requiring additional therapy.

A total of 70 patients (51%) had hypocortisolism-related adverse events at any point during the study, most commonly being classified as adrenal insufficiency (38 [28%] of 137) or glucocorticoid deficiency (29 [21%]), which reflect the same condition. These events mostly occurred and resolved during the dose-titration period (study period 1), were typically single episodes of grade 1–2 severity, and were managed by dose reductions or interruptions and corticosteroid supplementation when clinically indicated (data now shown).

In the core study in female participants, AEs of hirsutism (12 [11%] of 106) were reported (grade 1–2) and did not lead to study discontinuation. No additional cases of hirsutism occurred in the extension period (up to week 72).

Table 23 LINC-3 Adverse events requiring additional treatment at data cutoff (SAS)

	Randomized to osilodrostat during RW N=36 n (%)		Randomized to placebo during RW* N=35 n (%)		Non-randomized N=66 n (%)		All patients N=137 n (%)	
Category	**All grades N (%)**	**Grade 3/4 N (%)**	**All grades N (%)**	**Grade 3/4 N (%)**	**All grades N (%)**	**Grade 3/4 N (%)**	**All grades N (%)**	**Grade 3/4 N (%)**
AEs requiring additional therapy	33 (91.7)	12 (33.3)	33 (94.3)	16 (45.7)	64 (97.0)	27 (40.9)	130 (94.9)	55 (40.1)
Suspected to be drug-related	20 (55.6)	4 (11.1)	20 (57.1)	6 (17.1)	46 (69.7)	16 (24.2)	86 (62.8)	30 (19.0)

*Key: * For patients receiving placebo during the RW Period and excluding data while on placebo.*

Abbreviations: AE, adverse event; RW: Randomized Withdrawal; SAS: safety analysis set; SAE, serious adverse events.

Notes: Categories are not mutually exclusive. Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories. Deaths occurring >30 days after end of treatment are not included. Additional therapy includes all non-drug therapy and concomitant medications.

Sources: Pivonello et al 2020 (4) and LINC-3 data on file.[25]

Table 24 presents an overview of the adverse events of special interest (AESIs) observed in LINC-3. AESIs were suspected to be study drug-related (anticipated based on the mechanism of action of osilodrostat), although they were infrequently reported during the RW Period. AESI leading to study drug discontinuation were infrequent and included adrenal insufficiency (in four patients [2.9%]), hypokalemia, blood pressure diastolic increase, blood pressure systolic increase, and electrocardiogram (ECG) QT prolonged (in one patient (0.7%), each). Five patients (3.6%) had ECG QT prolonged AEs and despite one being reported as Grade 3, all five were considered non-serious. (25) In total, at time of data cut-off, 18 (13%) patients discontinued treatment because of an adverse event.

Table 24 LINC-3 – Anticipated AEs of special interest (SAS)

	All patients N=137, n (%)	
	All grades	**Grade 3-4**
Adrenal hormone precursor accumulation related	58 (42.3)	22 (16.1)
Hypocortisolism related	70 (51.1)	14 (10.2)
Pituitary tumour enlargement related	3 (2.2)	0
QT prolongation related	5 (3.6)	1 (0.7)
Arrythmogenic potential	1 (0.7)	1 (0.7)

Abbreviations: AE, adverse event; AESI, adverse event of special interest; SAS: safety analysis set.

Notes: Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

Source: Pivonello et al 2020 (4)

Table 25 Summary of adverse events (all grades and grade 3/4)

	All patients N=137	
	All grades	**Grade 3-4**
Any adverse event	137 (100%)	78 (56.9%)
Any serious adverse event	50 (36.5%)	39 (28.5%)
AEs requiring dose interruption and/or change	106 (77.4%)	39 (28.5%)
Most common study emergent AEs (occurring in >20% of patients overall		
Nausea	57 (41.6%)	3 (2.2%)
Headache	46 (33.6%)	4 (2.9%)
Fatigue	39 (28.5%)	3 (2.2%)
Adrenal insufficiency*	38 (27.7%)	6 (4.4%)
Nasopharyngitis	31 (22.6%)	1 (0.7%)
Vomiting	30 (21.9%)	4 (2.9%)
Glucocorticoid deficiency†	29 (21.2%)	5 (3.6%)

*Patients with multiple events in the same category are counted only once in that category. *Adrenal insufficiency includes 'relative adrenal insufficiency', 'adrenocortical insufficiency', 'hypoadrenalcorticism', 'suspected hypoadrenalism', 'mild adrenal insufficiency', and 'adrenal deficiency'; †Glucocorticoid deficiency includes 'hypocortisolism', 'symptoms of hypocortisolism', 'relative hypocortisolism', 'suspicion of hypocortisolism', 'asymptomatic/symptomatic hypocortisolism', and 'subjective symptoms of hypocortisolism'; clinical signs and serum cortisol measurements were not systematically collected.*
Abbreviations: AE, adverse event
Source: Pivonello et al 2020 (4)

Most hypocortisolism-related AEs occured during the first 26 weeks of treatment. AEs related to adrenal hormone precursor accumulation were less frequent in the extension Phase than the core (occurring in 46%, 19%, 15% and 15% of patients with a safety assessment during the following intervals: baseline–W26, W26–48, W48–72 and W72–study end). In addition, the mean (SD) testosterone level tended to decrease in females during the extension (0.8 [0.7] ×ULN at W72). The final results of the extension phase (week 72) showed that osilodrostat was well tolerated, with no new safety signals reported during long-term treatment. (26) No additional cases of hirsutism occurred in the extension period.

5.1.2.3 LINC-2

Efficacy

LINC-2 is an extension of LINC-1 (described in section 4.2.4). mUFC data at week 4 is to be found in the result section for LINC-1. In LINC-2 the mUFC measurement at week 10 is the closest timepoint to week 12 requested by DMC, and will be reported in this section. The longest efficacy timepoint of LINC-2 is at week 22. The longest efficacy timepoint is 19 months, i.e. 83 weeks, which is part of the optional extension phase.

In LINC-2, all patients had normalization of mUFC at some point during the study. At Week 10, all 19 patients were considered to have controlled disease. 84.2% (CI 60.4, 96.6) of all patients had controlled disease, and in each cohort the proportion was 80.0 % (CI 51.9, 98.3) and 100% (CI 39.8, 100.0) in the Expansion cohort and Follow-up cohort, respectively. At week 22, 78.9% (CI 54.4,94.0) of the overall (N=19) patient population achieved complete response (safety analysis set). (5)

Quality of Life

Quality of life was not assessed, hence not included in this section.

Safety

Data in this subsection are based on data on file (Report date: 24 November 2014) which presented efficacy data for patients who completed 22 weeks of treatment with osilodrostat and safety data from the 12-month long-term extension phase up to the data cut-off date of 23 December 2013 when the last patient completed 22 weeks of osilodrostat treatment (and other patients had been enrolled for up to 50 weeks). Safety data is presented by treatment cohort (Expansion or Follow-up).

The majority of patients (94.7%; [n=18/19]) experienced at least one AE (Table 26). Only two patients had a SAE (Grade 3/4), both were in the Expansion Cohort. A total of nine patients (Expansion, n=7; Follow-up, n=2) had an AESI. One patient in the Expansion cohort discontinued due to Grade 3/4/ AEs. No deaths were reported in the study. The median duration of exposure was 25.1 and 38.9 weeks in the Expansion cohort and Follow-up cohort, respectively.

Table 26 LINC-2 Core - Incidence of AEs, SAEs, and Other Significant AEs (SAS)

Category	Expansion Cohort N=15		Follow-up Cohort N=4	
	All grades, n (%)	Grade 3/4, n (%)	All grades, n (%)	Grade 3/4, n (%)
All deaths*	0		0	
Total AEs	14 (93.3)	4 (26.7)	4 (100)	3 (75.0)
AEs suspected to be drug-related	14 (19.3)	3 (20.0)	3 (75.0)	3 (75.0)
Serious AEs	2 (13.3)	2 (13.3)	0	0
AEs leading to discontinuations	1 (6.7)	1 (6.7)	0	0
AEs requiring dose interruption and/or change	7 (46.7)	1 (6.7)	2 (50.0)	1 (25.0)
AEs of special interest	7 (46.7)	1 (6.7)	2 (50.0)	1 (25.0)

Abbreviations: ACTH, Adrenocorticotropic hormone; AEs, adverse events; SAS, safety analyses set

*Key: * Severity grade assessed by National Cancer Institute Common Terminology Criteria, version 4.03*

Source: data on file

Seven (46.7%) patients in the Expansion cohort and 2 (50%) patients in the Follow-up cohort reported AEs requiring dose adjustment or study drug interruption. The most frequent AEs requiring does adjustment or study-drug interruption were adrenal insufficiency and fatigue. Proportion of patients who experience treatment-requiring side effects have not reported, hence not included.

Table 27 Most common AEs

Clinical AEs	All grades, N=19 n (%)	Grade 3-4 , N=19 n (%)
Nausea	6 (31.6)	0
Diarrhea	6 (31.6)	0
Asthenia	6 (31.6)	0
Adrenal insufficiency	6 (31.6)	1 (5.3)
Nasopharyngitis	5 (26.3)	0

Source: Fleseriu et al 2016 (5)

LINC-2 extension results (data on file)

Data in this subsection are based on the LINC-2 data on file (Report date: 29 June 2020) which reported on the cumulative, long-term safety for all patients who were enrolled in Part II of C2201 consisting of extension -1 and -2. The analyses were conducted after all enrolled patients had completed the extension phase or discontinued earlier. This data cut-off date was 22 October 2019.

16 of the 17 patients (male: female, 5:11) who completed week 22 of LINC-2 entered the extension.

Efficacy

Results of the long-term efficacy analyses (patients who completed extension phase or discontinued in Part II of LINC-2) demonstrated that the response rate following osilodrostat treatment remained at least 50.0% throughout the study except at the End of study visit, when only four patients (21.1%) responded to the treatment.

The study showed with long-term data that normal mUFC levels were maintained up to 19 months in most CD patients who entered the extension and no patients experienced escape. The number of controlled UFC responders was 13/16 (81.3%) at 19 months.

Safety Data – At Study Completion (Extension Phase)

Safety data are presented by all patients group, which include patients who discontinued or completed the extension phase in Part II of C2201.

Overview of Safety

Median treatment duration was 281.7 (2.0–350.6) weeks, with more than half of the patients receiving treatment for >234 weeks. All patients experienced at least one AE including 18 patients (94.7%) who experienced AEs considered to be related to study treatment. (Table 28) Twelve patients (63.2%) experienced Grade ≥3 AEs, including 8 patients (42.1%) who experienced treatment related AEs of severity Grade ≥3. Six patients (31.6%) experienced SAEs and 3 patients (15.8%) experienced treatment related SAEs. Five subjects (26.3%) experienced Grade ≥3 SAEs, of which 1 patient experienced treatment related Grade ≥3 SAE. No patient died either during the study or the 30 days follow-up period.

Table 28 LINC-2 – Overview of AEs (Long-Term Safety; SAS)

Category	Patients N=19	
	All grades, n (%)	Grade ≥3, n (%)
AEs	19 (100)	12 (63.2)
Treatment-related	18 (94.7)	8 (42.1)
SAEs	6 (31.6)	5 (26.3)
Treatment-related	3 (15.8)	1 (5.3)

AEs leading to discontinuation	3 (15.8)	1 (5.3)
Treatment-related	2 (10.5)	1 (5.3)
AEs leading to dose adjustment/interruption	15 (78.9)	5 (26.3)
AEs requiring additional therapy	17 (89.5)	8 (42.1)

Abbreviations: AEs, adverse events; SAS, Safety Analysis Set; SAEs, serious adverse events.

Note: Numbers (n) represent counts of patients. A patient with multiple severity grades for an AE is only counted under the maximum grade.

Source: Data on File

Common AEs

The most common (occurring in ≥20% of patients) reported AEs were nausea (52.6%), adrenal insufficiency (47.4%), headache (47.4%), blood corticotrophin increased (42.1%), asthenia (36.8%), diarrhea (36.8%) and abnormal hormone level (36.8%) (Table 29). The most commonly (>15% overall) reported Grade ≥3 AEs were hypertension (21.1%) and pituitary-dependent CS (15.8%).

Table 29 LINC-2 – Commonly (≥20% of Patients) Reported AEs (Long-Term Safety; SAS)

Category	Patients N=19	
	All grades, n (%)	Grade ≥3, n (%)
Number of patients with at least one event	**19 (100)**	**12 (63.2)**
Nausea	10 (52.6)	0
Adrenal Insufficiency	9 (47.4)	2 (10.5)
Headache	9 (47.4)	1 (5.3)
Blood corticotrophin increased	8 (42.1)	0
Asthenia	7 (36.8)	0
Diarrhea	7 (36.8)	0
Hormone level abnormal	7 (36.8)	0
Arthralgia	6 (31.6)	0
Blood testosterone increased	6 (31.6)	0
Fatigue	6 (31.6)	0
Urinary tract infection	6 (31.6)	0
Abdominal pain	5 (26.3)	1 (5.3)
Nasopharyngitis	5 (26.3)	0
Blood creatine phosphokinase increased	4 (21.1)	1 (5.3)
Dizziness	4 (21.1)	0
Hypertension	4 (21.1)	4 (2.1)
Malaise	4 (21.1)	0
Oedema peripheral	4 (21.1)	0

Abbreviations: AEs, adverse events; SAS, Safety Analysis Set.

Note: Numbers (n) represent counts of patients. A patient with multiple severity grades for an AE is only counted under the maximum grade.

Serious Adverse Events

SAEs were reported in 31.6% of patients. Adrenal insufficiency (10.5%) and pituitary-dependent Cushing's syndrome (10.5%) were the most frequent and occurred in two patients each. SAE Grade ≥3 (Pituitary-dependent Cushing's syndrome) was reported in two patients (Table 30). Two patients experienced an SAE (adrenal insufficiency) suspected by the Investigator to be related to study treatment, of which one patient experienced SAE with Grade ≥3 severity.

Table 30 Serious Adverse Events (Long-Term Safety; SAS)

Category	Patients N=19	
	All grades, n (%)	Grade ≥3, n (%)
Number of patients with at least one event	**6 (31.6)**	**5 (26.3)**
Adrenal insufficiency	2 (10.5)	2 (10.5)
Pituitary-dependent Cushing's syndrome	2 (10.5)	1 (5.3)
Abdominal pain	1 (5.3)	0
Electrocardiogram QT prolonged	1 (5.3)	1 (5.3)
Food poisoning	1 (5.3)	1 (5.3)
Gastroenteritis	1 (5.3)	1 (5.3)
Headache	1 (5.3)	1 (5.3)
Neoplasm progression	1 (5.3)	1 (5.3)
Non-cardiac chest pain	1 (5.3)	1 (5.3)
Pituitary tumor benign	1 (5.3)	0
Pyelonephritis	1 (5.3)	1 (5.3)
Supraventricular extrasystoles	1 (5.3)	1 (5.3)
Ventricular extrasystoles	1 (5.3)	0

Abbreviations: SAS, Safety Analysis Set.

Note: Numbers (n) represent counts of patients. A patient with multiple severity grades for an AE is only counted under the maximum grade.

AEs Leading to Discontinuation, Dose Adjustment And/or Interruption, and Requiring Additional Therapy

Three patients (15.8%) experienced AEs, which lead to discontinuation of the study treatment of which one patient experienced Grade ≥3 AE. Fifteen patients (78.9%) experienced AEs that lead to dose adjustment or dose interruption, of which the most frequent were adrenal insufficiency (47.4%), nausea (15.8%) and fatigue (15.8%). Five patients reported Grade ≥3 AEs requiring the dose adjustment or dose interruption. Seventeen patients (89.5%) experienced AEs requiring additional therapy, of which the most frequent (>20%) were urinary tract infections (26.3%), headache (26.3%), adrenal insufficiency (21.1%), nausea (21.1%), abdominal pain (21.1%), and hypertension (21.1%).

AEs of Special Interest/Safety Topics of Interest

AEs with a specific clinical interest are presented in Table 31. Twelve patients (63.2%) experienced adrenal hormone-related AEs of whom 4 patients (21.1%) experienced Grade 3 AEs. Seven patients (36.8%) experienced AEs suspected to be related to the study treatment. Two patients (10.5%) experienced AEs requiring study treatment dose adjustment. Ten patients (52.6%) experienced AEs requiring additional therapy. There were no fatal AE or SAE related to adrenal hormones.

One patient (5.3%) experienced arrhythmogenic potential AE (syncope) requiring dose adjustment for study treatment. Eleven patients (57.9%) experienced hypocortisolism related AEs and all these AEs were suspected to be related to the study treatment. Two patients (10.5%) experienced Grade 3 AEs. Two patients (10.5%) experienced SAEs with one SAE leading to hospitalization. Eleven patients (57.9%) experienced AEs requiring study treatment dose interruption and 4 patients (21.1%) experienced AEs requiring additional therapy. One patient (5.3%) experienced QT prolongation, which was related to study treatment and lead to hospitalization and dose adjustment.

Table 31 LINC-2 – Adverse Events of Special Interest, Irrespective of Study Treatment (Long-Term Safety; SAS)

Number of patients with at least one event	Patients		
	Expansion Cohort, N=15	Follow-up Cohort, N=4	All Patients, N=19
Adrenal Hormone Precursor Accumulation related AEs	8 (53.3)	4 (100)	12 (63.2)
Arrhythmogenic potential AEs	1 (6.7)	0	1 (5.3)

Hypocortisolism related AEs	7 (46.7)	4 (100)	11 (57.9)
QT-prolongation-related AEs	1 (6.7)	0	1 (5.3)

Abbreviations: AEs, adverse events; SAS, Safety Analysis Set.

Note: Numbers (n) represent counts of patients.

Proportion of treatment required adverse events were not reported for this, hence not included in this section.

5.1.2.4 LINC-1

Efficacy

mUFC was measured at various time points and includes the measurement at 4 weeks requested by DMC. The study also includes a measurenent at week 12 (84 days in study), However, the period week 10-12 being the washout period, we find it more apporporate to use week 10 (day 70 in study). The longest efficacy timepoint is 19 months, i.e. 83 weeks, which is part of the optional LINC-2 extension phase.

At week 10 (day 70) 100 % (4 of 4 patients) of the patients were at complete response.

Quality of Life

Quality of life was not assessed, hence not included in this section.

Safety

In LINC-1, all patients experienced at least one AE, with the majority being mild or moderate in nature and none led to treatment discontinuation (Table 32). The most common AEs were fatigue (58%), nausea (42%), headache (25%), diarrhoea (25%), hypokalemia (25%), muscle spasms (25%), and vomiting (25%).

Table 32 LINC-1 – Incidence of Most Frequent AEs* by Preferred Term (Experienced By at Least Two Patients (SAS)

Preferred Term, n (%)	All patients N=12
Patients with AE (s)	**12 (100)**
Fatigue	7 (58.3)
Nausea	5 (41.7)
diarrhoea	3 (25.0)
Headache	3 (25.0)
Hypokalemia	3 (25.0)
Muscle spasms	3 (25.0)
Vomiting	3 (25.0)
Abdominal discomfort	2 (16.7)
Abdominal pain	2 (16.7)
Arthralgia	2 (16.7)
Arthropod bite	2 (16.7)
Dizziness	2 (16.7)
Lipase increased	2 (16.7)
Pruritus	2 (16.7)

*Key: * Assessed based on MedDRA preferred terms*

Abbreviations: AEs, adverse events; SAS: safety analysis set.

Four patients had AEs that were managed with dose reduction (from 20 to 10 mg/d in three patients and from 10 to 4 mg/d in one patient, which lasted from 4 to 34 days) or temporary interruption (maximum of two consecutive doses were withheld); these AEs were consistent with adrenal insufficiency and/or steroid withdrawal (moderate fatigue in three patients, mild nausea in two patients, and mild dizziness, mild muscle spasms, and moderate hypotension

[systolic/diastolic BP 90/60 mmHg] in one patient each). No patient withdrew due to AEs. No deaths were reported in LINC-1.

In LINC-1, one SAE was reported, but this was not suspected to be related to study drug. The patient experienced anemia (hemoglobin level rapidly decreased from 7.5 to 4.1 g/dL), with palpitations and chest pain secondary to reactivation of previous Takayasu arteritis. This event resolved with transfusion and may have been related to resolution of hypercortisolemia. There were no reported AEs of hirsutism in the female patients.

Adverse events requiring additional treatment was not gathered during the clinical trials and data is not available in the Data on File.

5.1.2.5 C1201

Efficacy

This is a study with a small number of patients. Nine patients were enrolled into the study. Of the nine patients enrolled in the study, seven completed the 12-week core treatment period. Of the seven patients who completed 12 weeks of study treatment, two completed 48 weeks of study treatment.

Patients were considered complete responders if mUFC ≤ upper limit of normal ULN. mUFC was recorded at various timepoints, including the timepoints of 4 weeks and 12 weeks requested by the DMC and week 48 was identified as the longest recorded timepoint. At week 12, 67.7% (6 of 9 patients) were complete responders (Table 33). When analysed over time, notable reductions were seen in mUFC as early as the 4th week. By Week 8 median mUFC levels were within normal range and maintained up to week 12 of treatment (Table 34). The percentage change from baseline was -83.32%, -94.57% and -95.04% at 4 weeks, 12 weeks and 48 weeks respectively.

Table 33 Proportions of mUFC responders by visit (FAS)

	n (%) [95% CI]
Week 12 (n=9)	6 (66.7) [29.9–92.5]
Week 24 (n=3)	2 (66.7) [9.4–99.2]
Week 48 (n=2)	1 (50.0) [1.3–98.7]

CI: confidence interval, mUFC: mean urinary free cortisol, FAS: full analysis set (who received at least one dose of osilodrostat)

Source: Tanaka et al. 2020 (7)

Table 34 Actual mUFC values for all patients (N=9) (FAS)

Timepoint	Patients	Actual value, nmol/24h	% change from baseline
Baseline	N	9	-
	Median (range)	841.80 (277.9, 10,595.6)	-
Week 4	N	8	8
	Median (range)	185.70 (26.1, 635.8)	-83.32 (-99.4, -38.8)
Week 8	N	8	8
	Median (range)	72.60 (-9.0, 723.5)	-94.37 (-99.8, 94.0)
Week 12	N	7	7
	Median (range)	77.10 (6.2, 141.2)	-94.47 (-99.0, -52.6)
Week 24	N	3	3
	Median (range)	63.90 (40.9, 893.6)	-91.57 (-99.5, -85.2)
Week 48	N	2	2
	Median (range)	511.30 (67.5, 955.1)	-95.04 (-99.1, -91.0)

FAS: full analysis set (who received at least one dose of osilodrostat)

Source: Tanaka et al. 2020 (7)

Quality of life

The Cushing QoL questionnaire was one of the tools used to assess the quality of life. No clinically relevant differences were observed in any of the HRQoL assessments at Week 12, indicating osilodrostat treatment at least sustained the QoL of patients. Moreover, due to the short treatment exposure, no major clinically relevant changes in QoL were expected.

Safety

The time of final data cut-off, all nine patients experienced at least one AE; 6 patients had at least one Grade 3/4 AE. Four of the nine patients had a SAE and three patients discontinued the study drug due to an AE (33.3%). The AEs that led to study drug discontinuation were myocardial infarction (Grade 3), abdominal distention (Grade 1), and reactive psychosis (Grade 2), each in one patient. The majority (77.8%) of patients had AEs that required dose adjustment or interruptions and all these events were suspected to be study drug related. No deaths were reported.

No Grade 4 AEs were observed. Four patients (44.4%) had serious AEs (adrenal insufficiency in 2 patients; myocardial infarction, pneumonia and psychiatric symptom in 1 patient each) all of which were Grade 3 in severity. Adrenal insufficiency in both patients was suspected to be related to the study drug by the investigator. Adrenal insufficiency was also the most commonly observed AE (all grade,77.8% and Grade 3, 22.2%).

Table 35 C1201 - AEs by Preferred Term in >20% of Patients (SAS)

MedDRA Preferred Term	All grades N (%)	Grade 3 N (%)
Total	9 (100)	6 (66.7)
Adrenal insufficiency*	7 (77.8)	2 (22.2)
Gamma-glutamyl transferase increased	3 (33.3)	1 (11.1)
Malaise	3 (33.3)	0
Nasopharyngitis	3 (33.3)	0
Alanine aminotransferase increased	2 (22.2)	2 (22.2)
Aspartate aminotransferase increased	2 (22.2)	0
Blood alkaline phosphatase increased	2 (22.2)	0
Constipation	2 (22.2)	0
Dermatitis acneiform	2 (22.2)	0
Hypokalemia	2 (22.2)	1 (11.1)
Pruritus	2 (22.2)	0
Rash	2 (22.2)	0

Abbreviations: AEs, adverse events; MedDRA, Medical Dictionary of Regulatory Activities; SAS: safety analysis set (all patients who received at least one dose of osilodrostat and had at least one valid post-baseline safety assessment).

*Note: * Adrenal insufficiency includes the reported terms of adrenal insufficiency, hypoadrenalism and adrenal gland hypofunction*

Source: Tanaka et al. 2020 (7)

The high incidence of hypocortisolism-related AEs was seen during the 12-week dose-titration phase, but results should be interpreted with caution because the median duration of treatment in this study was 12 weeks and long-term exposure was limited. Most of the patients with hypocortisolism-related AEs required dose adjustments or interruptions and treatment with glucocorticoids, but none of the patients discontinued study treatment due to this event.

Table 36 C1201 – AESIs by AE Category and Preferred Term (SAS)

AE of special interest MedDRA Preferred Term	All grades N (%)	Grade 3 N (%)
Any AE of special interest	7 (77.8)	3 (33.3)
Hypocortisolism-related AEs	7 (77.8)	2 (22.2)
Adrenal insufficiency*	7 (77.8)	2 (22.2)
Steroid withdrawal syndrome†	1 (11.1)	1 (11.1)

Adrenal hormone precursor accumulation-related AEs	3 (33.3)	1 (11.1)
Hypokalemia	2 (22.2)	1 (11.1)
Weight increased	1 (11.1)	0

Abbreviations: AEs, adverse events; AESI, adverse events of special interest; MedDRA, Medical Dictionary of Regulatory Activities; SAS: safety analysis set.

*Note: *Adrenal insufficiency includes the reported terms of adrenal insufficiency, hypoadrenalism and adrenal gland hypofunction; [l]Steroid withdrawal syndrome includes the reported term of glucocorticoid withdrawal syndrome*

Tanaka et all noted that a total of 8 patients (89.9%) experienced AEs at any primary system organ class requiring additional treatment. The proportion of patients requiring additional therapy for grade 3/4 events was 55.6%. AEs that were most common to require treatment were adrenal insufficiency (66.7%) and gastrointestinal disorders (44.4%).

Table 37 C1201 Adverse events requiring additional treatment (SAS)

Category	All grades N (%)	Grade 3/4 N (%)
AEs requiring additional therapy	8 (88.9)	5 (55.6)
Suspected to be drug-related	5 (55.6)	2 (22.2)

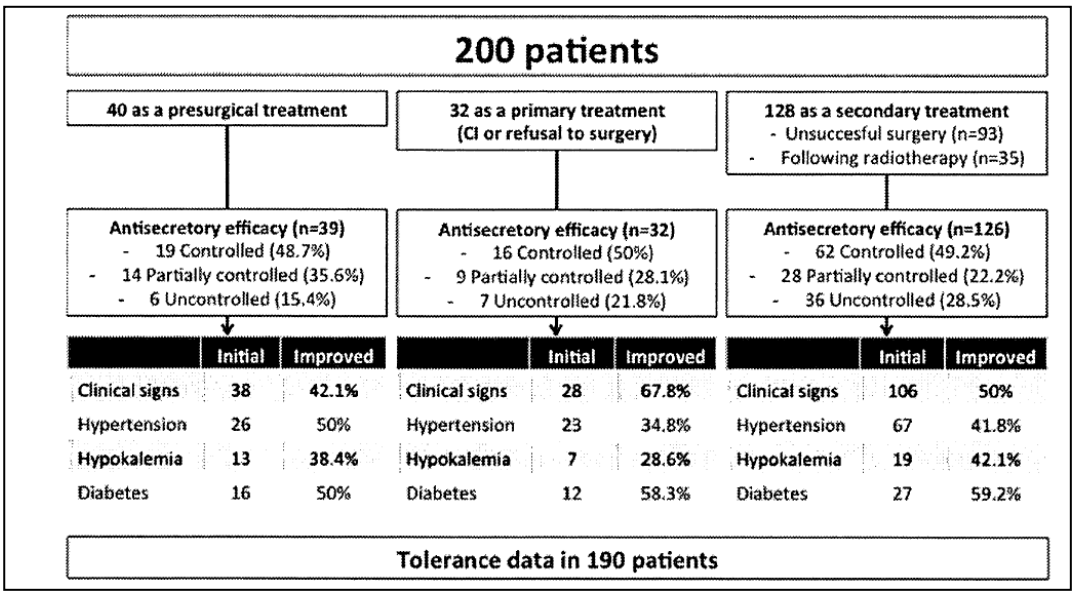
5.1.2.6 Castinetti et al 2014

Results for ketoconazole are based on the largest retrospective patient series currently availabe in the literature. The DMC requested outcomes are not available based on the Castinetti et al 2014 study and have therefore not been included in a table overview. The available results for the study by Castinetti et al 2014 are reported below.

Efficacy

Patients were considered controlled if they had normal 24-hour UFC at 2 consecutive evaluations.
In Figure 3, the most important results are shown, divided by patients who received ketoconazole prior to surgery (n=40), instead of surgery (n=32) or as secondary treatment after failure for first-line treatment (n=128).

Figure 3 Most important results from Castinetti et al 2014



Source: Figure taken from Castinetti et al 2014 (8)

As seen in the figure, ketoconazole achieved complete response in 48,5% of the patients (97 of the 200 patients). A partial response, namely a reduction in the concentration of free cortisol in the urine of 50% or more, but without normalization, occurred in 51 of 200 patients (25.5%). The overall response rate was thus 74.0%.

Fifty-one were treated for more than 24 months with ketoconazole (mean treatment duration, 108.5 ± 244.4 months, ranging from 24.1-135 months). At the last follow-up (more than 24 months), UFC was normalized in 33 of the 51 patients, thus a complete response was achieved by 64.7% in this long-term treated population.

Despite the fact that this phenomenon is not clearly apparent due to the retrospective study design, it seems that in 10-15% of the patients on ketoconazole, the escape phenomenon occurs in which an initial response is lost, probably due to an ACTH-driven feedback mechanism.

Quality of Life

Quality of life was not assessed.

Safety

The most common side effect is an increase in liver enzymes in the blood. Hepatotoxicity occurred mainly at initiation of treatment or after dose escalation. There may be an increased risk of hepatotoxicity in adolescents. Long-term treatment with ketoconazole does not appear to increase the risk of hepatotoxicity. Severe hepatotoxicity, including acute hepatocellular or cholestatic injury or a mixed toxicity pattern, caused by ketoconazole treatment is rare (1/15,000). Most deaths that occur during ketoconazole treatment are due to the underlying condition. Fatal cases have been reported especially when treatment was continued despite an increase in liver enzymes. The second most relevant side effect is adrenal insufficiency caused by overtreatment or stress (mainly infections). This side effect is not associated with any specific dose and usually occurs between 5 and 90 days after initiation of treatment. A serious but uncommon side effect is QT prolongation.

It should be noted that EMA reported in the special warnings of the smpc the need for monitoring of liver function in all patients receiving ketoxonazole. Close follow-up of patients is required due to the risk of serious hepatic toxicity. (16)

Table 38 Overview adverse effects induced by ketoconazole*

Adverse event	Frequency, n (%)
Liver enzyme increase	30 (15.8%)
Gastrointestinal complaints	25 (13.1%)
Adrenal insufficiency	10 (5.4%)
Pruritus	7 (3.7%)
Intense fatigue	2 (1.25%)
Hair loss	2 (1.25%)
Leg edema	2 (1.25%)
Muscle pain	2 (1.25%)
Dyspnea	1 (0.6%)
Hypertriglyceridemia	1 (0.6%)
Leukoneutropenia	1 (0.6%)
Dizziness	1 (0.6%)
Increased creatine level	1 (0.6%)

*For these results, n= 190

5.1.3 Comparative analyses

Comparative analyses of osilodrostat with the current clinical trial evidence in CD are challenging as there are no head-to-head randomized controlled trials of osilodrostat versus other treatments. As shown in the overview from Table 39, due to the variabilities in the included patient populations, differences in timepoints, baseline characteristics, study designs (retrospective/case studies for ketoconazole and prospective randomised placebo controlled trials for osilodrostat), and limited evidence on relevant outcomes it is not feasible to conduct any traditional indirect comparisons to assess the relative efficacy between osilodrostat and ketoconazole. The comparative analysis for this assessment is based on narrative synthesis.

The Committee for Orphan Medicinal Products (COMP) used a naïve comparison based on the scientifically recognized GRADE system in their Orphan Maintenance Assessment Report for osilodrostat to showcase the comparative relative efficacy between osilodrostat and comparators, including ketoconazole. The conclusion of the COMP is of relevance for this assessment:
'Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Isturisa may be of potential significant benefit to those affected by the orphan condition still holds. The sponsor provided data to demonstrate that the use of Isturisa leads to a high response rate in treatment–naïve and pre-treated patients and that the responses are maintained, with no treatment escape cases reported in the pivotal clinical study. ***This constitutes a clinically relevant advantage over all existing authorised products as established in the pivotal trial and by indirect comparisons***.' (2)

The recently published guideline update with consensus on diagnosis and management of Cushing's disease, showed how the Pituitary Society perceived the different available treatments. The Society acknowledges that osilodrostat achieves the highest rates of cortisol normalisation with a more convenient dosing schedule. The following statement is taken from the article: '*When using UFC normalisation as a target, osilodrostat has the highest efficacy on the basis of data from several prospective clinical trials, followed by metyrapone (retrospective and prospective data), ketoconazole (retrospective data), pasireotide (prospective data), and cabergoline (retrospective and prospective data)'. (27)* This statement is aligned withs the submitted data and conclusions written in this reimbursement application.

In this section the outcome parameters requested by DMC form the basis for the comparison (Table 39). As described in the previous sections, two relevant studies were identified for ketoconazole: Castinetti et al. 2008 and Castinetti et al. 2014. However, it was chosen not to use Castinetti et al. 2008 as this patient population is also included in the 2014 paper. Four relevant studies were identified in the SLR for osilodrostat: Pivonello et al. 2020 (LINC-3), Fleseriu et al. 2016 (LINC-2), Bertagna et al. 2014 (LINC-1) and Tanaka et al. 2020 (C1201). In addition, a more recently conducted Phase III trial showing the efficacy and safety with osilodrostat (LINC-4) has been included.

The pivotal LINC-3 Phase III trial with osilodrostat was used for the marketing authorisation. LINC-3 has a randomized clinical trial design and includes the largest number of patients. LINC-4 confirms the efficacy and safety as demonstrated in the LINC-3 trial and shows even better results for some endpoints including mUFC normalisation at week 12 and 36, better tolerance with a longer titration period, long-term response and lack of escape. For this assessment, the LINC-4 study was considered by the expert committee most relevant for the assessment. To support the data for ketoconazole, Castinetti et al. 2014 was considered the most relevant study to be included in this assessment given that this study was used for the marketing authorisation and considered by the COMP report.

Table 39 Naïve Comparison of Evidence for Treatments for Cushing's Syndrome

	Osilodrostat (Gadelha 2022) (3)	Osilodrostat (Pivonello 2020) (4)	Osilodrostat (Fleseriu 2016) (5)	Osilodrostat (Bertagna 2014) (6)	Osilodrostat (Tanaka 2020) (7)	Ketoconazole (Castinetti 2014) (8)
Study design	Phase III Prosspective Randomized Double blind 48 weeks (n=73) *Low risk of bias*	Phase III Prospective Randomized Double blind 48 Weeks (n=137) *(Note: 71 patients were randomized at W26)* *Low risk of bias*	Phase II Prospective Open label (n=19) *Low risk of bias*	Phase II Single arm Non-randomized (n=12) *Low risk of bias*	Phase II Single arm Open label (n=9) *Low risk of bias*	Phase II Retrospective Cohort (n=~200) *High risk of bias*
Efficacy Outcome	Complete response was defined as mUFC ≤ ULN	Complete response was defined as mUFC ≤ ULN	Complete response was defined as mUFC ≤ upper limit of normal ULN.	Complete response was defined as mUFC ≤ upper limit of normal ULN.	Complete response was defined as mUFC ≤ upper limit of normal ULN.	Controlled disease was defined as normal 24-hour UFC at 2 consecutive evaluations
CR at **- Week 4** **- Week 12** **- Longest FU** *(Proportion of patients with CR defined as mUFC <ULN)*	W4: NR W12: 77.1% (37/48) - osilodrostat arm W72: 61.5% (40/65) Overall population	W4: NR W12: 71.5% (98/137) (end dose titration phase – overall population) W72: 81.1% (86/106) (open label phase) 80.2% of those receiving osilodrostat	W4: See LINC-1 W10: 84.2% (16/19) W83 (19m): 81.3% (13/16)	W4: NR W10: 100% (4/4) Longest FU time: See LINC-2	W4: NR W12: 66.7% (6/9) W48: 50% (1/2)	W4: NR W12: NR Variable timing: 48.5%
HRQoL Cushings Disease *(CushingQoL Questionnaire)*	CushingQoL (mean actual change from baseline 12.0 (95% CI: 8.2-15.9) at week 48	CushingQoL (w48: mean absolute change from baseline 14.1 points (95% CI: 10.9-17.3)	No data available	No data available	At week 12 a sustained QoL was observed.	No data available
AEs requiring treatment *(Proportion of patients with treatment requiring AEs)*	91.8% (67/73)	94.9% (130/137); 40.1% (55/137) grade 3/4	89.5% (17/19) (Data from LINC2 extension study)	No data available	89.9% (8/9); 55.6% (5/9) grade 3/4	No data available

	Osilodrostat (Gadelha 2022) (3)	Osilodrostat (Pivonello 2020) (4)	Osilodrostat (Fleseriu 2016) (5)	Osilodrostat (Bertagna 2014) (6)	Osilodrostat (Tanaka 2020) (7)	Ketoconazole (Castinetti 2014) (8)
Treatment discontinuation due to AEs	11.0%	13.1% (9.5% drug related)	15.8% (LINC-2 extension)	0%	33.3% (3/9)	20.5% (41/200)
Common AEs	Decreased appetite (45.2%), Arthralgia (45.2%), Fatigue (38.4%), Nausea (37%), Headace (32.9%), Myalgia (26%), Dizziness (26%)	Nausea (45.3%), Headache (36.5%), Fatigue (32.8%), Adrenal insufficiency (29.2%), Vomiting (24.8%)	Nausea (52.6%), Adrenal insufficiency (47.4%), Headache (47.4%), Blood corticotrophin increased (42.1%), Asthenia (36.8%), Diarrhea (36.8%) and a Abnormal hormone level (36.8%) (LINC-2 extension)	Fatigue (58%), Nausea (42%), Headache (25%), Diarrhoea (25%), Hypokalemia (25%), Muscle spasms (25%), Vomiting (25%)	Adrenal insufficiency (77.8%), Gamma-glutamyl transferase increased (33.3%), Malaise (33.3%), Nasopharyngitis (33.3%)	Liver enzyme increase 15.8% Gastrointestinal complaints 13.1% Adrenal insuffiency 5.4% Pruritus 3.7% Others <1.25%
Grade 3-4 AEs	Hypertension 12.3%, Myalgia 6.8%, Adrenal insufficiency 4.1%, Fatigue 4.1%	Hypertension 11.7%, Headache 4.4%, Adrenal insufficiency 4.4%, Hypokalaemia 4.4%,	Adrenal insufficiency 10.5%, Headache 5.3%, Abdominal pain 5.3% (LINC-2 extension)	NR	Adrenal insuffiency 22.2%, alanine aminotransferase increased 22.2%, Gamma-glutamyl transferase increased 11.1%, Hypokalemia 11.1%	NR Note EMA included a special warning for serious hepatic toxicity in the SmPC

Abbreviations: AEs, adverse events; CD, Cushing's disease; CR, complete response; FU, follow up; HRQoL, health-related quality of life; mUFC, mean urinary free cortisol; RW, randomized withdrawal; UFC, urinary free cortisol; ULN, upper limit of normal

Study design
Osilodrostat has been assessed via randomized prospective trials, including a pivotal Phase III and an additional Phase III study (LINC-4). Comparing the design versus the retrospective cohort study for ketoconazole, we consider the quality in terms of clinical study design higher for osilodrostat and with a low risk of bias. Given the retrospective and non-comparative nature of Castinetti 2014, as well as the lack of statistical adjustment and the presence of various patient profiles, the quality of the evidence should be considered as low and the results described for ketoconazole as exploratory in nature. The trial design also comes with a high risk of bias which may lead to overestimation of the efficacy and underreporting of AEs. The efficacy of ketoconazole has been described using two endpoints, biochemical (normalization or reduction of 24-hour urinary free cortisol levels) and clinical (improvement of clinical symptoms and comorbidities, including high blood pressure and diabetes).

Patient population
The study design of a prospective trial versus a retrospective cohort study also plays a role in the review of the included patient population. Firstly, the inclusion and exclusion criteria for the ketoconazole cohort study were minimal, with no detailed requirement despite being on treatment with ketoconazole for a diagnosed active CD. Secondly, minimal information is available regarding the included patients and therefore it is not feasible to make a comparison between the different patient populations. At minimum, we can conclude that across the various studies for the two treatments, the age of the patients and percentage female enrolled was similar.

The patients on ketoconazole had an average 24-hour urinary free cortisol level of 4.1 times the upper limit of normal. The normal value used in this study was dependent on the test kit used per center and for this reason cannot be compared exactly with the baseline values in LINC-3 and LINC-4. In LINC-4, patients had a mean mUFC at baseline of 3.1xULN. However, since patients in LINC-3 featured a mean 24-hour urinary free cortisol level of 7.3 times the upper limit of normal at baseline, it is evident that the patients in study LINC-3 had a more severe degree of CD compared to ketoconazole.

In addition it should be mentioned that the study C1201 (Tanaka 2020) shows that osilodrostat is safe and efficious in a patient population with non-CD CS. Further information regarding the patient characteristics can be found in Table 16 in section 5.1.1 where the relevant studies are presented in more detail.

Complete response
None of the included studies measured the complete response at week 4. LINC-4 reported a complete response at week 12 of 77.1% in the osilodrostat arm, which is similar to LINC-3 where 71.5% patients randomized to osilodrostat achieved complete response at week 12. The longest follow-up time varied between the osilodrostat studies and complete response ranged from 61.5% (week 72) in LINC-3 till 81.3% (week 83) in LINC-2, showing sustained efficacy for patients on osilodrostat treatment. Regardless of the variable timing it was shown that the complete response with ketoconazole is 48.5%.

An important caveat when indirectly comparing the results of the study by Castinetti et al. 2014 with those of LINC-4 is that response in the ketoconazole study is defined as two consecutive measurements with a normalized cortisol level at the last measurement. This leads to an overestimation of the percentage of responders relative to how response has been defined in studies with osilodrostat in two ways. First, in the osilodrostat studies, patients who discontinued treatment prematurely are by definition counted as non-responders, even though these patients may have had a response before they stopped treatment. While these patients are counted as responders in the retrospective analysis with ketoconazole, this is not the case in the studies of methodologically high quality. Secondly, in studies with osilodrostat, the response is measured at a predefined moment, whereas the retrospective analysis by Castinetti et al. 2014 refers to the last known measurement, and not to a predefined time.

Despite the above afactors which do not favor osilodrostat in the indirect comparison of complete response rates between osilodrostat and ketoconazole (higher pre-treatment cortisol levels, patients who discontinue counted as non-responders and, failure to measure response after a predefined treatment duration), the complete response rate with osilodrostat is 71% in LINC-3 and 77.1% in LINC-4 at week 12 (randomised to osilodrostat) and and 81,1% in LINC-

3 and 61.5% in LINC-4 at week 72 (all patients). Outcomes are significantly higher comparing to the complete response rate of 48.5% as observed with ketoconazole and indicating an improved sustained cortisol normalisation for patients on osilodrostat.

Quality of life

No data is available from the study assessing ketoconazole, therefore a comparison regarding the QoL outcome cannot be made. Nonetheless, it is worth mentioning that osilodrostat achieved a mean absolute change from baseline of 12.0 and 14.0 points at week 48 in LINC-4 and LINC-3 respectively. In view of the established MID of 10.1 point difference, we can conclude that treatment with osilodrostat improves the patient's QoL. This clinically significant improvement was seen from week 12 and maintained throughout the study.

Adverse events

An overview of the most common AEs for both osilodrostat and ketoconazole is provided in Table 39. Before reviewing the different AEs, it should be mentioned that in retrospective studies, such as Castinetti et al 2014, there tends to be an underreporting of AEs due to a less systematic approach of reporting. This bias and thereby underestimation is a common risk in retrospective studies and challenges the comparison to data from RCT which is the basis for the osilodrostat safetey evidence.

Nevertheless, the most significant safety concern of ketoconazole treatment is a potentially increased risk of hepatotoxicity caused by increased liver enzymes. Therefore, the SmPC of ketoconazole includes a special warning in this regard. The increased risk of of a severe AE (hepatotoxicity) is not applicable for the treatment with osilodrostat, where the most common AE is adrenal insufficiency. The data shows that treatment discontinuation due to AEs occurs in higher percentage of patients on ketoconazole versus osilodrostat, with 20.5% versus 11.1% (LINC-4). The percentage of patients requiring additional treatment is not reported in the study by Castinetti et al. 2014 and a comparison with osilodrostat is therefore not feasible. Overall, during the long-term treatment (week 48 till week 72) osilodrostat was well tolerated and no new safety signals were reported.

Overall conclusion

To answer the question 'What is the value of osilodrostat compared ketoconazole in adult patients with endogenous Cushing Syndrome?' we have reviewed the difference in study design, patient population, complete response, QoL and AEs.

- Osilodrostat has been investigated in more robust and multiple prospective studies with a low risk of bias versus ketoconazole's retrospective study, which represents a high risk of bias that may cause overestimation of efficacy respectively underestimation of AEs as compared to an RCT.
- The comparison regarding the complete response as it relates to cortisol normalisation shows a higher efficacy both short and long-term with osilodrostat versus ketoconazole. Osilodrostat shows a sustained cortisol normalisation, with a large proportion of the patients remaining on treatment.
- Osilodrostat demonstrated a clinically significant QoL improvement as demonstrated by the CushingQoL
- Patients on ketoconazole have a risk of severe hepatic toxicity requiring regular monitor of the liver enzyme function, whereas the risk of adrenal insufficiency with osilodrostat is manageable by dose reductions or interruptions.
- In addition, there are potential clinically relevant drug-drug interactions with ketoconazole which does not occur with osilodrostat.
- Overall, osilodrostat has been assessed in more robust studies, shows better and sustained efficacy while being well tolerated.

5.2 Clinical question 2: What is the value of osilodrostat compared to metyrapone in adult patients with endogenous Cushing's syndrome?

Population
Adult patients with endogenous Cushing's syndrome.
Intervention
Osilodrostat (starting dose 2 mg twice daily, then individual dosing on background of response and tolerability).
Comparator
Metyrapone 250mg x 3-4 daily, max dose 6000mg

Outcomes

- Proportion of patients with complete response at Week 4
- Proportion of patients with complete response at Week 12
- Proportion of patients with complete response at longest follow up
- Quality of Life (CushingQoL)
- Proportion of patients with adverse events requiring treatment

5.2.1 Presentation of relevant studies

As previously described in section 5.1.3 comparative analyses of osilodrostat are challenging as there are no head-to-head randomized controlled trials of osilodrostat versus other treatments

Study characteristics

A summary of the study characteristics is presented in Table 40. The present literature review identified 5 full-texts studies addressing the clinical question defined above and one additional study (PROMPT). For more details per individual study, please refer to section 4.2 and 4.3 where the main characteristics of the studies are desrcibed.

Table 40 Study characteristics for question 2

Study name (Trial name / NCT)	Intervention/ comparator	Number screened Number enrolled Number randomized	Study setting Study country	Study design Blinding Study phase	Duration of study (weeks)
Pivonello, 2020 (LINC3/ NCT02180217/ EUCTR2013-004766-34-NL)	Osilodrostat/LCI699 (Period 1 +2) Osilodrostat/LCI699 (Period 3-RCT) Placebo (Period 3-RCT) Osilodrostat/LCI699 (Overall patients)	Screened: 202 Enrolled: 137 Randomized: 71	Multi-centre international Argentina, Austria, Bulgaria, Canada, China, Colombia, France, Germany, India, Italy, Japan, Korea, Netherlands, Russian Federation, Spain, Thailand, Turkey, UK, and US	RCT Double blind Phase III	Overall study: 48 weeks RCT phase: 8 weeks Extension phase (optional): 72 weeks
Gadelha, 2022 (3) LINC-4	Osilodrostat Placebo	Screened: 119 Enrolled: 74 Randomized: 73	Multi-centre Belgium, Brazil, Canada, China, Costa Rica, Poland, Portugal, Russian Federation, Spain, Switzerland, Thailand, Turkey, United States,	RCT Double blind Phase III	Overall study: 48 weeks RCT phase: initial 12 weeks Extension phase (optional): up to week 96

Fleseriu, 2016 (LINC-2/NCT01331239)	Osilodrostat	Screened: 19 Enrolled: 19 Randomized: NA	Multi-centre NR	Prospective Open label Phase II	22 weeks Extension phase (optional): 83 weeks (converted from 19 months reported in study; calculated as 19X30.5/7)
Tanaka, 2020 (NCT02468193)	Osilodrostat	Screened: 9 Enrolled:9 Randomized: NA	Multi-centre Japan	Single arm Open label Phase II	Core study: 48 weeks Extension phase (optional): 24 weeks
Bertagna , 2014 (LINC1 (core study); (LINC 2 (extension study)/ NCT01331239)	Osilodrostat/LCI699 Osilodrostat/LCI699	Screened: NR Enrolled: 12 Randomized: NA	Multi-centre international Italy, France and US	nRCT single arm NR Phase II	Core study: 10 weeks Extension phase: 22 weeks
Daniel et al 2015	Metyrapone	Screened: NR Enrolled: 195 Randomized: NA	Multi-centre international England, Wales	Retrospective observational NA NA	Average duration of treatment was 8 months (median 3 months, range 3 d to 11.6 y).
Nieman, 2022 (PROMPT, NCT02297945)	Metyrapone	Screened: 89 Enrolled: 50 Randomized: NA	Multi-centre international Belgium, Germany, Hungary, Italy, Poland, Romania, Spain, Turkey	Prospective, open-label, Phase III/IV	Overall study: 36 weeks RCT phase: initial 12 weeks Extension phase (optional): up to week 36

Patient characteristics

A summary of the patient characteristics is presented in Table 41, for more details refer to the individual study characteristics in section 4.2 and 4.3.

Table 41 Patient characteristics for question 2

Study name	Intervention/ comparator	Mean age (years) Male, n (%)	Type of CS, n (%)	Weight Mean BMI (kg/m2)	Prior treatment, n (%) • Surgery • Medications • Radiation	Comorbidities	Mean mUFC (SD)
Gadelha, 2022 (3) LINC-4	Osilodrostat	41.0 5 (10.4)	Microadenoma: 30 (62.5) Macroadenoma: 17 (35.4) Missing 1 (2.1)	78.8 NR	41 (85.4) 26 (54.2) 6 (12.5)	NR	421.3 (291.3)
	Placebo	37.0 7 (28.0)	Microadenoma: 20 (80.0) Macroadenoma: 4 (16.0) Missing 1 (4.0)	77.3 NR	23 (92.0) 19 (76.0) 3 >(12.0)	NR	451.5 (535.1)
	All patients	41.2 12 (16.4)	Microadenoma: 50 (68.5) Macroadenoma: 21 (28.8) Missing 3 (2.7)	78.3 NR	64 (87.7) 45 (61.6) 9 (12.3)	NR	431.7 (388.6)
Pivonello, 2020 (LINC-3)	Osilodrostat (Period 1+2)	NR 31 (22.6)	Pituitary adenoma: 137 (100)	NR 30.3	102 (74.5) 120 (87.6) 22 (16.1)	NR	NR
	Osilodrostat (Period 3-RCT)	NR 6 (16.6)	Pituitary adenoma: 36 (100)	NR NR	26 (72.2) 32 (88.9) 6 (16.7)	NR	890.0 (1275.66)
	Placebo (Period 3-RCT)	NR 13 (37.1)	Pituitary adenoma: 35 (100)	NR NR	24 (68.6) 33 (94.3) 5 (14.3)	NR	560.0 (548.84)
	Osilodrostat (Overall patients)	NR 31 (22.6)	Pituitary adenoma: 137 (100)	NR 30.3	102 (74.5) 120 (87.6) 22 (16.1)	NR	1,006.0 (1,589.86)
Fleseriu, 2016 (LINC-2)	Osilodrostat	36,8 5 (26.3)	NR	NR NR	NR NR NR	NR	1371 (2734)
Tanaka, 2020 C1201	Osilodrostat	NR 2 (22.2)	Adrenal adenoma: 5 (55.5%) Ectopic CS: 3 (33.3) Other: 1 (11.1)	NR NR	5 (55.6) 1 (11.1) 0 (0)	NR	NR
Bertagna , 2014	Osilodrostat	39 4 (33.3)	Pituitary adenoma: 12 (100)	85.1 33.8	1 (8.3) 12 (100)	Hypertension: 3 (NR)	4.7-fold above the ULN (SEM

					0 (0)		1.3)
	Osilodrostat (expansion cohort + follow up cohort)	36.8 5 (26.3)	NR	NR NR	NR 17 (89.5) NR	NR	NR
	Osilodrostat (expansion cohort)	37.5 4 (26.7)	NR	NR NR	NR 13 (86.7) NR	NR	NR
	Osilodrostat (follow up cohort)	34.3 1 (25)	NR	NR NR	NR 4 (100) NR	NR	NR
Daniel, 2015	Metyrapone	49.6 NR	CD: 115 (59%) Ectopic ACTH syndrome (EAS): 37 (19%) Adrenal adenoma: 30 (15.4%) Adrenocortical carcinoma (ACC): 10 (5.1%) ACTH-independent adrenal hyperplasia: 3 (1.5%)	NR NR	NR NR NR	Hypertension: 126 (64.6) Diabetes mellitus: 69 (35.3)	For the pretreatment population (n=37) the UFC was: 1483 nmol/24 h (537 µg/24 h)
Nieman, 2022 (PROMPT, NCT02297945)	Metyrapone	46.8 15 (30.6)	NR	84 30.5	30 (61.2) 25 (51.0) 5 (10.2)	NR	1,041.7 (1,337.0)

5.2.2 Results per study

Osilodrostat (LIN-4 [Gadelha et al 2022], LINC-3 [Pivonello et al 2020], LINC-2 [Fleseriu et al 2016], LINC-1 [Bertagna et al 2014], C1201 [Tanaka et al. 2020])

Results related to the studies assessing osilodrostat are covered in clinical question 1. Details regarding the PROMPT study can be found in section 6.1

5.2.2.1 Daniel et al. 2015

The DMC requested outcomes are not available due to the lack of information reported in the Daniel et al. 2015 study and have therefore not been included in a table overview. The available results for the study by Daniel et al. 2015 are reported below.

Efficacy

Measurements included biochemical parameters such as mean serum cortisol "day-curve" (CDC) (target 150 –300 nmol/L), 9 AM serum cortisol and 24-hour urinary free cortisol (UFC), of which the latest is of interest for the question addressed by the DMC. Of the 195 patients, a total of 164 patients received metyrapone monotherapy, and all monitoring tests showed significant improvement during treatment.
The frequency of the monitoring visits was variable with some centers opting for inpatient tests at the introduction of treatment and other centers using outpatient monitoring every few weeks; 81% of patients were treated with dose titration and 19% with "block-and-replace" (where the dose of metyrapone was quickly up-titrated to achieve blockade of cortisol synthesis and a replacement dose of glucocorticoid was added to provide background physiological levels). One outcome which could be considered of relevance for this review is the control of cortisol levels at the last review in the patients on metyrapone monotherapy.

At the last review, the control of cortisol in patients who received metyrapone as monotherapy showed 43% of the patients who had UFC being controlled (n=37). The difference in UFC between first and last evaluation was (1483 nmol/24 h [537 µg/24 h] vs 452.6 nmol/24 h [164 µg/24 h]; P = 0.003).

Quality of Life

Quality of life was not assessed.

Safety

Adverse events occurred in 48/195 patients (25%). The most common adverse events were gastrointestinal upset (23%) and hypoadrenalism (7%, symptoms of dizziness, hypotension, with biochemical confirmation). Most AEs (39/56) occurred within two weeks of initiation or dose increase, all reversible.

Patients with confirmed hypoadrenalism were managed either by addition of glucocorticoid (regimen change to a block-and-replace) or temporary cover with glucocorticoid and simultaneous reduction of metyrapone dose. In 15% of cases, the metyrapone dose was reduced. In 12 cases (23%), metyrapone was withdrawn temporarily or permanently, with 11 out of 12 patients showing full resolution, and in one, symptoms continued but became less severe, muscle aches at presentation worsened during metyrapone therapy but returned to pretreatment levels after drug withdrawal. Symptoms of hyperandrogenism were not frequent; hirsutism was not reported, and there was only one case of worsening acne during treatment. Similarly, edema was only reported in one case, but the causative drug was

thought to be a calcium channel blocker. Hypoglycemia was reported in three patients on diabetic medications and was associated with improvement of hypercortisolism.

In the section other considerations, we have provided additional information relevant for metyrapone based on the PROMPT study which showed complete response based on a RCT (section 6.1). This study has not come up in the SLR, given that currently only abstracts and oral presentations are available.

5.2.3 Comparative analyses

As previously mentioned, due to the variabilities in the included patient populations, differences in timepoints, baseline characteristics, study designs (retrospective/case studies for metyrapone and prospective randomised placebo-controlled trials for osilodrostat), and limited evidence on relevant outcomes, it was in the original submissiono not feasible to conduct any traditional indirect comparisons to assess the relative efficacy between osilodrostat and metyrapone. However, recently more detialed data has become available for the PROMPT study and besides the naive analysis, been included for this assessment.

The COMP used a naïve comparison, based on the scientifically recognized GRADE system, in their Orphan Maintenance Assessment Report for osilodrostat to showcase the comparative relative efficacy between osilodrostat and metyrapone. (2) As shown in the comparative analysis for question 1 (section 5.3.3), the COMP acknowledged the superiority of osilodrostat versus comparators for the treatment of CS based on this comparative analysis.

One relevant study was identified in the literature search for metyrapone: Daniel et al 2015. This respective study is currently the largest study where the effect of metyrapone was assessed and considered in the COMP report. Four relevant studies were identified for osilodrostat: Pivonello et al. 2020 (LINC-3), Fleseriu et al. 2016 (LINC-2), Bertagna et al. 2014 (LINC-1) and Tanaka et al. 2020 (C1201).

In addition to the SLR, two studies have been included which support the evidence for both osilodrostat (LINC-4) and metyrapone (PROMPT). This recently conducted additional Phase III trial with osilodrostat (LINC-4) confirms the provided evidence on efficacy and safety as presented in the LINC-3 trial and shows even better results for some endpoints including normalisation at week 12 and 36, better tolerance with a longer titration period, long-term response and lack of escape. The most relevant results and details regarding trial design are shown in section 8.4**Error! Reference source not found.**. In addition to the selected study for metyrapone in the SLR, a more recently published study (PROMPT) presents results of the only prospective, multicenter, open-label, Phase III trial . This study provides the only evidence in terms of complete response gathered via a prospective study for metyrapone and thus should be considered for this assessment. Details regarding results and study design are reported in the other considerations section 6.1.

The pivotal LINC-3 Phase III trial with osilodrostat, was used for the marketing authorisation. LINC-3 has a randomized clinical trial design and includes the largest number of patients. LINC-3 has a randomized clinical trial design and includes the largest number of patients. For this assessment, the LINC-4 study was considered by the expert committee most relevant for the assessment.

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Table 42 Naïve Comparison of Evidence for Treatments for Cushing's Syndrome versus metyrapone

	Osilodrostat (Gadelha 2022) (21)	Osilodrostat (Pivonello 2020) (4)	Osilodrostat (Fleseriu 2016) (5)	Osilodrostat (Bertagna 2014) (6)	Osilodrostat (Tanaka 2020) (7)	Metyrapone (Daniel 2015) (10)
Study design	Phase III Prosspective Randomized Double blind 48 weeks (n=73) *Low ris of bias*	Phase III Prospective Randomized Double blind 48 Weeks (n=137) *(Note: 71 patients were randomized at W26)*	Phase II Prospective Open label (n=19)	Phase II Single arm Non-randomized (n=12)	Phase II Single arm Open label (n=9)	Retrospective Cohort (n=195)
Efficacy Outcome	Complete response was defined as mUFC ≤ ULN	Complete response was defined as mUFC ≤ ULN	Complete response was defined as mUFC ≤ upper limit of normal ULN.	Complete response was defined as mUFC ≤ upper limit of normal ULN.	Complete response was defined as mUFC ≤ upper limit of normal ULN.	UFC ≤ upper limit of normal ULN for the assey used
CR at **- Week 4** **- Week 12** **- Longest FU** *(Proportion of patients with CR, defined as mUFC <ULN)*	W4: NR W12: 77.1% (37/48) - osilodrostat arm W72: 61.5% (40/65) Overall population	W4: NR W12: 71.5% (98/137) (end dose titration phase – overall population) W72: 81.1% (86/106) (open label phase) 80.2% of those receiving osilodrostat	W4: See LINC-1 W10: 84.2% (16/19) W83 (19m): 81,3% (13/16)	W4: NR W10: 100% (4/4) Longest FU time: See LINC-2	W4: NR W12: 66.7% (6/9) W48: 50% (1/2)	43% at variable timepoints
HRQoL Cushings Disease *(CushingQoL Questionnaire)*	CushingQoL (mean actual change from baseline 12.0 (95% CI: 8.2-15.9)	CushingQoL (w48: mean absolute change from baseline 14.1 points (95% CI: 10.9-17.3)	No data available	No data available	At week 12 a sustained QoL was observed.	No data available
AEs requiring treatment *(Proportion of patients with*	91.8% (67/73)	94.9% (130/137); 40.1% (55/137) grade 3/4	89.5% (17/19) (Data from LINC2 extension study)	No data available	89.9% (8/9); 55.6% (5/9) grade 3/4	No data available

	Osilodrostat (Gadelha 2022) (21)	Osilodrostat (Pivonello 2020) (4)	Osilodrostat (Fleseriu 2016) (5)	Osilodrostat (Bertagna 2014) (6)	Osilodrostat (Tanaka 2020) (7)	Metyrapone (Daniel 2015) (10)
treatment requiring AEs)						
Treatment discontinuation due to AEs	11.0%	13.1% (9.5% drug related)	15.8% (LINC-2 extension)	0%	33.3% (3/9)	No data available
Common AEs	Decreased appetite (45.2%), Arthralgia (45.2%), Fatigue (38.4%), Nausea (37%), Headace (32.9%), Myalgia (26%), Dizziness (26%)	Nausea (45.3%), Headache (36.5%), Fatigue (32.8%), Adrenal insufficiency (29.2%), Vomiting (24.8%)	Nausea (52.6%), adrenal insufficiency (47.4%), headache (47.4%), blood corticotrophin increased (42.1%), asthenia (36.8%), diarrhea (36.8%) and abnormal hormone level (36.8%) (LINC-2 extension)	Fatigue (58%), nausea (42%), headache (25%), diarrhoea (25%), hypokalemia (25%), muscle spasms (25%), vomiting (25%)	Adrenal insufficiency (77.8%), gamma-glutamyl transferase increased (33.3%), malaise (33.3%), nasopharyngitis (33.3%)	Gastrointestinal upset (23%) hypoadrenalism (7%, symptoms of dizziness, hypotension, with biochemical confirmation)
Grade 3-4 AEs	Hypertension 12.3%, Myalgia 6.8%, Adrenal insufficiency 4.1%, Fatigue 4.1 %	Hypertension 11.7%, Headache 4.4%, Adrenal insufficiency 4.4%, Hypokalaemia 4.4%,	Adrenal insufficiency 10.5%, Headache 5.3%, Abdominal pain 5.3%	NR	Adrenal insuffiency 22.2%, alanine aminotransferase increased 22.2%, Gamma-glutamyl transferase increased 11.1%, Hypokalemia 11.1%	NR

Abbreviations: AEs, adverse events; CD, Cushing's disease; CR, complete response; FU, follow up; HRQoL, health related quality of life; mUFC, mean urinary free cortisol; RW, randomized withdrawal; UFC, urinary free cortisol; ULN, upper limit of normal

Study design
Osilodrostat has been assessed via randomized prospective trials, including a pivotal Phase III and additional Phase III study (LINC-4). Comparing the design versus the retrospective cohort study for metyrapone (Daniel et al. 2015), we consider the quality in terms of clinical study design higher for osilodrostat. Given the retrospective and non-comparative nature of Daniel et al. 2015, as well as the lack of statistical adjustment and the presence of various patient profiles, the results described for metyrapone in the naïve comparison should be considered as exploratory in nature. The trial design also comes with a high risk of selection bias, with only patients who are likely to respond and those staying on long-term treatment, thus excluding patients who do not respond or discontinue, included in the cohort. Lastly the efficacy of metyrapone has been reviewed by different monitoring tests and at variable timepoints, which challenges the interpretation of the results. Therefore, the recently developed matched adjusted indirect comparison (MAIC) between LINC-4 and PROMPT have been included. Both studies have a prospective study design.

Patient population
In this study there is a large variation in the reason and method of use of metyrapone. First, of 195 patients, 164 received metyrapone monotherapy. The subgroup of patients with CD (n=115) is the most suitable for comparison with osilodrostat. It is also notable that treatment was used in 58% of patients with CD as treatment for severe symptoms of CS and in 25% of patients before surgery, regardless of the cortisol level. Further details regarding the patient characteristics can be found in Table 41 in section 5.2.2 where the relevant studies are presented.

Complete response
Patients were treated according to either a titration schedule in which the metyrapone dose was titrated according to the cortisol level or according to a 'block-and-replace regimen'. Overall, the high degree of heterogeneity of the patients included in this retrospective analysis makes it very difficult to determine how effective metyrapone is when given as monotherapy for the treatment of patients with Cushing's disease with elevated cortisol levels. In addition, only limited information is available in this study on 24-hour urinary free cortisol and efficacy was mainly assessed on the basis of the much more variable cortisol level at 9 a.m. There are no good data available for metyrapone on the basis of which the effectiveness of metyrapone can be assessed, let alone in an indirect comparison with other drugs. In addition, with metyrapone, up to 19% of patients with initial response to treatment experience an escape from response. In the study with osilodrostat, there were no escape cases, which provides a clear advantage in terms of continued effectiveness.

Having said that, at the last review, the control of cortisol in patients who received metyrapone as monotherapy varied depending on the monitoring test, with 43% of the patients being controlled who had UFC (n=37). However, the choice of biochemical monitoring test and frequency of monitoring varied. This has affected the uniformity of the data presented. However, it should be noted that this is aligned with the 47% of the patients in the prospective PROMPT study (see section PROMPT study 6.1) achieving complete response defined as mUFC≤ULN at week 12. Compared to week 12 in the LINC-4 study where 77.1% patients of the patients randomized to osilodrostat achieved complete response, we conclude that osilodrostat shows better efficacy than metyrapone. In addition, longest follow up data showed complete response of 61.5% (week 72) in LINC-4 and 81.1% (week 72) in LINC-3. Looking at patients patients randomized to osilodrostat in LINC-4, 58.1% achieved complete response at week 72. Thus showing a sustained cortisol normalisation for patients on osilodrostat.

Quality of life
No data is available from the study assessing metyrapone, therefore a comparison regarding the QoL outcome cannot be made. Nonetheless, it is worth mentioning that osilodrostat achieved a mean absolute change from baseline of

12.0 points at week 48. Reviewing against the MID of 10.1 point difference required in the protocol, we state that treatment with osilodrostat improves the patient's QoL. This clinically significant improvement was seen from week 12 and maintained throughout the study. For more details regarding the QoL outcomes, refer to the results of the LINC-4 study in section 5.1.2.1.

Adverse events

An overview with the most common AEs for both osilodrostat and metyrapone is provided in Table 42. Before reviewing the different AEs, it should be mentioned that in retrospective studies, such as Daniel et al 2015, there tends to be an underreporting of AEs due to a less systematic approach of reporting. This selection bias and thereby underestimation is a common risk in retrospective studies and challenges the comparison to data from RCT which is the basis for the osilodrostat safetey evidence. Nevertheless commonly reported side effects of metyrapone include hypotension, nausea, vomiting, headache, and dizziness. Adrenal insufficiency rarely occurs with metyrapone. Serious side effects include bone marrow failure and hypertension. At high doses, metyrapone can lead to hirsutism. For women, this is an annoying but rare side effect. Due to the lack of safety data in the Daniel et al. 2015 publication regarding AEs requiring additional treatment and treatment discontinuations due to AEs, it is not feasible to make a comparison. Overall, during the long-term treatment (week 48 till week 72) osilodrostat was well tolerated and no new safety signals were reported.

Additional considerations

Even though the PROMPT study (available details can be found in section 6.1) was not included in the literature search, due to the design of the only prospective international multicenter Phase III study and available data, we consider the results relevant for the comparative analysis. At week 12, 47% (23/49) patients had a complete response, defined as mUFC ≤ ULN. (28, 29) Another 40% (19 /49) had mUFC ≤ 2xULN. At week 36, the mUFC was normal in 5/14 evaluable patients who had a mUFC 1-2x normal at week 12. (28, 29) The QoL of patients was assessed using the CushingQoL, but the MID of 10.1 was not reached, the CushingQoL increased by 10 points from baseline. Regarding safety data, one patient discontinued treatment and the abstract did not present the proportion of patients requiring additional treatment due to an AE. Based on the data from the PROMPT study, a statistical analysis has been conducted, confirming the already identified difference in complete response results between osilodrostat and metyrapone. Overall, the data from this new study, including the statistical analysis versus LINC-4, is more appropriate than Daniel et al. 2015 for a naive comparison versus osilodrostat.

Matching-adjusted indirect treatment comparison results

[redacted]

Table 43 MAIC results, complete response at Week 12

Scenario		Patients with CR (n/N [%])		OR (95% CI [robust SE])		RR (95% CI)
Imputation method	mUFC match	Osilodrostat (LINC-4)	Metyrapone (PROMPT)	Naïve	Adjusted	Adjusted
LOCF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: CI, confidence interval; CR, complete response; ESS, effective sample size; HR, hazard ratio; LOFC, last observation carried forward; mUFC, mean urinary free cortisol; OR, odds ratio; SE, standard error.

Table 44 MAIC results, complete response at Week 36

Scenario		Patients with CR (n/N [%])		OR (95% CI [robust SE])		RR (95% CI)
Imputation method	mUFC match	Osilodrostat (LINC-4)	Metyrapone (PROMPT)	Naïve	Adjusted	Adjusted
LOCF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: CI, confidence interval; CR, complete response; ESS, effective sample size; HR, hazard ratio; LOFC, last observation carried forward; mUFC, mean urinary free cortisol; OR, odds ratio; SE, standard error.

Overall conclusion

To answer the question 'What is the value of osilodrostat compared metyrapone in adult patients with endogenous Cushing Syndrome?' we have reviewed the difference in study design, patient population, complete response, QoL and AEs.

- Osilodrostat has been investigated in more robust and multiple prospective studies with a low risk of bias versus metyrapone's retrospective observational study with a variation in the choice of metyrapone use and methods of use for metyrapone (e.g. previous surgery or radiotherapy vs. no previous therapy, uptitration vs. block-and-replace regimen, monotherapy vs. combination therapy etc.), which is considered with a high risk of bias and may cause overestimation of efficacy and underestimation of AE's as compared to an RCT.
- The comparison regarding the complete response as it relates to cortisol normalisation shows a higher efficacy with osilodrostat versus metyrapone both in naïve and indirect comparison (MAIC) settings. Osilodrostat shows a sustained cortisol normalisation, with a large proportion of the patients remaining on treatment.
- Osilodrostat demonstrated a clinically significant QoL improvement as demonstrated by the CushingQoL, whereas metyrapone did not achieve the MID with the CushingQoL tool.
- Patients on metyrapone have a risk of the serious adverse event of hypertension, whereas the risk of adrenal insufficiency with osilodrostat is manageable by dose reductions or interruptions. Given that the majority of the patients are female, it is important to acknowlegde that hirsutism is more experienced by patients on metyrapone compared to osilodrostat.
- Statistical analysis showed the improved outcomes for a complete response at week 12 with osilodrostat versus metyrapone, based on a prospective metyrapone clinical trial.
- Overall, osilodrostat is assessed in more robust studies, shows better and sustained efficacy and is well tolerated in patients with CS.

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

5.3 Clinical question 3: What value does osilodrostat have compared to pasireotide in adult patients with endogenous Cushing's syndrome?

Population
Adult patients with endogenous Cushing's syndrome.
Intervention
Osilodrostat (starting dose 2 mg twice daily, then individual dosing on background of response and tolerability).
Comparator
Pasireotide, 600-900 micrograms subcutaneous x 2 daily or 10-40 mg intramuscular injection every 4 weeks.
Outcomes

- Proportion of patients with complete response at Week 4
- Proportion of patients with complete response at Week 12
- Proportion of patients with complete response at longest follow up
- Quality of Life (CushingQoL)
- Proportion of patients with adverse events requiring treatment

5.3.1 Presentation of relevant studies

This paragraph provides an overview of the relevant studies used to answer clinical question 3.

Study characteristics

A summary of the study characteristics is presented in Table 45. For more details refer to the individual study characteristics in sections 4.2 and 4.3. For more details per individual study, please refer to sections 4.2 and 4.3 where the main characteristics of the studies are described.

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Table 45 Study characteristics for question 3

Study name (Trial name / NCT)	Intervention/ comparator	Number screened Number enrolled Number randomized	Study setting Study country	Study design Blinding Study phase	Duration of study (weeks)
Gadelha, 2022 (3) LINC-4	Osilodrostat Placebo	Screened: 119 Enrolled: 74 Randomized: 73	Multi-centre Belgium, Brazil, Canada, China, Costa Rica, Poland, Portugal, Russian Federation, Spain, Switzerland, Thailand, Turkey, United States,	RCT Double blind Phase III	Overall study: 48 weeks RCT phase: initial 12 weeks Extension phase (optional): up to week 96
Pivonello, 2020 (LINC3/ NCT02180217/EUCTR2013-004766-34-NL)	Osilodrostat/LCI699 (Period 1 +2) Osilodrostat/LCI699 (Period 3-RCT) Placebo (Period 3-RCT) Osilodrostat/LCI699 (Overall patients)	Screened: 202 Enrolled: 137 Randomized: 71	Multi-centre international Argentina, Austria, Bulgaria, Canada, China, Colombia, France, Germany, India, Italy, Japan, Korea, Netherlands, Russian Federation, Spain, Thailand, Turkey, UK, and US	RCT Double blind Phase III	Overall study: 48 weeks RCT phase: 8 weeks Extension phase (optional): 72 weeks
Fleseriu, 2016 (LINC-2/NCT01331239)	Osilodrostat	Screened: 19 Enrolled: 19 Randomized: NA	Multi-centre NR	Prospective Open label Phase II	22 weeks Extension phase (optional): 83 weeks (converted from 19 months reported in study; calculated as 19X30.5/7)
Tanaka, 2020 (C1201, NCT02468193)	Osilodrostat	Screened: 9 Enrolled:9 Randomized: NA	Multi-centre Japan	Single arm Open label Phase II	Core study: 48 weeks Extension phase (optional): 24 weeks
Bertagna, 2014 (LINC1 (core study); (LINC 2 (extension study)/ NCT01331239)	Osilodrostat/LCI699 Osilodrostat/LCI699	Screened: NR Enrolled: 12 Randomized: NA	Multi-centre international Italy, France and US	nRCT single arm NR Phase II	Core study: 10 weeks Extension phase: 22 weeks

Lacroix 2018 (G2304/NCT01374906)	Pasireotide 10 mg Pasireotide 30 mg	Screened: 477 Enrolled: 150 Randomized: 150	Multi-centre international Argentina, Belgium, Brazil, Canada, China, France, Germany, India, Israel, Italy, Japan, Netherlands, Peru, Poland, Russian Federation, Spain, Thailand, Turkey, UK, and US	RCT Triple blind Phase III	Core study: 52.14 weeks Extension phase: 156.43 weeks
Colao 2012 (B2305/NCT00434148)	Pasireotide, 600 µg, BID Pasireotide, 900 µg, BID	Screened: 329 Enrolled: NR Randomized: 162	Multi-centre international Argentina, Belgium, Brazil, Canada, China, Denmark, Finland, France, Germany, Greece, Israel, Italy, Mexico, Poland, Portugal. Spain, Turkey, and US	RCT Double blind Phase III	RCT phase: 48 weeks Open label phase: 240 weeks
Fleseriu et al. 2019 (SEASCAPE/ NCT01582061)	Pasireotide 600 µg BID Pasireotide 900 µg BID Pasireotide	Screened: NR Enrolled: 104 Randomized: NA	Multi-centre International Brazil, Czechia, Germany, Greece, Korea, Republic of, Lebanon, Romania, Russian Federation, Spain, Thailand, United States, Czech Republic	nRCT single arm Open label Phase III	NR
Boscaro et al. 2014 (B2208/ NCT00088608)	Pasireotide 600 µg BID	Screened: NR Enrolled: 39 Randomized: NA	Multi-centre international US, France, Germany, Italy, UK	nRCT single arm Open label Phase II	104.3 weeks
Pivonello 2019 (NR)	Pasireotide	Screened: NR Enrolled: 32 Randomized: NA	Multi-centre Italy	nRCT single arm NR NR	24 weeks

Abbreviations: NA, not applicable; NR, not reported; RCT, randomized controlled trial; nRCT, non-randomized controlled trial

Table 46 Patient characteristics for question 3

Study name	Intervention/ comparator	Mean age (years) Male, n (%)	Type of CS, n (%)	Prior treatment, n (%) Surgery Medications Radiation	Comorbidities, n (%)	Mean mUFC (SD) nmol/24hours
Gadelha, 2022 (3) LINC-4	Osilodrostat	41.0 5 (10.4)	Microadenoma: 30 (62.5) Macroadenoma: 17 (35.4)	41 (85.4) 26 (54.2) 6 (12.5)	NR	421.3 (291.3)

			Missing 1 (2.1)			
	Placebo	37.0 7 (28.0)	Microadenoma: 20 (80.0) Macroadenoma: 4 (16.0) Missing 1 (4.0)	23 (92.0) 19 (76.0) 3 (12.0)	NR	451.5 (535.1)
	All patients	41.2 12 (16.4)	Microadenoma: 50 (68.5) Macroadenoma: 21 (28.8) Missing 3 (2.7)	64 (87.7) 45 (61.6) 9 (12.3)	NR	431.7 (388.6)
Pivonello, 2020 (LINC-3)	Osilodrostat (Period 1+2)	NR 31 (22.6)	Pituitary adenoma: 137 (100)	102 (74.5) 120 (87.6) 22 (16.1)	NR	NR
	Osilodrostat (Period 3-RCT)	NR 6 (16.6)	Pituitary adenoma: 36 (100)	26 (72.2) 32 (88.9) 6 (16.7)	NR	890.0 (1275.66)
	Placebo (Period 3-RCT)	NR 13 (37.1)	Pituitary adenoma: 35 (100)	24 (68.6) 33 (94.3) 5 (14.3)	NR	560.0 (548.84)
	Osilodrostat (Overall patients)	NR 31 (22.6)	Pituitary adenoma: 137 (100)	102 (74.5) 120 (87.6) 22 (16.1)	NR	1,006.0 (1,589.86)
Fleseriu, 2016 (LINC-2)	Osilodrostat	36,8 5 (26.3)	NR	NR NR NR	NR	1371 (2734)
Tanaka, 2020 (C1201)	Osilodrostat	NR 2 (22.2)	Adrenal adenoma: 5 (55.5%) Ectopic CS: 3 (33.3) Other: 1 (11.1)	5 (55.6) 1 (11.1) 0 (0)	NR	NR
Bertagna , 2014 (LINC-1)	Osilodrostat	39 4 (33.3)	Pituitary adenoma: 12 (100)	1 (8.3) 12 (100) 0 (0)	Hypertension: 3 (NR)	4.7-fold above the ULN (SEM 1.3)
	Osilodrostat (expansion cohort + follow up cohort)	36.8 5 (26.3)	NR	NR 17 (89.5) NR	NR	NR
	Osilodrostat	37.5 4 (26.7)	NR	NR 13 (86.7)	NR	NR

	(expansion cohort)			NR		
	Osilodrostat (follow up cohort)	34.3 1 (25)	NR	NR 4 (100) NR	NR	NR
Lacroix, 2018 (G2304/ NCT01374906)	Pasireotide 10 mg	38.3 16 (22)	De novo: 15 (20) Pituitary adenoma: 74 (100)	59 (80) 32 (43) NR	Diabetes: 27 (36) Prediabetes: 12 (16)	2.8 (1.5)
	Pasireotide 30 mg	38.6 16 (21)	De novo: 12 (16) Pituitary adenoma: 76 (100)	64 (84) 30 (39) NR	Diabetes: 33 (43) Prediabetes: 12 (16)	2.9 (2.0)
	Pasireotide	40.7 20 (24.7)	NR	67 (82.7) 81 (100) NR	Diabetes: 66 (81.5)	2.8 (1.8)
Colao, 2012 (B2305/ NCT00434148)	Pasireotide, 600 µg, BID	41 20 (24.4)	Pituitary adenoma: 82 (100)	64 (78) 36 (44) 3 (4)	Severity of hypercortisolism: Mild: 12 (15) Moderate: 26 (32) Severe: 28 (34) Very severe: 11 (13) Missing data: 5 (6)	1156
	Pasireotide, 900 µg, BID	40 16 (20)	Pituitary adenoma: 80 (100)	64 (80) 42 (52) 4 (5)	Severity of hypercortisolism: Mild: 14 (18) Moderate: 40 (50) Severe: 13 (16) Very severe: 9 (11) Missing data:4 (5)	782
Fleseriu, 2019 (SEASCAPE/ NCT01582061)	Pasireotide 600 µg BID	45.5 1 2 (24.5)	De novo: 8 (16.3) Pituitary adenoma: 49 (100)	38 (77.6) NR 12 (24.5)	NR	NR
	Pasireotide 900 µg BID	39.9 18 (14.5)	De novo: 5 (9.1) Pituitary adenoma: 55 (100)	46 (83.6) NR 15 (27.3)	NR	NR
	Pasireotide	42.5 20 (19.2)	De novo: 13 (12.5)	84 (80.8) NR	98 (94.2) Hypertension: 62 (59.6)	NR

			Pituitary adenoma: 104 (100)	27 (26)	Hypothyroidism 21 (20.2) Dyslipidemia: 20 (19.2%) Diabetes mellitus: 16 (15.4)	
Boscaro, 2014 (B2208/ CT00088608)	Pasireotide	41.5 10 (26)	NR	NR NR NR	NR	NR
Pivonello, 2019 (NR)	Pasireotide	47 7 (21.8)	Pituitary adenoma: 32 (100)	NR 20 (62.5) 25 (78.1)	NR	Mean Urinary cortisol – ULN 1.55
	Pasireotide	NR 5 (19.2)	Pituitary adenoma: 26 (100)	NR 16 (61.5) 8 (30.8)	Overweight: 8 (30.8) Obesity: 15 (57.7) Arterial hypertension: 16 (61.5) Impaired glucose metabolism: 14 (53.8) Diabetes: 9 (34.6) Impaired glucose tolerance: 4 (15.4) Impaired fasting glucose: 1 (3.8) Dyslipidemia: 16 (61.5) Hypercholesterolaemia: 7 (26.9) Hypertriglyceridemia: 4 (15.4) Mixed dyslipidemia: 5 (19.2)	NR

5.3.2 Results per study

Osilodrostat (LINC-4 [Gadelha et al 2022], LINC-3 [Pivonello et al 2020], LINC-2 [Fleseriu et al 2016], LINC-1 [Bertagna et al 2014], C1201 [Tanaka et al. 2020])

Results related to the studies assessing osilodrostat are covered in clinical question 1.

5.3.2.1 G2304

Efficacy

If the mUFC concentration was missing at month 7, the authors imputed values using the last available measurement between month 4 and month 7; we considered patients who discontinued before month 4 non-responders. In order to obtain mUFC results in time for the Month 4 and Month 7 evaluations, samples were collected at 3.5 and 6.5 months after baseline. The ULN mUFC was determined to be 166.48 nmol/24 hours and reflects the normalization of mUFC; the reduction of circulating cortisol, with the eventual goal of normalization, is a well-established clinical goal in the treatment paradigm for patients with CD. The evaluation of primary efficacy at 7 months after baseline was chosen due to PK and PD considerations given that some patients required a dose adjustment at Month 4.

The primary endpoint was the proportion of patients in each treatment arm that attained a mUFC ≤ 1.0 x ULN at Month 7 regardless of dose titration (Table 47). The proportions of controlled responders between the 2 treatment arms were comparable. The proportion controlled responders for the overall population, shows 41.3% (62/150) of the patients achieved complete response regardless of dose increase.

Table 47 G2304 – Complete response at Month 7 regardless of dose increase

	Pasireotide LAR 10 mg, n=74	Pasireotide LAR 30 mg, n=76	All patients, N=150
Controlled responders, n (%)	31 (41.9)	31 (40.8)	41.3%
95% CI	30.5, 53.9	29.7, 52.7	NR

Abbreviations: CI, confidence interval; LAR, long-acting release.
Source: Lacroix et al. 2018 (11)

The key secondary endpoint was the proportion of patients that attained a mUFC ≤ 1.0 x ULN at Month 7 who did not have a dose increase at Month 4. The results are shown in Table 48.

Table 48 G2304 – Complete response at Month 7 without dose increase

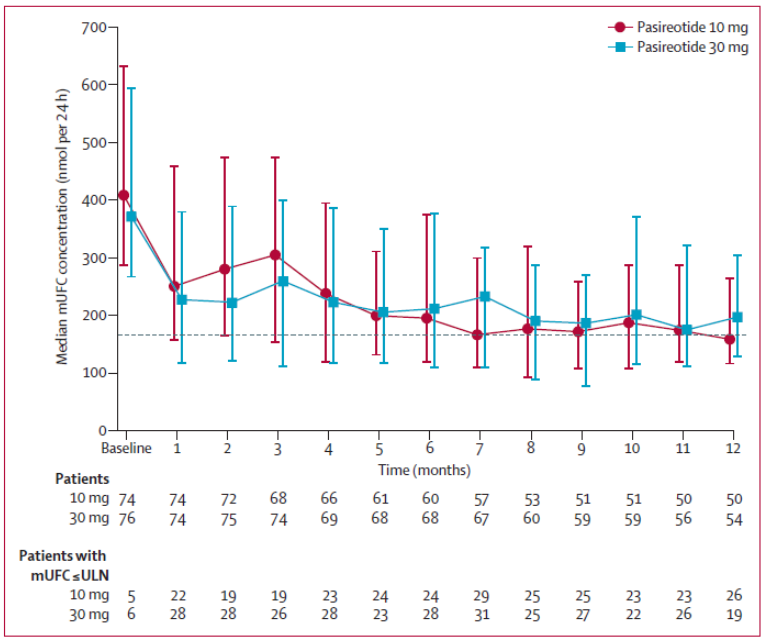
	Pasireotide LAR 10 mg, n=74	Pasireotide LAR 30 mg, n=76
Controlled responders, n (%)	21 (28.4)	24 (31.6)
95% CI	18.5, 40.1	21.4, 43.3

Abbreviations: CI, confidence interval; LAR, long-acting release.

The article states that at month 12, 26 (35.1% [24.4‑47.1]) of 74 patients (10mg) had an mUFC concentration less than or equal to the ULN compared with 19 (25.0% [15.8‑36.3]) of 76 patients on 30mg pasireotide. Adding the two arms together, a total of 45 patients (30%) were controlled at month 12 with pasireotide.

Figure 4 shows that at month 3, 27.9% (19/68) patients on 10mg pasireotide and 35.1% (26/74) patients on 30mg achieved complete response.

Figure 4 Median mUFC concentration from baseline until month 12



Error bars represent IQRs. The dashed line represents the ULN for urinary free cortisol. mUFC: mean urinary free cortisol. ULN: upper limit of normal.

Improvements in weight, waist circumference, BMI, and HRQoL were seen over 12 months, indicating a sustained clinical benefit.

Quality of Life

Quality of life was assessed by using Cushing's QoL tool at baseline, month 2, month 4, month 7, month 10 and month 12. Improvements in HRQoL were seen over 12 months, indicating a sustained benefit.

Table 49 Mean change (95%) from baseline in HRQoL at month 7 and 12

Outcome / treatment	Month 7		Month 12	
	Pasireotide 10mg	Pasireotide 30mg	Pasireotide 10mg	Pasireotide 30mg
HRQoL score (mean change from baseline [95%CI])	5.7 (1.4, 10.0)	7.8 (4.9, 10.7)	6.4 (1.3, 11.6)	7.0 (3.0, 10.9)

Safety

Safety analyses were based on AEs reported up to data cutoff (Nov 10, 2015), including data beyond month 12 for some patients.

The most common AEs with pasireotide were hyperglycemia, diarrhea, cholelithiasis, diabetes mellitus and nausea in more than 20% of the patients.

Table 50 Common AEs of Any Grade and Grade 3/4 AEs

	Pasireotide LAR 10 mg, N=74 n (%)	Pasireotide LAR 30 mg, N=76 n (%)	Overall N=150 n (%)
Any AE	73 (98.6)	76 (100)	NR
Hyperglycemia	36 (48.6)	36 (47.4)	72 (48)
Diarrhea	26 (35.1)	33 (43.4)	59 (39)
Cholelithiasis	15 (20.3)	34 (44.7)	49 (33)*
Diabetes mellitus	14 (18.9)	18 (23.7)	32 (21)
Nausea	15 (20.3)	16 (21.1)	31 (21)
Headache	18 (24.3)	10 (13.2)	28 (19)
Nasopharyngitis	16 (21.6)	12 (15.8)	28 (19)
Fatigue	12 (16.2)	14 (18.4)	26 (17)
Abdominal pain	10 (13.5)	12 (15.8)	22 (15)
Hypertension	10 (13.5)	12 (15.8)	22 (15)
Hypoglycemia	9 (12.2)	12 (15.8)	21 (14)†
Peripheral oedema	9 (12.2)	12 (15.8)	21 (14)
Influenza	12 (16.2)	6 (7.9)	18 (12)
Dizziness	9 (12.2)	8 (11)	17 (11)
Urinary tract infection	8 (11%)	9 (12.2)	17 (11)
Grade 3–4 AEs	40 (54.1)	46 (60.5)	NR
Diabetes mellitus	10 (13.5)	14 (18.4)	24 (16)
Hypertension	7 (9.5)	7 (9.2)	14 (9)
Hyperglycemia	6 (8.1)	3 (3.9)	4 (3)

Abbreviations: AE, adverse event; GGT, gamma-glutamyl transferase; LAR, long-acting release.
*Data are n (%). Hypocortisolism-related adverse events were reported in six (8%) patients in the 10 mg group and seven (9%) in the 30 mg group. Injection site-related adverse events were reported in two (3%) patients each in the 10 mg (one [1%] pain and one [1%] haemorrhage) and 30 mg (one [1%] pain and one [1%] hypersensitivity) groups. *Four (8%) patients required surgery, 24 (49%) required medical treatment, and two (4%) had a temporary interruption to long-acting pasireotide treatment.*
†17 (81%) patients were receiving antidiabetic medication (ten [48%] receiving insulin and seven [33%] oral antidiabetic medication); none of these events required admission to hospital or medical intervention.
Source: Lacroix et al 2018 (11) and G2304 Data on File (30)

In G2304, two on-treatment deaths were reported, both in the 30 mg arm. Both deaths were not suspected to be drug-related. The incidence of SAEs was higher in the 10 mg arm, at 28.4%, compared with 22.4% in the 30 mg arm. None of the SAEs were reported in more than 3 patients in each arm. Twelve patients (8%) reported SAEs that were suspected to be drug-related. (30)

Hyperglycaemia-related AEs were the most commonly reported AEs of special interest, occurring in 72% of patients in the 10 mg group and 82% in the 30 mg group, leading to discontinuation in four patients per group. (11)

The number of patients with at least one dose reduction, at least one dose up-titration, and discontinuation due to AEs are shown in Table 51. A majority of patients increased the dosage of their regimen post-baseline, while 27.3% of patients experienced at least one dose reduction, mostly due to AEs. The discontinuation rate due to AEs was low, at 8-9% across both arms.

Table 51 G2304: Drug Reductions, Up-titrations, and Discontinuations Due to AEs

	Pasireotide LAR 10 mg, N=74 n (%)	Pasireotide LAR 30 mg, N=76 n (%)
At least one reduction	17 (23.0)	24 (31.6)
At least one dose up-titration	48 (65)	51 (76)
Discontinuation due to AEs	6 (8.1)	7 (9.2)

Abbreviations: AE, adverse event; LAR, long-acting release.
Source: Lacroix et al 2018 (11)

5.3.2.2 B2305

Efficacy

The mUFC was measured during several timepoints throughout the study. Based on the DMC protocol week 12 (Month 3) and Month 24 are included in this section. However, only using these timepoints would not show the results during the randomization phase. We, therefore, find it important that the measurements from Month 6 are included. No measurements are available for week 4, hence not included.

At month 3, 16% (95% CI, 8 to 24) of patients in the 600-µg group and 28% (95% CI, 18 to 37) of those in the 900-µg group had urinary free cortisol levels at or below the upper limit of the normal range.

The primary efficacy endpoint in B2305 was the proportion of patients with mUFC ≤ 1.0 x ULN at Month 6 who had not had a dose increase. The proportion of responders receiving pasireotide s.c. was slightly reduced in the 600µg subgroup with 15% (95% CI: 7, 22) of patients achieving complete response compared to 26% (95% CI: 17, 36) of patients in the 900µg subgroup had UFC ≤ 1.0 x ULN at Month 6 without an increased dose. Calculating the two treatment arms together, 33 patients of the total 162 achieved complete response (20.3%).

Table 52 Complete response per treatment arm and timepoint without dose increase

	Pasireotide 600 µg BID N=82* n; % (95% CI)	Pasireotide 900 µg BID N=80* n; % (95% CI)
Month 3*	13; 16% (8-24)	22; 28% (18-37)
Month 6	12; 15% (7-22)	21; 26% (17-36)
Month 12	13; 16% (8-24)	23; 29% (16-35)

*N was not reported for the 3-month timepoint, therefore a calculation using the overall N per treatment arm has been used to calculate the number of patients achieving complete response (using rounding of the numbers to overall patient numbers)
Source: Colao et al. 2012 (12)

One of the secondary endpoints in B2305 study was the proportion of patients who were UFC ≤ 1.0 x ULN at Month 6 regardless of dose increases: 16% (95% confidence interval [CI]: 8, 24) of patients in the 600µg subgroup and 29% (95% CI: 19, 39) of patients in the 900µg subgroup had UFC ≤ 1.0 x ULN at Month 6.

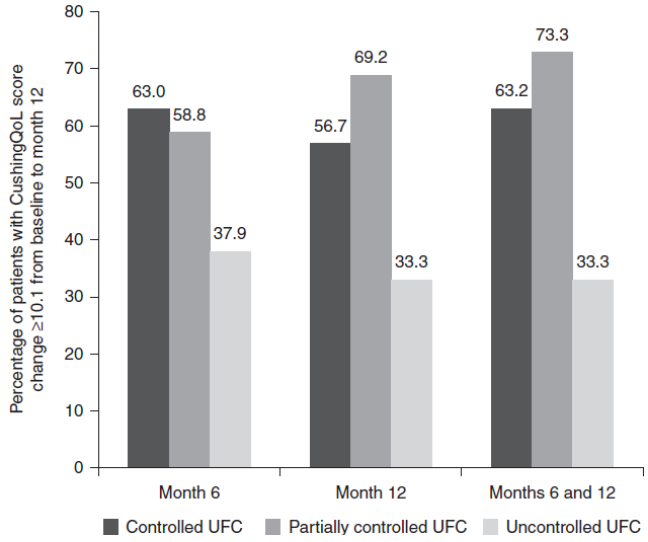
The open-label extension trial from Schopohl et al. 2015 (19), reported the complete response data at month 24. Of the 26 patients on pasireotide 600-µg, 8 patients (30.8%) achieved CR compared, a slightly higher percentage of patients (37.5%) achieved CR with pasireotide 900-µg (12/32 patients).

Quality of Life

At month 12, the mean change from baseline with CushingQoL was 11.1 (95% CI: 6.8-15.5) (12).

The publication by Webb et al. 2014 (20), presents further details regarding the HRQoL in patients with CD who are treated with pasireotide. Figure 5 presents an overview of the percentage of patients with CushingQoL improvement of ≥10.1 from baseline to Month 12 by mUFC control status.

Figure 5 Percentage of patients with CushingQoL improvement 10.1 from baseline to Month 12 by mUFC control status



Source: Webb et al 2014 (20)

To assess the relationship between HRQOL and depression among CD patients, the correlations between baseline BDI-II and baseline CushingQoL item and total scores were estimated. The Spearman's rank sum correlation coefficients ranged between -0.27 and -0.70 (all P<0.001). Change in CushingQoL was significantly correlated with changes in mUFC (r=-0.40), BMI (r=-0.39), weight (r=-0.41), and BDI-II (r=-0.54) at month 12 but not at month 6. A significant 4.9 reduction in the BDI-II score was observed at 12 months in UFC responders. No correlation was observed between changes in CushingQoL and changes in waist circumference, blood pressure, facial rubor, striae, bruising, supraclavicular fat pad, and dorsal fat pad. (20)

Safety

The authors concluded that the safety profile of pasireotide was similar to other somatostatin analogues, except for a higher frequency of hyperglycemia with pasireotide.

Table 53 Most frequently reported adverse events by all grades in either dose group and overal patient population

	Pasireotide 600 µg BID N=82 n (%)	Pasireotide 900 µg BID N=80 n (%)	Overall (N=162)	
			Grade 3 or 4 n (%)	*All grades* n (%)
Diarrhea	48 (59)	46 (58)	5 (3)	94 (58)
Nausea	38 (46)	46 (58)	4 (2)	84 (52)
Hyperglycemia	31 (38)	34 (42)	21 (13)	65 (40)
Cholelithiasis	25 (30)	24 (30)	2 (1)	49 (30)
Headache	23 (28)	23 (29)	3 (2)	46 (28)
Abdominal pain	19 (23)	20 (25)	3 (2)	39 (24)
Fatigue	12 (15)	19 (24)	13 (2)	31 (19)
Diabetes mellitus	13 (16)	16 (20)	12 (7)	29 (18)

Source: Colao et al 2012 (12)

As with other somatostatin analogues, the most common adverse events were related to transient gastrointestinal discomfort. Hyperglycemia and diabetes mellitus were the most common grade 3 and 4 AEs, occurring in 13% and 7% of patients, respectively (Table 53). Overall, 118 of 162 patients (73%) had a hyperglycemia-related AE with 6% of patients discontinuing treatment due to a hyperglycemia-related AE. (12)

Hypocortisolism-related adverse events (i.e., clinical symptoms consistent with adrenocortical insufficiency or glucocorticoid withdrawal) were reported in 13 patients (8%). In 11 of the patients, hypocortisolism resolved with a reduction in the pasireotide dose or temporary interruption of treatment, and subsequently, normal urinary free cortisol levels were maintained.

A total of 145 patients (89.5%) required additional treatment due to AEs, data was retrieved from the data on file. (31)

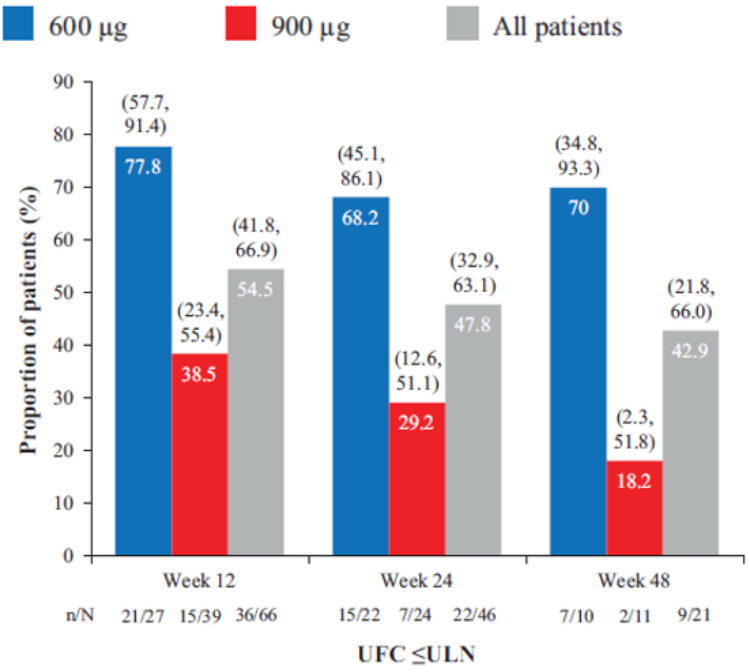
Discontinuations
In the first 3 months, 29 patients discontinued the study: 13 because of AEs, 4 because of lack of efficacy, 9 because of withdrawal of consent, and 3 because of a protocol violation. By month 6, an additional 26 patients had discontinued the study: 7 because of AE, 15 because of lack of efficacy, and 4 because of withdrawal of consent. By month 12, an additional 29 patients had discontinued the study: 6 because of AE, 18 because of lack of efficacy, 4 because of withdrawal of consent, and 1 because of a protocol violation. (12)
A total of 26 patients discontinued treatment due to AEs.

5.3.2.3 SEASCAPE

Efficacy

Of the patients with evaluable UFC measurement at week 12, 36/66 (54.5%) patients had mUFC≤ULNC and were considered controlled. For this study week 48 was considered the longest follow up and 9/21 (42.9%) patients were controlled.

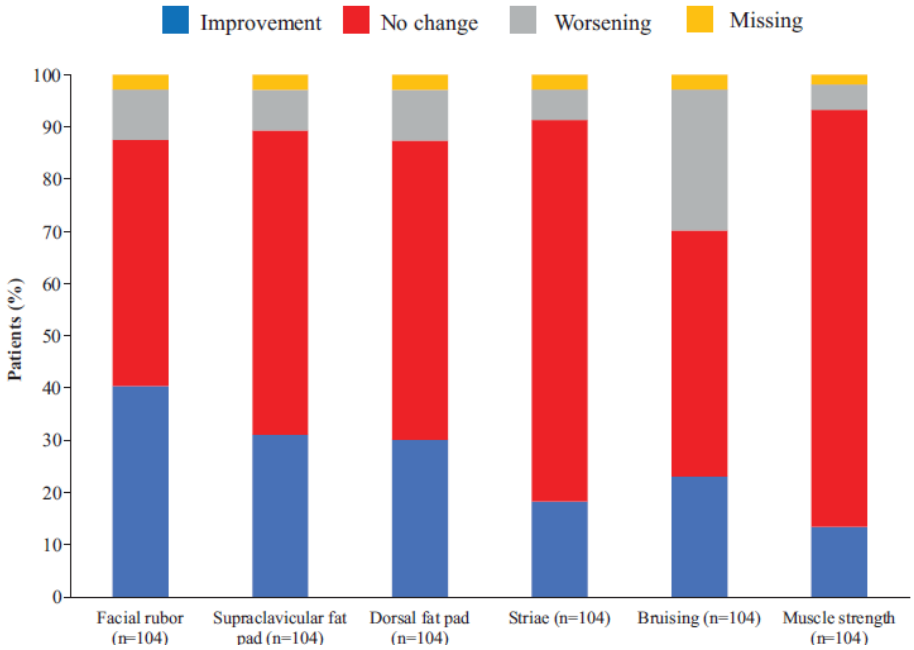
Figure 6 Proportion of patients with normalized mUFC



Values in parentheses are two-sided 95% exact Cis Source: Fleseriu et al 2019 (13)

In addition to the proportion of patients with response, continuous signs and symptoms, such as BP, weight, waist, circumference and hirsutism, were improved at week 12 and maintained up to week 48. A favourable shift in all studied categorical signs of CD (facial rubor, striae, bruising, muscle strength, supraclavicular, and dorsal fat pads) was observed from baseline to last postbaseline assessment overall (Figure 7).

Figure 7 Proportion of patients with improvement, no change or worsening of categorical signs of Cushing's disease from baseline to last post-baseline value in



Source: Fleseriu et al 2019 (13)

Quality of Life

Improvements in the quality of life, assessed with the CushingQol tool, were observed by week 12 and maintained to week 48, indicating a continued therapeutic benefit during long-term treatment pasireotide.
The mean (95% CI) percentage increase from baseline in CushingQoL score of 67.1% (30.0, 104.3) at week 12, 82.3% (25.2, 139.4) at week 24, and 34.4% (19.5, 49.4) at week 48.

Table 54 Mean percentage change from baseline in CushingQoL score

	Pasireotide 600mg BID N= 49, Mean, % (95% CI)	Pasireotide 900mg BID N= 55, Mean, % (95% CI)	All patients N=104, Mean, % (95% CI)
Week 12	21.3 (7.4, 35.2)	100.8 (37.6, 164.0)	67.1 (30.0, 104.3)
Week 24	36.7 (15.5, 57.9)	119.7 (16.2, 223.2)	82.3 (25.2, 139.4)
Week 48	24.0 (6.8, 41.1)	42.3 (18.8, 65.8)	34.4 (19.5, 49.4

Safety

The primary objective of this study was to document the safety of pasireotide sc in patients with CD. This study showed that in an international, real-world, clinical-practice setting, pasireotide was generally well-tolerated and no new safety signals were identified. The safety results are based on a large population (N=104) of patients with CD in clinical practice.

The most common reasons for discontinuation were unsatisfactory therapeutic effect (n = 26, 25.0%) and AEs (n = 20, 19.2%). Out of the patients discontinuing due to AE, six had hyperglycemia-related AEs. Most drug-related AEs were grade 1 or 2 and resolved without dose modification. The most frequently reported grade 3 or 4 AEs were hyperglycemia and diabetes mellitus, occurring in 13% and 7% of patients, respectively. Overall, 87.5% of the patients required additional therapy due to AEs (Table 55). Again, hyperglycemia was the most common AE requiring additional treatment (n=31, 29.8%).

Table 55 Patients with adverse events requiring additional therapy

Pasireotide 600mg BID N=49, n (%)		Pasireotide 900mg BID N= 55, n (%)		All patients N=104, n (%)	
All grades	**Grace 3/4**	**All grades**	**Grace 3/4**	**All grades**	**Grace 3/4**
44 (89.8%)	25 (59.2%)	47 (85.5%)	18 (32.7%)	91 (87.5%)	47 (45.2%)

5.3.2.4 B2208

Efficacy

This study is an extension from a previous 15-day Phase II study, and of the 38 patients who completed the first 15 days, 19 entered this extension phase.

Data for efficacy in terms of complete response are not available for week 4 and 12, as requested by the DMC protocol. Due to the small sample size, data available at month 6 was considered as the longest follow-up data for this assessment.

Definition of response was mean UFC level at month 6 in the normal range (55–276 nmol/24 h; 20–100 µg/24 h). Of the 18 patients included in the primary efficacy analysis, four had normal UFC levels at month 6 (responders, 22.2 %; 95 %CI: 6.4–47.6). Six patients (33.3 %) achieved a reduction in mean UFC, but not to within normal range (reducers). One patient had a mean UFC level greater than at baseline and was classified as a non-reducer; the remaining seven patients were also considered to be non reducers because they discontinued treatment prior to month 6.

In addition to the reduction in UFC levels, a decrease was seen in mean serum cortisol and plasma ACTH levels at month 6 compared with baseline.

Of the four patients who remained on study drug at month 24, one had normalized UFC, and three patients had > 50% reduction in mean UFC from core baseline.

Quality of Life

Quality of life was not assessed.

Safety

All patients expereinced at least one AE during the study. Except for hyperglycemia, the AEs were expected and mostly related to gastrointestional discomfort. During the study, one patient discontinued treatment as a result of an AE. One patient required additional treatment due to an AE (5.3%). The most frequently occured AEs are presented in Table 56. Two patients had grade 4 AEs: one was increased γ-glutamyltransferase levels and the other was type 2 diabetes mellitus. Both events were suspected by the investigator to be related to study drug. No patients died during the study.

Table 56 Most frequently occuring adverse events regardless of study-drug relationship

Adverse event	n (%)
Diarrhea	13 (68.4)
Nausea	12 (63.2)
Hyperglycemia	11 (57.9)
Abdominal pain	9 (47.4)
Headache	7 (36.8)
Injection-site pain	6 (31.6)
Dizziness	5 (26.3)
Fatigue	5 (26.3)
Injection-site pruritus	5 (26.3)

Source: Boscaro et al. 2014 (14)

5.3.2.5 Italian pasireotide real-world evidence

Efficacy

The aim of this study was to evaluate the efficacy and safety of pasireotide treatment according to real-world evidence. Using the following definition of normalization (<1 the upper limit of normal range, ULN) or near normalization (>1 and ⩽1.1 ULN) of UC levels. Twenty-nine out of the 32 patients enrolled in the study reached the 3-month follow-up; 22 patients were responsive (19 fully controlled [59,37%], 3 nearly controlled), whereas the remaining 7 patients were non-responsive to the treatment.

Considering all the 32 patients with any degree of disease, according to an "intention-to-treat" approach, including all patients in the study, the proportion of responsive patients (including both fully controlled and nearly controlled, see the definition normalization above) was 68.75% (22/32).

Table 57 Responsiveness of patients at 3 and 6 months according to ITT and per-protocol approach

	Pasireotide – ITT N=32, n(%)	Pasireotide – Per protocol N=32 (M3), N=27 (M6), n(%)
3 months (M3)	19 (59.37)	21 (65.5)
6 months (M6)	20 (62.5)	20 (74.1)

Abbreviations: ITT: intention-to-treat
Note that this is not according to the definition of complete response

Using the ITT approach, the percentage of fully controlled patients in the very mild, mild and moderate group, reaching 6-month follow-up, was 85.7% (12/14), 83.3% (5/6) and 33.3% (2/6), respectively.

A significant reduction in BMI, weight, and waist circumference was seen after 3 and 6 months of treatment in the 26 patients with very mild to moderate disease. After 3 and 6 months of treatment, weight and BMI were significantly decreased both in responsive and non-responsive patients, however, waist circumference was only significantly decreased in the responsive patients, but not in nonresponsive patients. No significant difference has been registered in the prevalence of overweight and obesity.

The article concludes that in real-world clinical practice, pasireotide treatment normalizes or nearly normalizes UC in at least 68% of patients with very mild to moderate disease, with improvement in weight, visceral adiposity and lipid profile.

Quality of Life

Quality of life was not assessed.

Safety

The most frequent AE was hyperglycaemia, occurring in 26 (81.2%) patients, followed by gastrointestinal disorders, occurring in 13 (40.6%) patients; in particular, diarrhoea was registered in 12 (37.5%), abdominal pain in 5 (15.6%), nausea in 4 (12.5%) patients and meteorism in 1 (3.1%) patient.

Five (15.6%) patients discontinued treatment for AEs. The article did not clearly state if patients required additional treatment due to AEs.

5.3.3 Comparative analyses

As there are no other randomized trials comparing efficacy of other agents used in CS (many are used off-label with evidence generated via single arm studies and sometimes using a retrospective design) and no other placebo-controlled trials to assess mUFC response, it was not possible to conduct an indirect comparison using e.g. Buchers' method or a network meta-analysis of osilodrostat versus other active agents, even via placebo. The only treatment next to osilodrostat which showed lower mUFC levels in a published prospective study is pasireotide, but the Phase III trials compared different pasireotide doses, with no placebo arm.
Patient-level data were available for LINC-4 and LINC-3 (osilodrostat), Colao 2012 (pasireotide SC) and Lacroix 2018 (pasireotide LAR), therefore a more robust comparison for osilodrostat versus pasireotide LAR was formed using PLD population adjustment methods. The methods and results of the propensity weighted analysis for LINC-3 can be found in section 8.7.

Table 58: Population-adjusted ITC results for complete response based on LINC4 study: osilodrostat versus pasireotide LAR and SC

Time point	Target population	Intervention		Comparator		Weighted OR (95% CI)	Weighted RR (95% CI)
		Treatment	Proportion of patients with CR (%)	Treatment	Proportion of patients with CR (%)		
4 weeks*	LINC-4	Osilodrostat	28/48 (58.3%)	Pasireotide LAR	21/74 (28.4%)	[redacted]	[redacted]
12 weeks	LINC-4	Osilodrostat	37/48 (77.1%)	Pasireotide LAR	18/74 (24.3%)	[redacted]	[redacted]
Longest follow up**	LINC-4	Osilodrostat	35/48 (72.9%)	Pasireotide LAR	33/74 (44.6%)	[redacted]	[redacted]
4 weeks*	LINC-4	Osilodrostat	28/48 (58.3%)	Pasireotide SC	22/82 (26.8%)	[redacted]	[redacted]
12 weeks	LINC-4	Osilodrostat	37/48 (77.1%)	Pasireotide SC	13/82 (15.9%)	[redacted]	[redacted]
Longest follow up**	LINC-4	Osilodrostat	35/48 (72.9%)	Pasireotide SC	13/82 (15.9%)	[redacted]	[redacted]

*Please note that the following data has been used for the week 4 time point when matching to the CSR: LINC-4 – 5 weeks (no week 4 data available), Colao 2012 – 30 days, Lacroix – 1 month

**Longest follow up as end of treatment visit

[redacted]

Table 59: Population-adjusted ITC results for complete response based on LINC3 study: osilodrostat versus pasireotide LAR

Time point	Target population	Intervention		Comparator		Weighted OR (95% CI)	Weighted RR (95% CI)
		Treatment	Proportion of patients with CR (%)	Treatment	Proportion of patients with CR (%)		
4 weeks	LINC-3	Osilodrostat	55/137 (40.1%)	Pasireotide LAR	21/74 (28.4%)	[redacted]	[redacted]
12 weeks	LINC-3	Osilodrostat	101/137 (73.7%)	Pasireotide LAR	18/74 (24.3%)	[redacted]	[redacted]
Longest follow up	LINC-3	Osilodrostat	86/137 (62.8%)	Pasireotide LAR	33/74 (44.6%)	[redacted]	[redacted]

[redacted]

The COMP also used a naïve comparison, based on the scientifically recognized GRADE system, in their Orphan Maintenance Assessment Report for osilodrostat to showcase the comparative relative efficacy between osilodrostat and pasireotide and acknowledged osilodrostat's superiority based in the available evidence.

As described in previous sections, the literature search identified five relevant studies for pasireotide: G2304, B2305, SEASCAPE, B2208 and an Italian real-world evidence study. The study by Colao et al. 2012 (B2305) assessed the effect of the pasireotide with a subcutaneous injection and Lacroix et al. 2018 (G2304) assessed the effect of the pasireotide for intramuscular injection. As both studies formed the basis of the marketing authorisation and have been reviewed in the COMP report (2), they form the basis for this assessment from the pasireotide perspective. The Italian real-

world evidence study is not considered in this comparative review; however, it should be acknowledged that the results do support the efficacy of pasireotide in clinical practice.

Four relevant studies were identified for osilodrostat: Pivonello et al. 2020 (LINC-3), Fleseriu et al. 2016 (LINC-2), Bertagna et al. 2014 (LINC-1) and Tanaka et al. 2020 (C1201). In addition, a more recently conducted Phase III trial showing the efficacy and safety with osilodrostat (LINC-4) has been included. This additional Phase III trial with osilodrostat (LINC-4) confirms the provided evidence on efficacy and safety as presented in the LINC-3 trial and shows even better results for some endpoints (including better tolerance with a longer titration period, normalisation at week 12 and week 36 versus placebo, long-term response and no escape). Results of the complete response at week 12 from LINC-4 are specifically reported in the latest clinical guidelines update for CS. (27)

The pivotal LINC-3 Phase III trial with osilodrostat, was used for the marketing authorisation. LINC-3 has a randomized clinical trial design and includes the largest number of patients. LINC-3 has a randomized clinical trial design and includes the largest number of patients. In addition, a more recently conducted Phase III trial, showing the long-term efficacy and safety with osilodrostat (LINC-4), has been included in the section other considerations to support the evidence available for osilodrostat. This recently conducted additional Phase III trial with osilodrostat (LINC-4) confirms the provided evidence on efficacy and safety as presented in the LINC-3 trial and shows even better results for some endpoints including normalisation at week 12 and 36, better tolerance with a longer titration period, long-term response and lack of escape. For this assessment, the LINC-4 study was considered by the expert committee most relevant for the assessment.

In this section, the outcome parameters requested by DMC form the basis for the comparison (Table 60 and Table 61)

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Table 60 Naïve Comparison of Evidence for Treatments for Cushing's Syndrome versus pasireotide (1/2)

	Osilodrostat (Gadelha 2022) (21)	Osilodrostat (Pivonello 2020) (4)	Osilodrostat (Fleseriu 2016) (5)	Osilodrostat (Bertagna 2014) (6)	Osilodrostat (Tanaka 2020) (7)
Study design	Phase III Prosspective Randomized Double blind 48 weeks (n=73) *Low ris of bias*	Phase III Prospective Randomized Double blind 48 Weeks (n=137) *(Note: 71 patients were randomized at W26)*	Phase II Prospective Open label (n=19)	Phase II Single arm Non-randomized (n=12)	Phase II Single arm Open label (n=9)
Efficacy Outcome	Complete response was defined as mUFC ≤ ULN	Complete response was defined as mUFC ≤ ULN	Complete response was defined as mUFC ≤ upper limit of normal ULN.	Complete response was defined as mUFC ≤ upper limit of normal ULN.	Complete response was defined as mUFC ≤ upper limit of normal ULN.
CR at **- Week 4** **- Week 12** **- Longest FU** *(Proportion of patients with CR, defined as mUFC <ULN)*	W4: NR W12: 77.1% (37/48) - osilodrostat arm W72: 61.5% (40/65) Overall population	W4: NR W12: 71.5% (98/137) (end dose titration phase – overall population) W24: 67.9% (93/137) W72: 81.1% (86/106) (open label phase) 80.2% of those receiving osilodrostat	W4: See LINC-1 W10: 84.2% (16/19) W83 (19m): 81.3% (13/16)	W4: NR W10: 100% (4/4) Longest FU time: See LINC-2	W4: NR W12: 66.7% (6/9) W48: 50% (1/2)
HRQoL Cushings Disease *(CushingQoL Questionnaire)*	CushingQoL (mean actual change from baseline 12.0 (95% CI: 8.2-15.9)	CushingQoL (w48: mean absolute change from baseline 14.1 points (95% CI: 10.9-17.3)	No data available	No data available	At week 12 a sustained QoL was observed.
AEs requiring treatment *(Proportion of patients with treatment requiring AEs)*	91.8% (67/73)	94.9% (130/137); 40.1% (55/137) grade 3/4	89.5% (17/19) (Data from LINC2 extension study)	No data available	89.9% (8/9); 55.6% (5/9) grade 3/4

	Osilodrostat (Gadelha 2022) (21)	Osilodrostat (Pivonello 2020) (4)	Osilodrostat (Fleseriu 2016) (5)	Osilodrostat (Bertagna 2014) (6)	Osilodrostat (Tanaka 2020) (7)
Treatment discontinuation due to AEs	11.0%	13.1% (9.5% drug related)	15.8% (LINC-2 extension)	0%	33.3% (3/9)
Common AEs	Decreased appetite (45.2%), Arthralgia (45.2%), Fatigue (38.4%), Nausea (37%), Headace (32.9%), Myalgia (26%), Dizziness (26%),	Nausea (45.3%), Headache (36.5%), Fatigue (32.8%), Adrenal insufficiency (29.2%), Vomiting (24.8%)	Nausea (52.6%), adrenal insufficiency (47.4%), headache (47.4%), blood corticotrophin increased (42.1%), asthenia (36.8%), diarrhea (36.8%) and abnormal hormone level (36.8%) (LINC-2 extension)	Fatigue (58%), nausea (42%), headache (25%), diarrhoea (25%), hypokalemia (25%), muscle spasms (25%), vomiting (25%)	Adrenal insufficiency (77.8%), gamma-glutamyl transferase increased (33.3%), malaise (33.3%), nasopharyngitis (33.3%)
Grade 3-4 AEs	Hypertension (12.3%), Myalgia (6.8%), Adrenal insufficiency (4.1%), Fatigue (4.1 %)	Hypertension 11.7%, Headache 4.4%, Adrenal insufficiency 4.4%, Hypokalaemia 4.4%,	Adrenal insufficiency 10.5%, Headache 5.3%, Abdominal pain 5.3%	NR	Adrenal insuffiency 22.2%, alanine aminotransferase increased 22.2%, Gamma-glutamyl transferase increased 11.1%, Hypokalemia 11.1%

Abbreviations: AEs, adverse events; CD, Cushing's disease; CR, complete response; FU, follow up; HRQoL, health-related quality of life; mUFC, mean urinary free cortisol; RW, randomized withdrawal; UFC, urinary free cortisol; ULN, upper limit of normal

Table 61 Comparison of Evidence for Treatments for Cushing's Syndrome versus pasireotide (2/2)

	Pasireotide (Lacroix et al 2018) (11)	Pasireotide (Colao et al 2012) (12)	Pasireotide (Fleseriu et al 2019) (13)	Pasireotide (Boscaro et al 2014) (14)	Pasireotide (Pivonello 2019) (15)
Study design	Phase III Randomized Triple blind (n=150)	Phase III Randomized Double blind (n=162)	Phase III Single arm Non-randomized (n=104)	Phase II Single arm Open label Non-randomized (n=39)	Single arm Non-randomized (n=32)
Efficacy Outcome	Defined as participants attaining a mUFC ≤ 1.0 x ULN	Urinary free cortisol level at or below the upper limit of the normal range	UFC≤ULN in patients with an evaluable UFC measurement	Mean UFC level at month 6 was in the normal range (55–276 nmol/24 h; 20–100 µg/24 h)	Fully controlled (UC ≤ ULN, normal UC) in ITT
CR at **- Week 4** **- Week 12** **- Longest FU** *(Proportion of patients with CR, defined as mUFC <ULN)*	W4: NA W12 (month 3): 27.9% (10mg) vs. 35.1% (30mg) Month 7: 41.9% (10mg) vs. 40.8% (30mg) Month 12: 30%	W4: NR W12 (month 3): 16% (600 µg) vs. 28% (900 µg) Month 6: 15% (600 µg) vs. 26% (900 µg) Month 24: 30.8% (600 µg) vs. 37.5% (900 µg)	W4: NA W12: 54.5% (36/66) (all patients) W48: 42.9% (9/21) (all patients)	W4: NA W12: NR Month 6: 22.2% (4/18)	W4: NA W12: 59,37% (19/32) Month 6: 62,5% (20/32)
HRQoL Cushings *(CushingQoL Questionnaire – change from baseline)*	CushingQoL at month 12: Pasireotide 10mg: 6.4 Pasireotide 30mg: 7.0	CushingQoL at month 12: 11.1 (95% CI: 6.8-15.5)	Data available measured by mean percentage incrase from baseline in CushingQoL score with 34.4% increase at week 48	NA	NA
AEs requiring treatment *(Proportion of patients with treatment requiring AEs)*	96.7% (145/150); 48.0% (72/150) grade 3/4	89.5% (145/162)	87.5% (91/104) 45.2% (47/104) grade 3/4	NR	NR

	Pasireotide (Lacroix et al 2018) (11)	Pasireotide (Colao et al 2012) (12)	Pasireotide (Fleseriu et al 2019) (13)	Pasireotide (Boscaro et al 2014) (14)	Pasireotide (Pivonello 2019) (15)
Treatment discontinuation due to AEs	8.7% (13/150)	16.0% (27/162)	19.2% (20/104)	5.3% (1/19)	6.25% (12/49)
Common AEs	Hyperglycemia 48%, Diarrhea 39%, Cholelithiasis 33%, Diabetes mellitus, 21%, Nausea 21%	Diarrhea 58%, Nausea 52%, Hyperglycemia 40%, cholelithiasis 30%, headache 28%	Only reported for treatment-emergent AEs	Diarrhea 68.4%, Nausea 63.2%, Hyperglycemia 57.9%, Abdominal pain 47.4%, Headache 36.8%, Injection-site pain 31.6%, Dizziness 26.3%, Fatigue 26.3%, Injection-site pruritus 26.3%	Hyperglycaemia 81.2%, gastrointestinal Disorders 40.6%, diarrhoea 37.5%, abdominal Pain 15.6%, nausea 12.5% and meteorism 3.1%
Grade 3-4 AEs	Diabetes mellitus 16%, Hypertension 9%, Hyperglycemia 3%	Hyperglycemia 13%, Diabetes mellitus 7%, Diarrhea 3%	Hyperglycemia 13%, Diabetes mellitus 7%	NR	NR

Abbreviations: AEs, adverse events; CD, Cushing's disease; CR, complete response; FU, follow up; HRQoL, health related quality of life; mUFC, mean urinary free cortisol; RW, randomized withdrawal; UFC, urinary free cortisol; ULN, upper limit of normal

Study design
The only other drug tested in controlled trials of methodologically high quality is pasireotide. The main studies with pasireotide concern the B2305 study by Colao et al. 2012 and the G2304 study by Lacroix et al. 2018. Despite small differences in the patient populations examined in the different studies, there is a well-comparable and uniform study population consisting of patients with a confirmed diagnosis of CD for whom surgery was not possible or for whom surgery was unsuccessful.

Patient populations
Despite small differences in the patient populations examined in the different studies, there is a well-comparable and uniform study population consisting of patients with a confirmed diagnosis of CD for whom surgery was not possible or for whom surgery was unsuccessful.

It should be noted, however, that the mean 24-hour urinary cortisol level at the start of treatment in the study by Colao et al. and study LINC-3 was well comparable (970 and 1006 nmol/24 hours, respectively) while in the study by Lacroix et al. this value was comparable to LINC-4 (470 and nmol/24 hours, respectively) This lower baseline might make it relatively easier to achieve normalization, compared to the more severe patients included in the LINC-3 study where more severe patients were included.

Complete response
None of the included studies measured the complete response at week 4, however data for week 5 has been included to support the efficacy of osilodrostat see section 5.1.2.1 for more information.

The percentage of complete response with pasireotide in the respective treatment arms (600 µg and 900 µg) at month 3 lies between 16% and 28% (Colao et al. 2012 (12)) and 27.9% (10mg) till 35.1% (30mg) (Lacroix et al. 2018 (11)), which is well below the complete response of patients treated with osilodrostat at week 12 (77.1%) (3).

Although the response rate at week 24 in the study by Lacroix et al. is higher (41.3%, 62/150) than observed in Colao et al., (20.3%, 33/162) it is still well below the response rates observed with osilodrostat in the overall patient population of LINC-4, showing a complete response of 82.2% (60/73) week 26. We can conclude that there is a greater change of complete response with osilodrostat than with pasireotide at week 24.

Maintenance of effect was better in osilodrostat overall population with 61.5% complete responders at week 72 (LINC-4) (3), compared to month 12 with pasireotide LAR (11) and month 24 on pasireotide (30% and 37.5%, respectively), the latter was reported in the open-label extension trial from Schophohl et al. 2015 (19). Looking at patients randomized to osilodrostat in LINC-4, 61.0% achieved complete response at week 72. Thus showing a sustained cortisol normalisation for patients on osilodrostat.

Quality of life
Both treatments indicate improvements with QoL, assessed with the CushingQoL tool. Although patients treated with pasireotide s.c. showed an improvement between 6.4-7.0 at month 12 (G2304 (11)), versus patients on pasireotide LAR who achieved a mean change from baseline of 11.1 at month 12 (B2305 (12)). Osilodrostat achieved a mean absolute change from baseline of 12.0 points at week 48 in LINC-4. This clinically significant improvement was seen from week 12 and maintained throughout the study. Reviewing against the MID of 10.1 point difference

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00
medicinraadet@medicinraadet.dk www.medicinraadet.dk

required in the protocol, we state that treatment with pasireotide BID and osilodrostat improves the patient's QoL. It should be mentioned that osilodrostat reached and sustained the clinically significant improvement MID of a 10.1-point change from baseline at W 26, 30, 32, 34, and 48 in LINC-3.

Adverse events

An overview with the most common AEs and grade 3-4 AEs for both osilodrostat and pasireotide are provided in Table 60 and Table 61. The presence of gallstones, gastrointestinal problems, bradycardia, prolongation of the QT interval, inhibition of pituitary hormones, (acute) pancreatitis and alteration of the release of insulin and incretin hormones are known side effects of treatment with a somatostatin analogue. Since diabetes is a frequent comorbidity in patients with CS, the hyperglycaemic effect of pasireotide may therefore limit the treatment of these patients with pasireotide. Furthermore, during treatment with pasireotide, rapid suppression of ACTH could decrease circulating cortisol concentrations could lead to transient hypocortisolism/hypoadrenalism.

A similar proportion of patients require additional treatment due to adverse events (around 90%) or discontinued treatment for both pasireotide and osilodrostat. With the exception of Lacroix et al., where the proportion of patients discontinuing was slightly less. Overall, during the long-term treatment (week 48 till week 72) osilodrostat was well tolerated and no new safety signals were reported.

Overall conclusion

To answer the question 'What is the value of osilodrostat compared pasireotide in adult patients with endogenous Cushing Syndrome?' we have reviewed the difference in study design, patient population, complete response, QoL and AEs.

- Both osilodrostat and pasireotide have been assessed in prospective, double-blind studies and can be considered comparable.
- The comparison regarding the complete response as it relates to cortisol normalisation shows higher response rates and thus efficacy with osilodrostat versus pasireotide in both the ITC and naïve comparison. In addition, osilodrostat showed a significantly better maintenance of efficacy. Osilodrostat shows a sustained cortisol normalisation, with a large proportion of the patients remaining on treatment.
- Osilodrostat and pasireotide demonstrated a significant clinical QoL improvement as demonstrated by the CushingQoL, however with osilodrostat achieving a larger improvement.
- Patients on pasireotide have a risk of the serious adverse event hyperglycemia, whereas the risk of adrenal insufficiency with osilodrostat is manageable by dose reductions or interruptions.
- Overall, compared to pasireotide, osilodrostat shows better and sustained efficacy and is well tolerated in patients with CS.

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk
www.medicinraadet.dk

6. Other considerations

Summary of the complete response in the main studies assessed for this assessment are shown in the table below.

Table 62 Summary table complete response

	Osilodrostat	Ketoconazole	Metyrapone	Pasireotide	
	LINC-3 (ITT: N=137)	Castinetti et al. 2014 (retrospective: n=200)	Daniel et al. 2015 (retrospective: n=195)	Colao et al. 2012 B2305 (ITT:N162)	Lacroix et al. 2018 G2304 (ITT: N=150)
Timepoint	Week 12 Longest FU (W72)	Variable	Variable	Week 12 Longest FU (M24)	Week 12 Longest FU (M12)
Efficacy outcome	Complete response was defined as mUFC ≤ ULN	Controlled disease was defined as normal 24-hour UFC at 2 consecutive evaluations	UFC ≤ upper limit of normal ULN for the assey used	Urinary free cortisol level at or below the upper limit of the normal range	Defined as participants attaining a mUFC ≤ 1.0 x ULN
Complete response	71.5% 81.1%	48.5%	43%	16%-28% 30.8%-37.5%	27.9%-35.1% 30%

Abbreviations: *FU, follow up; mUFC, mean urinary free cortisol; ITT, intention-to-treat, UFC, urinary free cortisol; ULN, upper limit of normal*

6.1 PROMPT study

As previously stated, the PROMPT study is the first prospective clinical study assessing the efficacy and safety of metyrapone in patients with CS. This study showed that mUFC was normal in 47-49% of the completers at week 12 and week 36. Thus showing that the complete response remains below 50% when CS patients are treated with metyrapone.

Main study characteristics PROMPT study (29) (32)	
Trial name	PROMPT
NCT number	NCT02297945
Objective	The purpose of this prospective, international phase III/IV study is to assess the efficacy and safety of metyrapone in patients with endogenous Cushing's syndrome during up to 36 weeks of treatment. The PROMPT study is the first prospective study designed to confirm metyrapone efficacy and good tolerance in patients with CS.
Publications – title, author, journal. year	**Prospective, single arm, open-label, multicenter, international study to assess the effects of metyrapone in patients with endogenous Cushing's syndrome during a 12-week treatment period followed by an extension period of 24 weeks.** HRA Pharma. Clinicaltrials.gov. 2022. **Metyrapone Treatment in Endogenous Cushing's Syndrome: Results at Week 12 From PROMPT, a Prospective International Multicenter, Open-Label, Phase III/IV Study** Nieman LK, Boscaro M, Scaroni CM, Deutschbein T, Mezosi E, Driessens N, Georgescu CE, Hubalewska-D

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk
www.medicinraadet.dk

Main study characteristics PROMPT study (29) (32)	
	A, Berker D, Jarzab BM, Maiter DM. Journal of the Endocrine Society. 2021 Apr;5(Supplement_1):A515-. **Metyrapone treatment in endogenous Cushing's syndrome. Long term efficacy and safety results of the extension of the phase III/IV study PROMPT.** Nieman, L., Boscaro, M., Carla, S., Deutschbein, T., Mezosi, E., Driessens, N., Georgescu, C.E., Hubalewska-Dydejczyk, A., Berker, D., Jarzab, B. and Maiter, D., 2021 May; In Endocrine Abstracts (Vol. 73). Bioscientifica.
Study type and design	This single arm, open-label, multicenter, international trial enrolled patients with CS who had three baseline 24 hours urine free cortisol (UFC) values at least 50% above the upper limit of normal (ULN=165 nmol/24h). This was a single arm, open-label, 24Wk extension of PROMPT that enrolled patients whose mean of 3 UFC (mUFC) was normal or less than 2-fold the upper limit of normal (ULN, 165 nmol/d) at Wk12. The EXT measured UFC at Wk24 (for dose titration) and Wk36 by liquid chromatography tandemmass spectrometry. Metyrapone was titrated over 12 weeks (W12) to achieve normal urine (mean of 3 values, mUFC) and serum cortisol levels.
Follow-up time	Patients whose mUFC did not exceed 2-fold the ULN could enter a 6-month extension period.
Population (inclusion and exclusion criteria)	**Inclusion Criteria:** Patients with endogenous Cushing's syndrome: • Cushing disease patients with persistent or recurrent disease (after pituitary surgery) or who are newly diagnosed but are unsuitable for early surgery or wish to defer surgery; • Patients with ectopic ACTH syndrome (either occult, after surgery failure, or inoperable or metastatic); • Patients with Cushing's syndrome from adrenal causes • Patients that received glucocorticoid replacement therapy must have discontinued such therapy for at least seven days or 5 half-lives prior to screening, whichever is longer. • Patients with de novo CD can be included only if they are not considered candidates for surgery (e.g., poor surgical candidates due to co-morbidities, inoperable tumors, patients who refuse to have surgical treatment, or surgical treatment is not available). **Exclusion Criteria:** • Pseudo Cushing's syndrome • Cyclic Cushing's syndrome defined by at least one normal UFC value among at least three 24-hour urinary sampling measurements over the previous 2 months • Advanced adrenocortical carcinoma or ectopic ACTH secretion (EAS) secondary to a small cell lung carcinoma • Life expectancy less than 3 months • Pituitary or adrenal surgery or pituitary irradiation or surgery of the ACTH-secreting ectopic tumor or bilateral adrenalectomy planned before the week 12 visit • Pituitary irradiation within the previous 5 years (for Cushing's disease patients)

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk
www.medicinraadet.dk

Main study characteristics PROMPT study (29) (32)	
	• Enlarged pituitary adenoma (greater than 1 cm in vertical diameter and leaving less than 2 mm from the chiasma) or compression of the optic chiasma on the pituitary MRI for patients with Cushing's disease • Severe uncontrolled hypertension (>180/110 mmHg) despite anti-hypertensive therapy (for otherwise eligible patients, blood pressure medication may be adjusted to meet this criterion) • Severe hypokalemia (< 2.5 mmol/L) despite corrective measures • White blood cell counts <3 x 109 /L; hemoglobin <10 g/dL; platelets <100 x 109 /L • Any other severe acute or chronic medical or psychiatric condition, or laboratory abnormality that in the judgment of the investigator, would present excess risk associated with study participation or study drug administration, or which, in the judgment of the investigator, would make the patient inappropriate for entry into this study.
Intervention	Two possible initiation doses will be used depending on the severity of hypercortisolism, dose will then be adjusted (up or down-titrated) during the first month on an individual basis according to clinical tolerance and cortisol levels achieved.
Baseline characteristics	Mean age was 47 years, median mUFC (range) was 570 (291 - 8476) nmol/24h (3.5 x ULN). Hypercortisolism was in 96% of patients either moderate (mUFC ≥ 2xULN; < 5x ULN) in 63% or severe (≥5 x ULN) in 33%. Hypertension (69%) and diabetes mellitus (47%) were the most common comorbidities.
Primary and secondary endpoints	The primary efficacy endpoint was the proportion of patients with mUFC ≤ ULN at W12 assessed in a central laboratory using LC-MS/MS. The most important secondary endpoint was mUFC decrease of ≥ 50% at W12. Secondary endpoints were to: 1) assess the effects of metyrapone after 12 weeks of treatment on, 2) assess the effects of long-term MTP treatment on efficacy and safety parameters (up to 36 weeks of treatment).
Method of analysis	• NR
Subgroup analyses	None

Results from Nieman et al 2021 (29),Niemand et al 2021 (28) and CSR synopis (32)

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk
www.medicinraadet.dk

Efficacy

At W12: 47% (23/ 49) had mUFC ≤ULN. Another 40% (19/49) had mUFC ≤ 2xULN. Secondary endpoint was met by 80% of patients who had a mUFC decrease of 50%. (29)At Wk36 12 maintained normal values, indicating an escape from week 12.(28) Using the ITT approach, at week 36, 41.5% (17/41) were normalized.

Overall, the authors conclude that mUFC was normal in 47−49% of completers at Wk12 and Wk36, and good tolerability continued. Note that within this percentage, the patients who discontinued are not included. (28)

Wk36 metyrapone dose was higher in mUFC 2-fold ULN group than others (2357 vs 1618-1750 mg/d).(28)

Physical signs and symptoms were normalized or improved in 66% of patients. Circulating cholesterol, HbA1C and fasting glucose and insulin improved with median decrease of 12%, 3%, 5% and 9% respectively.

Quality of Life

CushingQoL increased 10 points from baseline at week 12 (29). The mean (SD) increase further improved at weeks 24 and 36 by 11.3 (13.2) and 10.4 (13.1) from baseline, respectively. (32)

Safety

Twenty-six (52%) patients experienced mild to moderate study drug related AEs. One patient discontinued before W12 because of an unrelated SAE. The most common AEs were nausea (24%), decreased appetite (18%), fatigue (14%), headache (10%), peripheral edema (6.0%), hypokalemia (6.0%) and hypertension (6.0%). Reversible adrenal insufficiency occurred in 6 (12%) patients. Few patients 14% (7/50) experienced at least one AE that led to a dose interruption or dose adjustment.(29)

In the additional weeks following from week 12 to 36, a good tolerabily profile was maintained with no patients treated fro adrenal insufficiency. Three new cases of female hirsutism and one new case of hypertension occurred. (28)

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00
medicinraadet@medicinraadet.dk www.medicinraadet.dk

6.2 Hypocortisolism

The DMC request in the protocol an overview of how hypocortisolism is measured (e.g. blood test, patient assessment) and assessed in the included studies as a side effect. Including which assays (immunoassay or mass spectrometry assey) are used to measure cortisol levels specifically in plasma in the included studies. The table below provides the available information included in the publications regarding these assessments.

Trial name	Hypocortisolism measured	Assays used in the study	Assessed as side effect?
LINC-3	Bodyweight, BMI, fasting plasma glucose, systolic and diastolic blood pressure, and total and LDL cholesterol	Clinical and laboratory evaluations, assessed by the central laboratory, included total testosterone (LC-MS/MS), plasma adrenocorticotropic hormone (Immulite 2000 ACTH kit; PIL2KAC-18, Siemens Medical Solutions Diagnostics, Los Angeles, CA, USA), early-morning serum cortisol (LC-MS/MS), serum 11-deoxycortisol (LC-MS/MS), late-night salivary cortisol (LC-MS/MS), plasma aldosterone (LC-MS/MS), dehydroepiandrosterone sulfate (Chemiluminescent Immunoassay; UniCel DxI 800 Access Immunoassay System; Beckman Coulter, Brea, CA, USA), 11-deoxycorticosterone (LC-MS/MS), active renin (Chemiluminescent Immunoassay; Liaison XL Direct Renin kit, DiaSorin, Vercelli, Italy), serum oestradiol (LC-MS/MS), and oestrone (LC-MS/MS).	Yes
LINC-2	Not reported in the article	UFC was measured at a central laboratory (Quest Diagnostics, Valencia, CA, USA) using liquid chromatography–tandem mass spectrometry (LC–MS/MS; normal range 11–138 nmol/24 h). Pharmacodynamic parameters, including serum (measured at 08:00) and salivary cortisol [measured in the morning (08:00) and late at night (23:00–24:00)], plasma ACTH, serum 11-deoxycortisol, plasma 11-deoxycorticosterone, plasma aldosterone, plasma renin, total serum testosterone, serum luteinizing hormone (LH), serum follicle-stimulating hormone (FSH), and serum estradiol.	Unclear
LINC1 (core study); LINC 2 (extension study)	Not reported in the article	See LINC 2	See LINC 2

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Trial name	Hypocortisolism measured	Assays used in the study	Assessed as side effect?
C1201	Patients should be alerted to the signs and symptoms associated with hypocortisolism (e.g., nausea, vomiting, fatigue, abdominal pain, loss of appetite and dizziness).	Validated liquid chromatography - tandem mass spectrometry assay (LC-MS/MS).	Yes
Castinetti 2014	Bloodpressure, plasma potassium and glucose tolerance	NR	Yes
Castinetti 2008	Weight, bloodpressure, bloodglucose	NR	NR
Daniel et al. 2015	Not reported in the article	NR	NR

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Trial name	Hypocortisolism measured	Assays used in the study	Assessed as side effect?
G2304	Not specifically defined Blood pressure, body mass index, waist circumference, fasting serum lipid profile, weight, bone density and body composition	UFC values were determined by ultra-performance liquid chromatography–tandem mass spectrometry (LC-MS/MS; Waters Corp., Milford, MA, USA; normal: 15·9–166·5 nmol/24h [5·8–60·3 µg/24h]); intra- and inter-assay coefficients of variation were 2·4–7·1% and 4·5–5·6%, respectively. All samples were analysed by central laboratories (Quintiles, Marietta, GA, USA and Q2 Solutions [Beijing] Co. Ltd, Beijing, China). Fasting morning blood samples were tested for serum cortisol by ultra-performance LC-MS/MS (Waters Corp., Milford, MA, USA) and for plasma ACTH (Immulite 2000 ACTH PIL2KAC-15, Siemens Medical Solutions Diagnostics, Los Angeles, CA, USA). Late-night saliva samples were tested for salivary cortisol by ultra-performance LC-MS/MS (Waters Corp., Milford, MA, USA). Intra- and inter-assay coefficients of variation were, respectively: serum cortisol, 1·7–3·9% and 4·6–5·8%; salivary cortisol, 1·8–3·2% and 3·5–4·5%; plasma ACTH, 3·2–4·3% and 3·2–4·7%. All samples were analysed by central laboratories (serum and salivary cortisol: Quintiles, Marietta, GA, USA and Q2 Solutions [Beijing] Co. Ltd, Beijing, China; plasma ACTH: Quintiles, Marietta, GA, USA, Q2 Solutions [Beijing] Co. Ltd, Beijing, China, Q2 Solutions Pte Ltd, Singapore, and Q2 Solutions, Tokyo, Japan). Serum cortisol and plasma ACTH levels were assessed monthly until month 12. Late-night salivary cortisol was assessed monthly until month 7, and then at months 9 and 12. Serum insulin-like growth factor 1 (IGF-1) samples were measured using a chemiluminescent immunometric assay (Immulite® 2000; Diagnostic Products Corp. [Siemens], Los Angeles, CA, USA) and analysed at central laboratories (Q2 Solutions, Valencia, CA, USA). Age- and sex-specific reference ranges were used to calculate an IGF-1 standard deviation score (SDS) for each patient (Brabant G et al. J Clin Endocrinol Metab 2007;92:2604–2609; Brabant G et al. Horm Res 2003;60:53–60).	No

Trial name	Hypocortisolism measured	Assays used in the study	Assessed as side effect?
B2305	Yes	UFC values were determined by high-pressure liquid chromatography (Alliance® 2795 High Throughput System, Waters Corp, Milford, MA, USA; normal UFC range: 30–145nmol/24h [10.8–52.5µg/24h]). All samples were analyzed by central laboratories (Eurofins Medinet B.V., Breda, The Netherlands; CRL Medinet Inc, Lenexa, KS, USA; and Eurofins Technology Services [Suzhou] Co. Ltd., Suzhou, China). Blood samples were tested for serum cortisol (assay: ADVIA Centaur® CP Immunoassay System, Siemens Healthcare Diagnostics Inc, Tarrytown, NY, USA) and plasma ACTH (assay: Immulite® 2000 ACTH kit, DPC, Los Angeles, CA, USA). Saliva samples were tested for salivary cortisol (assay: cortisol ELISA RE52611, IBL-Hamburg GmbH, Germany).	Yes
SEASCAPE	Yes	NR	Yes
B2208	Not reported in the article	UFC levels were measured with two 24-hour urine specimens collected in the 48 hours prior to core baseline and at study visits during the extension study. Serum cortisol was measured with electrochemiluminescence immunoassay (ECLIA), using the Elecsys® cortisol reagent kit (Roche Diagnostics, Indianapolis, IN, USA), which has a lower limit of quantification (LLOQ) of 0.05 nmol/L (0.018 µg/dL) and intra- and inter-assay coefficients of variation of 1.2% and 1.4%, respectively. UFC levels were measured with ECLIA, using the Elecsys® cortisol reagent kit with prior dichloromethane extraction to reduce the amount of cortisol metabolites and conjugates.	NR

Trial name	Hypocortisolism measured	Assays used in the study	Assessed as side effect?
Real-World study	Not reported in the article Weight, body mass index, waist circumference, blood pressure and heart rate by standard methods	Hypothalamic–pituitary–adrenal axis function was assessed by evaluating UC, plasma ACTH and serum cortisol levels, by commercially available kits. At the Universities of Naples and Palermo, UC as well as morning plasma ACTH and serum cortisol were measured by solid-phase chemiluminescent enzyme immunoassay. At the Ospedali Riuniti of Ancona, UC as well as morning plasma ACTH and serum cortisol, were measured by electrochemiluminescent automated assay. At the University of Messina, UC was measured by radioimmunoassay, whereas morning plasma ACTH and serum cortisol were measured by solid-phase chemiluminescent enzyme immunoassay. At the University of Padova, UC was measured by mass spectrometry, plasma ACTH by immunoradiometric assay and serum cortisol was measured by radioimmunoassay. As UC was measured with variable methodology and considering different normal ranges, these were expressed as ratio on ULN values.	No

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

6.3 Compliance

The protocol requests information regarding the compliance of the different treatments included in this report. This table provides an overview, based on the respective SmPC documents, information regarding the compliance of the treatments. This overview shows that the storage of osilodrostat is equal to ketoconazole and metyrapone and no special precautions to the handling of the product. Due to the mode of administration being injections, pasireotide special precautions for both storage and the handling of the treatment that should be considered. Therefore, it is anticipated, that compared to its competitors osilodrostat should not have an impact on compliance versus the currently available treatments in Denmark for treating CS.

Table 64 Overview storage and handling of the treatments

Product	Shelf life	Special precautions for storage	Special precautions for disposal or handling
Osilodrostat	3 years	Do not store above 25°C. Store in the original package in order to protect from moisture	No special requirements for disposal.
Ketoconazole	3 years	Does not require any special storage conditions	No special requirements for disposal
Metyrapone	3 years After opening: 2 months	Keep the bottle tightly closed in order to protect from moisture. Do not store above 25 ° C	No special requirements for disposal
Pasireotide LAR	3 years	Store in a refrigerator (2°C – 8°C). Do not freeze	There are two critical steps in the reconstitution of Signifor. Not following them could result in failure to deliver the injection appropriately. • The injection kit must reach room temperature. Remove the injection kit from the fridge and let the kit stand at room temperature for a minimum of 30 minutes before reconstitution, but do not exceed 24 hours. • After adding the solvent, shake the vial moderately for a minimum of 30 seconds until a uniform suspension is formed. Included in the injection kit: a One vial containing the powder b One pre-filled syringe containing the solvent c One vial adapter for medicinal product reconstitution d One safety injection needle (20G x 1.5”) Follow the instructions below carefully to ensure proper reconstitution of Signifor powder and solvent for suspension for injection before deep intramuscular injection. Signifor suspension must only be prepared immediately before administration. Signifor should only be administered by a trained healthcare professional. To prepare Signifor for deep intramuscular injection, please adhere to the instructions provided in the SmPC.

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk
www.medicinraadet.dk

Pasireotide	3 years	Store in the original package in order to protect from light	Signifor solution for injection should be free of visible particles, clear and colorless. Do not use Signifor if the solution is not clear or contains particles. For information on the instructions for use, please see the end of the package leaflet "How to inject Signifor". Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6.4 Duration of treatment

The protocol requests information regarding how long patients can be expected to be on treatment with osilodrostat and the comparators.
In general Danish clinicians aim to avoid long-term medical treatment for patients with CS and the expected duration of current medical treatment of CS is anything between a few days and one year. In Denmark clinicians do not often use pre-surgical medical treatment, as the waiting time till surgery is short. Equally while waiting for another treatment decision (second surgery, bilateral adrenalectomy, radiation etc), clinicians will reduce the time spend on medical therapy. (33)

6.5 Subsequent treatment lines

The DMC requests information regarding whether and how the introduction of osilodrostat in Danish clinical practice will affect treatments in subsequent lines of treatment.

A conversation with a Danish clinical expert (33) provided insights that surgery will remain the first treatment option, however medical treatment remains important if surgery is not feasible and as bridging therapy. Given the medical treatments come with different efficacy and AE profiles, which justify new alternatives. The introduction of osilodrostat would provide a good alternative to find the optimal treatment for each individual patient.

In addition, the presented evidence shows that osilodrostat has higher complete response rates compared to ketoconazole, metyrapone and pasireotide. In addition, the conclusion of the COMP is of relevance for this assessment: *'Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Isturisa may be of potential significant benefit to those affected by the orphan condition still holds. The sponsor provided data to demonstrate that the use of Isturisa leads to a high response rate in treatment–naïve and pre-treated patients and that the responses are maintained, with no treatment escape cases reported in the pivotal clinical study.* ***This constitutes a clinically relevant advantage over all existing authorised products as established in the pivotal trial and by indirect comparisons****.'(2)*

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk
www.medicinraadet.dk

7. References

1. Osilodrostat SmPc. Summary of Product Characteristics.
2. European Medicines Agency. Orphan Maintenance Assessment Report: Isturisa (osilodrostat). In: Committee for Orphan Medicinal Products, editor. 2020.
3. Gadelha M, Bex M, Feelders RA, Heaney AP, Auchus RJ, Gilis-Januszewska A, et al. Randomized trial of osilodrostat for the treatment of Cushing's disease. The Journal of Clinical Endocrinology & Metabolism. 2022.
4. Pivonello R, Fleseriu M, Newell-Price J, Bertagna X, Findling J, Shimatsu A, et al. Efficacy and safety of osilodrostat in patients with Cushing's disease (LINC 3): a multicentre phase III study with a double-blind, randomised withdrawal phase. The Lancet Diabetes & Endocrinology. 2020;8(9):748-61.
5. Fleseriu M, Pivonello R, Young J, Hamrahian AH, Molitch ME, Shimizu C, et al. Osilodrostat, a potent oral 11β-hydroxylase inhibitor: 22-week, prospective, Phase II study in Cushing's disease. Pituitary. 2016;19(2):138-48.
6. Bertagna X, Pivonello R, Fleseriu M, Zhang Y, Robinson P, Taylor A, et al. LCI699, a potent 11β-hydroxylase inhibitor, normalizes urinary cortisol in patients with Cushing's disease: results from a multicenter, proof-of-concept study. The Journal of Clinical Endocrinology & Metabolism. 2014;99(4):1375-83.
7. Tanaka T, Satoh F, Ujihara M, Midorikawa S, Kaneko T, Takeda T, et al. A multicenter, phase 2 study to evaluate the efficacy and safety of osilodrostat, a new 11β-hydroxylase inhibitor, in Japanese patients with endogenous Cushing's syndrome other than Cushing's disease. Endocrine journal. 2020;67(8):841-52.
8. Castinetti F, Guignat L, Giraud P, Muller M, Kamenicky P, Drui D, et al. Ketoconazole in Cushing's disease: is it worth a try? The Journal of Clinical Endocrinology & Metabolism. 2014;99(5):1623-30.
9. Castinetti F, Morange I, Jaquet P, Conte-Devolx B, Brue T. Ketoconazole revisited: a preoperative or postoperative treatment in Cushing's disease. European Journal of Endocrinology. 2008;158(1):91-100.
10. Daniel E, Aylwin S, Mustafa O, Ball S, Munir A, Boelaert K, et al. Effectiveness of metyrapone in treating Cushing's syndrome: a retrospective multicenter study in 195 patients. The Journal of Clinical Endocrinology & Metabolism. 2015;100(11):4146-54.
11. Lacroix A, Gu F, Gallardo W, Pivonello R, Yu Y, Witek P, et al. Efficacy and safety of once-monthly pasireotide in Cushing's disease: a 12 month clinical trial. The Lancet Diabetes & Endocrinology. 2018;6(1):17-26.
12. Colao A, Petersenn S, Newell-Price J, Findling JW, Gu F, Maldonado M, et al. A 12-month phase 3 study of pasireotide in Cushing's disease. N Engl J Med. 2012;366:914-24.
13. Fleseriu M, Iweha C, Salgado L, Mazzuco TL, Campigotto F, Maamari R, et al. Safety and efficacy of subcutaneous pasireotide in patients with Cushing's disease: results from an open-label, multicenter, single-arm, multinational, expanded-access study. Frontiers in endocrinology. 2019;10:436.
14. Boscaro M, Bertherat J, Findling J, Fleseriu M, Atkinson A, Petersenn S, et al. Extended treatment of Cushing's disease with pasireotide: results from a 2-year, Phase II study. Pituitary. 2014;17(4):320-6.
15. Pivonello R, Arnaldi G, Scaroni C, Giordano C, Cannavò S, Iacuaniello D, et al. The medical treatment with pasireotide in Cushing's disease: an Italian multicentre experience based on "real-world evidence". Endocrine. 2019;64(3):657-72.
16. European Medicines Agency. SmPC ketoconazole. 2021.
17. Fleseriu M, Petersenn S, Biller BM, Kadioglu P, De Block C, T'Sjoen G, et al. Long-term efficacy and safety of once-monthly pasireotide in Cushing's disease: A Phase III extension study. Clinical endocrinology. 2019;91(6):776-85.
18. Petersenn S, Salgado L, Schopohl J, Portocarrero-Ortiz L, Arnaldi G, Lacroix A, et al. Long-term treatment of Cushing's disease with pasireotide: 5-year results from an open-label extension study of a Phase III trial. Endocrine. 2017;57(1):156-65.
19. Schopohl J, Gu F, Rubens R, Van Gaal L, Bertherat J, Ligueros-Saylan M, et al. Pasireotide can induce sustained decreases in urinary cortisol and provide clinical benefit in patients with Cushing's disease: results from an open-ended, open-label extension trial. Pituitary. 2015;18(5):604-12.
20. Webb SM, Ware JE, Forsythe A, Yang M, Badia X, Nelson LM, et al. Treatment effectiveness of pasireotide on health-related quality of life in patients with Cushing's disease. Eur J Endocrinol. 2014;171(1):89-98.
21. European Medicines Agency. Scientific advice: LCI699 [confidential]. 2013.
22. Data on File. LINC-4 CSR: A Phase III, multi-center, randomized, double-blind, 48 week study with an initial 12 week placebo-controlled period to evaluate the safety and efficacy of osilodrostat in patients with Cushing's disease. CLCI699C2302. 2020.
23. Button KS, Kounali D, Thomas L, Wiles NJ, Peters TJ, Welton NJ, et al. Minimal clinically important difference on the Beck Depression Inventory--II according to the patient's perspective. Psychol Med. 2015;45(15):3269-79.

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk
www.medicinraadet.dk

24. McClure NS, Sayah FA, Xie F, Luo N, Johnson JA. Instrument-Defined Estimates of the Minimally Important Difference for EQ-5D-5L Index Scores. Value Health. 2017;20(4):644-50.
25. Data on File. LINC-3: A Phase III, multi-center, double-blind, randomized withdrawal study of LCI699 following a 24 week, single-arm, open-label dose titration and treatment period to evaluate the safety and efficacy of LCI699 for the treatment of patients with Cushing's disease. 2018.
26. Fleseriu M, Biller B, Pivonello R, Akira S, Carla S, Belaya Z, et al., editors. Osilodrostat is an effective and well-tolerated treatment option for patients with Cushing's disease (CD): Final results from the LINC3 study. Endocrine Abstracts; 2021: Bioscientifica.
27. Fleseriu M, Auchus R, Bancos I, Ben-Shlomo A, Bertherat J, Biermasz NR, et al. Consensus on diagnosis and management of Cushing's disease: a guideline update. The Lancet Diabetes & Endocrinology. 2021.
28. Nieman L, Boscaro M, Carla S, Deutschbein T, Mezosi E, Driessens N, et al., editors. Metyrapone treatment in endogenous Cushing's syndrome. Long term efficacy and safety results of the extension of the phase III/IV study PROMPT. Endocrine Abstracts; 2021: Bioscientifica.
29. Nieman LK, Boscaro M, Scaroni CM, Deutschbein T, Mezosi E, Driessens N, et al. Metyrapone Treatment in Endogenous Cushing's Syndrome: Results at Week 12 From PROMPT, a Prospective International Multicenter, Open-Label, Phase III/IV Study. Journal of the Endocrine Society. 2021;5(Supplement_1):A515-A.
30. Data on File. G2304: A randomized, double-blind, multicenter, Phase III study to evaluate the efficacy and safety of pasireotide LAR in patients with Cushing's disease; full clinical study report. 2017.
31. Data on File. A randomized, double-blind study to assess the safety and efficacy of different dose levels of pasireotide (SOM230) sc over a 6-month treatment period in patients with de novo, persistent or recurrent Cushing's disease. 2014.
32. HRA Pharma. Prospective, single arm, open-label, multicenter, international study to assess the effects of metyrapone in patients with endogenous Cushing's syndrome during a 12-week treatment period followed by an extension period of 24 weeks. . Clinicaltrials.gov; 2022.
33. Recordati Rare Diseases. Communications with Jens Otto Jorgensen regarding CS disease in Denmark 2021.
34. Simeoli C, Ferrigno R, De Martino M, Iacuaniello D, Papa F, Angellotti D, et al. The treatment with pasireotide in Cushing's disease: effect of long-term treatment on clinical picture and metabolic profile and management of adverse events in the experience of a single center. Journal of endocrinological investigation. 2020;43(1):57-73.
35. Ceccato F, Zilio M, Barbot M, Albiger N, Antonelli G, Plebani M, et al. Metyrapone treatment in Cushing's syndrome: a real-life study. Endocrine. 2018;62(3):701-11.
36. Manetti L, Deutschbein T, Schopohl J, Yuen KC, Roughton M, Kriemler-Krahn U, et al. Long-term safety and efficacy of subcutaneous Pasireotide in patients with Cushing's disease: interim results from a long-term real-world evidence study. Pituitary. 2019;22(5):542-51.
37. Barbot M, Guarnotta V, Zilio M, Ceccato F, Ciresi A, Daniele A, et al. Effects of pasireotide treatment on coagulative profile: a prospective study in patients with Cushing's disease. Endocrine. 2018;62(1):207-14.
38. Winquist EW, Laskey J, Crump M, Khamsi F, Shepherd FA. Ketoconazole in the management of paraneoplastic Cushing's syndrome secondary to ectopic adrenocorticotropin production. J Clin Oncol. 1995;13(1):157-64.
39. Pivonello R, Petersenn S, Newell-Price J, Findling JW, Gu F, Maldonado M, et al. Pasireotide treatment significantly improves clinical signs and symptoms in patients with Cushing's disease: results from a Phase III study. Clinical endocrinology. 2014;81(3):408-17.
40. Correa-Silva SR, Nascif SO, Molica P, Sá LB, Vieira JG, Lengyel AMJ. Adrenocorticotrophic hormone (ACTH) responsiveness to ghrelin increases after 6 months of ketoconazole use in patients with Cushing's disease: comparison with GH-releasing peptide-6 (GHRP-6). Clinical endocrinology. 2010;72(1):70-5.
41. Boscaro M, Ludlam W, Atkinson B, Glusman J, Petersenn S, Reincke M, et al. Treatment of pituitary-dependent Cushing's disease with the multireceptor ligand somatostatin analog pasireotide (SOM230): a multicenter, phase II trial. The Journal of Clinical Endocrinology & Metabolism. 2009;94(1):115-22.
42. Correa-Silva SR, Nascif SO, Molica P, Sá LB, Vieira JG, Lengyel A-MJ. Partial restoration of GH responsiveness to ghrelin in Cushing's disease after 6 months of ketoconazole treatment: comparison with GHRP-6 and GHRH. European journal of endocrinology. 2009;161(5):681.
43. Nelson LM, Forsythe A, McLeod L, Pulgar S, Maldonado M, Coles T, et al. Psychometric evaluation of the Cushing's Quality-of-Life questionnaire. The Patient-Patient-Centered Outcomes Research. 2013;6(2):113-24.
44. Cuneo RC, Lee W, Harper J, Mitchell K, Ward G, Leigh Atkinson R, et al. Metyrapone pre-treated inferior petrosal sinus sampling in the differential diagnosis of ACTH-dependent Cushing's syndrome. Clinical endocrinology. 1997;46(5):607-18.

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk
www.medicinraadet.dk

45. Trementino L, Zilio M, Marcelli G, Michetti G, Barbot M, Ceccato F, et al. The role of an acute pasireotide suppression test in predicting response to treatment in patients with Cushing's disease: findings from a pilot study. Endocrine. 2015;50(1):154-61.
46. Moncet D, Morando DJ, Pitoia F, Katz SB, Rossi MA, Bruno OD. Ketoconazole therapy. An efficacious alternative to achieve eucortisolism in patients with Cushing's syndrome. MEDICINA-BUENOS AIRES-. 2007;67(1):26.
47. Tabarin A, Navarranne A, Guerin J, Corcuff JB, Parneix M, Roger P. Use of ketoconazole in the treatment of Cushing's disease and ectopic ACTH syndrome. Clinical endocrinology. 1991;34(1):63-70.
48. Tyas E., Piacentini A., Hemstock M., Lilley C., Lebbink E., Matthijsse S., et al. Comparative Efficacy of Osilodrostat Versus Pasireotide Subcutaneous and Pasireotide Long-Acting Release for the Treatment of Cushing's Disease – A Patient-Level Data Indirect Treatment Comparison Using Propensity Score Weighting. Value in Health. 2022;25(6):S1.
49. Phillippo D, Ades A, Dias S, Palmer S, Abrams K, Welton N. NICE DSU TSD 18: Methods for population-adjusted indirect comparisons in submissions to NICE 2016 [Available from: http://nicedsu.org.uk/wp-content/uploads/2018/08/Population-adjustment-TSD-FINAL-ref-rerun.pdf.
50. Greifer N. Covariate balance tables and plots: a guide to the cobalt package 2021 [updated 29 March. Available from: https://cran.r-project.org/web/packages/cobalt/vignettes/cobalt.html#references.
51. Signorovitch JE, Sikirica V, Erder MH, Xie J, Lu M, Hodgkins PS, et al. Matching-adjusted indirect comparisons: a new tool for timely comparative effectiveness research. Value Health. 2012;15(6):940-7.
52. Phillippo D, Ades A, Dias S, Palmer S, Abrams K, Welton N. NICE DSU TSD 18: Methods for Population-Adjusted Indirect Comparisons in Submissions To NICE 2016 [Available from: http://scharr.dept.shef.ac.uk/nicedsu/wp-content/uploads/sites/7/2017/05/Population-adjustment-TSD-FINAL.pdf.
53. Zeileis A, Köll S, Graham N. Various versatile variances: An object-oriented implementation of clustered covariances in R. J Stat Softw. 2020;95:1-36.

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk
www.medicinraadet.dk

8. Appendices

8.1 Literature search

Table 65 Literature search inclusion and exclusion criteria

Inclusion and exclusion criteria	
Inclusion criteria	Population: Adult patients with endogenous Cushing's syndrome Intervention(s): Osilodrostat (Isturisa), ketoconazole (Nizoral), metyrapone (Metopiron), pasireotide (Signifor) Comparator(s): Placebo, best supportive care, any pharmacological intervention Outcomes: normalization of cortisol level (complete response based on mUFC), health related quality of life (*CushingQoL Questionnaire*), adverse events Settings (if applicable): NA Study design: Randomized controlled trials, non-randomized controlled trials, cohort studies (both prospective and retrospective), long-term follow-up studies Language restrictions: English Other search limits or restrictions applied:
Exclusion criteria	Population: healthy volunteers, children only (<18 years), disease other than endogenous Cushing's syndrome Intervention(s): interventions not included in the list, all non-pharmacological interventions, surgery, radiotherapy, adjuvants and neoadjuvants Comparator(s): no exclusion on comparators Outcomes: pharmacokinetics/pharmacodynamics Settings (if applicable): Study design: preclinical studies, comments, letters, editorials, case reports, case series, both systematic and non-systematic reviews Language restrictions: non-English article Other search limits or restrictions applied:

8.2 Databases and search strategy

For this systematic literature review, two databases were consulted: Pubmed and CENTRAL. The search strings used for this assessment are provided in Table 66 andTable 67.

Table 66 Pubmed search string

Search	Hits
#1 Cushing Syndrome[mh]	12486
#2 Cushings syndrome[tiab] OR Cushing's syndrome[tiab] OR cushing syndrome[tiab]	10228
#3 hypercortisolism[tiab]	2808
#4 Pituitary ACTH Hypersecretion[mh]	1497
#5 cortisol hypersecretion[tiab] OR ACTH hypersecretion[tiab] OR adrenocorticotropic hormone secreti*[tiab] OR adrenocorticotrophic hormone secreti*[tiab] OR ACTH secreti*[tiab]	4099
#6 Cushings disease[tiab] OR Cushing's disease[tiab] OR cushing disease[tiab]	5102
#7 #1 OR #2 OR #3 OR #4 OR #5 OR #6	21082
#8 Osilodrostat[nm] OR osilodrostat[tiab] OR Isturisa*[tiab]	46
#9 Ketoconazole[mh] OR ketoconazole[tiab] OR Nizoral*[tiab]	9426

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk
www.medicinraadet.dk

#10 Metyrapone[mh] OR metyrapone[tiab] OR Metopiron*[tiab]	4626
#11 pasireotide[nm] OR pasireotide[tiab] OR Signifor*[tiab]	625
#12 #8 OR #9 OR #10 OR #11	14467
#13 #7 AND #12	1195
#14 english[la] AND hasabstract	20531575
#15 Animals[mh] NOT Humans[mh]	4860592
#16 Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Guideline[pt] OR Letter[pt] OR News[pt] OR Review[pt] OR case report[ti] OR Systematic Review[pt] OR review[ti]	7065829
#17 (#13 AND #14) NOT (#15 OR #16)	344
#18 Clinical Trial[pt] OR Comparative Study[pt] OR Multicenter Study[pt]	2730487
#19 (clinical[tiab] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] observationelle m.fl.) OR controlled[tiab] OR case-control[tiab] OR prospective[tiab] OR multicenter[tiab] OR multicentre[tiab] OR comparative[tiab] OR openlabel[tiab] OR phase II[tiab] OR phase III[tiab]) AND (trial[tiab] OR study[tiab])	1376365
#20 Observational Study[pt] OR Cohort Studies[mh]	2207807
#21 (observational[tiab] OR cohort[tiab] OR retrospective*[tiab]) AND (study[tiab] OR analy*[tiab])	1248970
#22 Registries[mh] OR registry[tiab] OR nation-wide[tiab] OR nationwide[tiab] OR population-based[tiab] OR real-world[tiab]	395664
#23 #18 OR #19 OR #20 OR #21 OR #22	544307
#24 #17 AND #23	**153**

Table 67 CENTRAL search string

Search	Hits
#1 (cushing* next (disease or syndrome)):ti,ab,kw	533
#2 hypercortisolism:ti,ab	101
#3 [mh "Pituitary ACTH Hypersecretion"]	30
#4 ((cortisol or ACTH or adrenocorticotropic or adrenocorticotrophic) next (secreti* or hypersecretion)):ti,ab	599
#5 #1 OR #2 OR #3 OR #4	1139
#6 (osilodrostat or Isturisa*):ti,ab,kw	9
#7 (ketoconazole or Nizoral*):ti,ab,kw	1110
#8 (metyrapone or Metopiron*):ti,ab,kw	147
#9 (pasireotide or Signifor*):ti,ab,kw	199
#10 #7 OR #8 OR #9	1448
#11 #5 AND #10	118
#12 (clinicaltrials.gov or trialsearch):so	369117
#13 ("conference abstract" or review):pt,ti	200608
#14 (abstract or conference or meeting or proceeding*):so	44966
#15 NCT*:au	210348
#16 #12 or #13 or #14 or #15	599557
#17 #11 not #16	76
#18 #17 not pubmed:an	**15**

8.3 List of excluded articles

Table 68 List of excluded studies

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk
www.medicinraadet.dk

Author and year	Title	Exclusion reason
Simeoli et al 2020 (34)	The treatment with pasireotide in Cushing's disease: effect of long-term treatment on clinical picture and metabolic profile and management of adverse events in the experience of a single center.	Study design not of interest – only one center in Italy
Ceccato et al 2018 (35)	Metyrapone treatment in Cushing's syndrome: a real-life study.	No relevant outcome assessed
Manetti et al 2019 (36)	Long-term safety and efficacy of subcutaneous pasireotide in patients with Cushing's disease: interim results from a long-term real-world evidence study.	Intervention – concomitant medication used
Barbot et al 2018 (37)	Effects of pasireotide treatment on coagulative profile: a prospective study in patients with Cushing's disease	No relevant outcome assessed
Winquist et al 1995 (38)	Ketoconazole in the management of paraneoplastic Cushing's syndrome secondary to ectopic adrenocorticotropin production.	No relevant outcome assessed
Pivonello et al 2014 (39)	Pasireotide treatment significantly improves clinical signs and symptoms in patients with Cushing's disease: results from a Phase III study.	Intervention – concomitant medication used
Correa-Silva et al 2010 (40)	Adrenocorticotrophic hormone (ACTH) responsiveness to ghrelin increases after 6 months of ketoconazole use in patients with Cushing's disease: comparison with GH-releasing peptide-6 (GHRP-6).	No relevant outcome assessed
Boscaro et al 2009 (41)	Treatment of pituitary-dependent Cushing's disease with the multireceptor ligand somatostatin analog pasireotide (SOM230): a multicenter, phase II trial.	Study design – only 15 days
Correa-Silva et al 2009 (42)	Partial restoration of GH responsiveness to ghrelin in Cushing's disease after 6 months of ketoconazole treatment: comparison with GHRP-6 and GHRH.	No relevant outcome assessed
Nelson et al 2013 (43)	Psychometric evaluation of the Cushing's Quality-of-Life questionnaire.	No relevant outcome assessed
Cuneo et al 1997 (44)	Metyrapone pre-treated inferior petrosal sinus sampling in the differential diagnosis of ACTH-dependent Cushing's syndrome.	Intervention not of interest - surgery
Trementino et al 2015 (45)	The role of an acute pasireotide suppression test in predicting response to treatment in patients with Cushing's disease: findings from a pilot study.	No relevant outcome assessed
Moncet et al 2007 (46)	Ketoconazole therapy: an efficacious alternative to achieve eucortisolism in patients with Cushing's syndrome.	Intervention not of interest – surgery and/or radiotherapy
Tabarin et al 1991 (47)	Use of ketoconazole in the treatment of Cushing's disease and ectopic ACTH syndrome.	No relevant outcome assessed

8.4 Main characteristics of included studies for this assessment

Studies that included relevant endpoints within relevant patient populations identified in the literature for the intervention, osilodrostat are described in the following sections. The literature search identified four studies for osilodrostat: LINC-3, LINC-2, LINC-1, C1201. This section will also provide an overview for the relevant studies identified in the SLR for the comparators: ketoconazole (Castinetti 2014 (8), Castinetti 2008 (9)), metyrapone (Daniel 2015 (10)) and pasireotide (G2304 (11), B2305 (12), SEASCAPE (13), B2208 (14), ” Italian real-world evidence study” (15)).

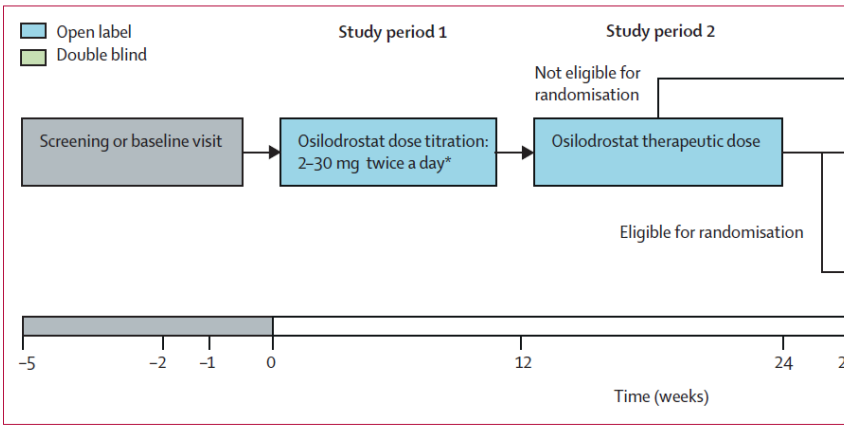
8.4.1 LINC-3 study characteristics

Table 69 Study characteristics: LINC-3 (Pivonello 2020)(4)

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk
www.medicinraadet.dk

Main study and patient characteristics (Pivonello 2020)	
Trial name	LINC-3; C2301
NCT number	NCT02180217
Objective(s)	**Primary:** To compare the complete response rate at the end of the 8-week period of randomized withdrawal (Week 34) between patients randomized to continued osilodrostat therapy versus those receiving placebo. **Secondary:** To assess the complete response rate at the end of individual dose-titration and treatment with osilodrostat in the initial single-arm open-label period (Week 24) **Other secondary:** • To compare the time-to-last control of mUFC during the RW Period between patients randomized to continued osilodrostat therapy and placebo • To assess the complete, partial and overall response rate at Week 12, Week 24, Week 48 and at scheduled timepoints during the Extension Period and the last available assessment • To assess the change in mUFC during the Core and Extension Periods of the stud • To assess the change in cardiovascular-related parameters associated with Cushing's Disease during the Core and Extension Periods of the study • To assess the change in PROs (HRQoL) during the Core and Extension Periods of the study using CushingQoL, BDI-II and EQ 5D-5L • Safety
Publications – title, author, journal. year	**Efficacy and safety of osilodrostat in patients with Cushing's disease (LINC 3): a multicentre phase III study with a double blind, randomised withdrawal phase.** Pivonello R, Fleseriu M, Newell-Price J, Bertagna X, Findling J, Shimatsu A, Gu F, Auchus R, Leelawattana R, Lee EJ, Kim JH. The Lancet Diabetes & Endocrinology. 2020
Study type and design	Phase lll, multi-center, double-blind randomized withdrawal phase, following a 24 week open-label, single-arm dose titration and treatment period which evaluated the efficacy and safety for the treatment of patients with Cushing's disease. **Four study periods (1–4) and an optional extension period:** **Study Period 1** (Week 1 to Week 12; dose-titration period): all patients received open-label osilodrostat 2 mg BID with dose adjustments every 2 weeks up to week 12 based on efficacy and tolerability. **Study Period 2** (Week 13 to Week 24; dose-titration and treatment period): during this study period, the efficacy and safety of osilodrostat were assessed at the therapeutic dose determined during study period 1. Of note, patients with mUFC > ULN had their osilodrostat dose increased as tolerated and the maximum dose of 30 mg BID had not yet been reached. These patients were followed for long-term efficacy and were not considered responders for the key secondary endpoint, hence were not randomized in Study Period 3. **Study Period 3** (Week 26 to Week 34; randomized withdrawal period): Patients were eligible to enter the randomized withdrawal phase at week 26 if they had mUFC ≤ULN at week 24 without a dose increase after week 12; patients were randomized (1:1) in a double-blind manner to continue osilodrostat at the same therapeutic dose or receive matching placebo for 8 weeks without further dose increases. Patients not eligible for randomization received open label osilodrostat until the end of the Core Period (Week 48) unless there was a reason to discontinue from the study prematurely. **Study Period 4** (Week 34 to Week 48): After week 34 all patients received open-label osilodrostat until week 48; dosing could be adjusted based on the mUFC levels during this treatment period.

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk
www.medicinraadet.dk

Main study and patient characteristics (Pivonello 2020)	
	***Extension** phase (optional) (Week 48 to Week 72)*  *Key: *Based on efficacy and tolerability* *Abbreviations: UFC, urinary free cortisol; ULN, upper limit of normal.* *Note: Patients were eligible for randomization if they had mean 24-h UFC concentration of less than or equal to the ULN at week 24 and no dose up-titration of osilodrostat during weeks 13–24.*
Follow-up time	Patients who continued to receive clinical benefit (as assessed by the study investigator) and who wished to enter the extension period, had to be re-consented at Week 48. Patients who entered the extension period did so without interruption of study drug or scheduled assessments. The optional extension period will end after all patients have completed Week 72 or discontinued prior to Week 72.
Population (inclusion and exclusion criteria)	**Key inclusion Criteria:** • Male or female patients aged 18 - 75 years • Patients with confirmed persistent or recurrent Cushing's disease (mUFC≥1.5x ULN and morning plasma ACTH above the LLN (lower limit of normal)) after primary pituitary surgery and/or irradiation, and also de novo patients with Cushing's disease who were not eligible for surgery or who refuse to undergo surgery • Patients with a history of prior pituitary surgery must be at least 30 days post-surgery to be eligible for inclusion in this study. • Patients that received glucocorticoid replacement therapy post-operatively must have discontinued such therapy for at least one week, or 5 half-lives, whichever is longer, prior to screening • Patients with de novo Cushing's disease can be included only if they are not considered candidates for surgery • Patients with a history of pituitary irradiation can be included, provided that at least 2 years (stereotactic radiosurgery) or 3 years (conventional radiation) have elapsed from the time of last radiation treatment to the time of enrollment into this study. *Note: Patients were permitted to wash out current drug therapy to meet entry criteria if they had a known diagnosis of Cushing's disease.* **Key exclusion Criteria:** • Patients who had a known inherited syndrome as the cause for hormone over secretion • Patients with CS due to ectopic ACTH secretion or ACTH-independent (adrenal) CS • Pregnant or nursing (lactating) women • Patients who had undergone major surgery within 1 month before screening

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk
www.medicinraadet.dk

Main study and patient characteristics (Pivonello 2020)

- Hypertensive patients with uncontrolled blood pressure defined as systolic blood pressure (SBP) >180 and/or diastolic blood pressure (DBP) >100
- Diabetic patients with poorly controlled diabetes as evidenced by glycosylated hemoglobin (HbA1c) >9 .0%
- Patients with a history of congestive heart failure (New York Heart Association Class III or IV), unstable angina, sustained ventricular tachycardia, clinically significant bradycardia, advanced heart block, acute MI less than one year before study entry, or clinically significant impairment in cardiovascular function
- Patients with moderate to severe renal impairment
- Patients with liver disease
- History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there was evidence of local recurrence or metastases
- Patients with risk factors for QTc prolongation or Torsade de Pointes
- Patients with compression of the optic chiasm due to a macroadenoma or patients at high risk of compression of the optic chiasm
- Patients who had had stereotactic radiosurgery in the past 2 years, conventional radiotherapy in the past 3 years or pituitary surgery in the past 29 days.

Intervention

Osilodrostat

Study period 1: The dosing regimen was up-titrated as follows: 2 mg BID, 5 mg BID, 10 mg BID, 20 mg BID, and 30 mg BID. The up titration continued until mUFC ≤ ULN. The maximum dose of osilodrostat was 30 mg BID. Dose was increased if mUFC (mean of three 24-hour samples) exceeded ULN. Throughout the study, osilodrostat dose was reduced if mUFC was below LLN or if mUFC was in the lower part of the normal range in patients with symptoms of hypocortisolism or adrenal insufficiency. Of note, at Week 0 and Week 2, dose increases were not permitted. (n=137)

Study period 2: Dose was determined in period 1 and no changes were made.

Study period 3: Same therapeutic dose (n=36, randomized and n=66, not randomized but continues treatment with osilodrostat)

Study period 4: Dose could be adjusted based on the mUFC levels during this treatment period.

Extension phase (optional): Dose could be adjusted based on the mUFC levels during this treatment period.

Baseline characteristics

Patient Characteristics, n (%)	Randomized to osilodrostat N=36	Randomized to placebo N=35	Not Randomized N=66	All Patients N=137
Age				
Mean (SD)	44.3 (11.27)	42.0 (13.47)	39.0 (13.38)	41.2 (12.98)
Median (range)	41.0	40.0	37.5	40.0 (19.0-70.0)
Age category (years) - n (%)				
18-<65	34 (94.4)	34 (97.1)	62 (93.9)	130 (94.9)
65-≤ 75	2 (5.6)	1 (2.9)	4 (6.1)	7 (5.1)
Sex - n (%)				
Female	30 (83.3)	22 (62.9)	54 (81.8)	106 (77.4)
Male	6 (16.7)	13 (37.1)	12 (18.2)	31 (22.6)
Race - n (%)				
Caucasian	27 (75.0)	23 (65.7)	39 (59.1)	89 (65.0)
Black	0	3 (8.6)	1 (1.5)	4 (2.9)

Main study and patient characteristics (Pivonello 2020)

Asian	7 (19.4)	7 (20.0)	25 (37.9)	39 (28.5)
Other	2 (5.6)	2 (5.7)	1 (1.5)	5 (3.6)
Body mass index (kg/m2)				
Mean (SD)	29.6 (7.35)	30.9 (8.37)	30.4 (7.73)	30.3 (7.76)
Median	28.5	29.0	28.8	28.8
Time (months) to first osilodrostat dose since diagnosis				
Mean (SD)	71.4 (63.54)	88.3 (67.46)	46.5 (43.26)	63.7 (58.20)
Median	53.6	76.8	34.7	47.2
CD status - n (%)				
De novo (no previous surgery)	4 (11.1)	2 (5.7)	11 (16.7)	17 (12.4)
Persistent/recurrent (with previous surgery)	32 (88.9)	33 (94.3)	55 (83.3)	120 (87.6)
Any previous treatments for Cushing's disease: n (%)				
Yes	35 (97.2)	33 (94.3)	63 (95.5)	131 (95.6)
No	1 (2.8)	2 (5.7)	3 (4.5)	6 (4.4)
Any previous pituitary irradiation: n (%)				
Yes	6 (16.7)	5 (14.3)	11 (16.7)	22 (16.1)
No	30 (83.3)	30 (85.7)	55 (83.3)	115 (83.9)
Baseline mUFC, nmol/24h				
Mean (SD)	890.0 (1275.66)	560.0 (548.84)	1,305.8 (2012.21)	1,006.0 (1,589.86)
Median	457.0	357.9	556.9	476.4

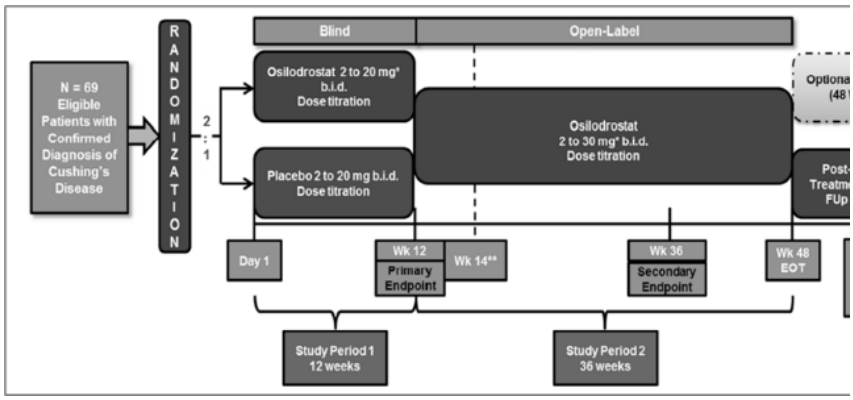
Primary and secondary endpoints	**Primary endpoint:** Proportion of randomized patients in each arm with: mUFC ≤ ULN at the end of 8 weeks of RW (Week 34), and were neither discontinued, nor had osilodrostat dose increase above the level at Week 26 during the RW period **Key secondary endpoint:** Proportion of enrolled patients with mUFC ≤ ULN at Week 24 and had no dose increase above the level established at Week 12 between Week 13 and Week 24 **Other secondary endpoints:** • To compare the time-to-last control of mUFC during the RW Period between patients randomized to continued osilodrostat therapy and placebo • To assess the complete, partial and overall response rate at Week 12, Week 24, Week 48 and at scheduled timepoints during the Extension Period and the last available assessment • To assess the change in mUFC during the Core and Extension Periods of the study • To assess the change in cardiovascular-related parameters associated with CD during the Core and Extension Periods of the study • To assess the change in PROs (HRQoL) during the Core and Extension Periods of the study using CushingQoL, BDI-II and EQ 5D-5L • Safety
Method of analysis	Analysis was by intention-to-treat (IIT) for all patients who received at least one dose of osilodrostat (full analysis set; key secondary endpoint) or randomized treatment (randomized analysis set; primary endpoint) and safety was assessed in all enrolled

Main study and patient characteristics (Pivonello 2020)	
	patients who received at least one dose of osilodrostat (safety analysis set) and had at least one post-baseline safety assessment.
Subgroup analyses	None

Abbreviations: ACTH, adrenocorticotropic hormone; BID, twice daily; CD, Cushing's disease; CS, Cushing's syndrome; HRQoL, health related quality of life; LLN=lower limit of normal; RW, randomized week; ULN, pper limit of normal; UFC=urinary free cortisol

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk
www.medicinraadet.dk

8.4.2 LINC-4 study characteristics

Main study and patient characteristics (LINC-4)	
Trial name	LINC-4
NCT number	NCT02697734
Objective	The LINC-4 trial was designed to demonstrate the superiority of osilodrostat compared to placebo in achieving a complete response (mUFC ≤ ULN) at Week 12, to evaluate the safety of osilodrostat compared to placebo, and to evaluate the long-term safety and efficacy of osilodrostat.
Publications – title, author, journal. year	Gadelha M, Bex M, Feelders RA, Heaney AP, Auchus RJ, Gilis-Januszewska A, Witek P, Belaya Z, Yu Y, Liao Z, Chen Ku CH. Randomized trial of osilodrostat for the treatment of Cushing's disease. The Journal of Clinical Endocrinology & Metabolism. 2022 Mar 23.
Study type and design	LINC-4 is a Phase III, global, multi-center, randomized, double-blind, 48-week study with an initial 12-week placebo-controlled period; the trial was designed to demonstrate the superiority of osilodrostat compared to placebo in achieving a complete response (mUFC ≤ ULN) at Week 12, to evaluate the safety of osilodrostat compared to placebo, and to evaluate the long-term safety and efficacy of osilodrostat (Figure 12).(127) LINC-4 comprised a Core Phase of 48 weeks with two periods: • Study Period 1 (Weeks 1–12): double-blind and placebo-controlled • Study Period 2 (Weeks 13–48): single arm, open-label treatment. • Optional Extension phase (Weeks 48–96). **LINC-4 Study Design**  *Key: * If needed, the dose may also be titrated to below the 2 mg b.i.d starting dose (e.g. 1mg b.i.d, 1 mg q.d. or 1 mg q.o.d; **The first UFC and lab results available to the investigator will be from samples collected prior to the Week 14 visit*
Follow-up time	At Week 48, patients had the option to enter an optional open-label Extension phase. During the optional extension phase the dose of osilodrostat was maintained at the established effective dose unless a change was required based on mUFC results collected at Week 48, and if applicable, at Weeks 60, 72, and 84. Patients benefitting

Main study and patient characteristics (LINC-4)	
	from study treatment had the option of entering a separate long-term safety follow-up study (Study LCI699C2X01B) once they completed the optional extension phase. The optional extension phase ended when all eligible patients transitioned into the long-term safety follow-up study or were discontinued from the study.
Population (inclusion and exclusion criteria)	**Inclusion Criteria:** • Confirmed CD that is persistent or recurrent as evidenced by all the following criteria being met (i.e., a, b and c): 4. mUFC > 1.3 x ULN (Mean of three 24-hour urine samples collected preferably on 3 consecutive days, during screening after washout of prior medical therapy for CD (if applicable), confirmed by the central laboratory and available before Day 1), with ≥2 of the individual UFC values being > 1.3 x ULN. 5. Morning plasma ACTH above Lower Limit of Normal 6. Confirmation (based on medical history) of pituitary source of excess ACTH as defined by any one or more of the following three criteria: i. Histopathologic confirmation of an ACTH-staining adenoma in patients who have had prior pituitary surgery. OR ii. MRI confirmation of pituitary adenoma > 6 mm OR iii. Bilateral inferior petrosal sinus sampling (BIPSS) with either CRH or DDAVP stimulation for patients with a tumor ≤ 6mm. The criteria for a confirmatory BIPSS test are any of the following: Pre-dose central to peripheral ACTH gradient > 2; Post-dose central to peripheral ACTH gradient > 3 after either CRH or DDAVP stimulation • Patients that received glucocorticoid replacement therapy must have discontinued such therapy for at least seven days or 5 half-lives prior to screening, whichever is longer. • Patients with de novo CD can be included only if they are not considered candidates for surgery (e.g., poor surgical candidates due to co-morbidities, inoperable tumors, patients who refuse to have surgical treatment, or surgical treatment is not available). **Exclusion Criteria:** • Patients with pseudo-Cushing's syndrome. This may be diagnosed by a normal late night salivary cortisol value collected during the screening period and after washout of prior CD medication. • Patients with risk factors for QTc prolongation or Torsade de Pointes, including: • patients with a baseline QTcF > 450 ms for males and QTcF > 460 ms for females; personal or family history of long QT syndrome; concomitant medications known to prolong the QT interval; patients with hypokalemia, hypocalcaemia, or hypomagnesaemia, if not corrected before pre-dose Day 1. • Patients likely to require adrenalectomy, pituitary surgery, or radiation therapy during the placebo-controlled period (Weeks 1-12) for the treatment of severe hypercortisolism or pituitary tumor growth causing compression of the optic chiasm. • Patients with compression of the optic chiasm due to a macroadenoma or patients at high risk of compression of the optic chiasm (tumor within 2 mm of optic chiasm). • Patients who have a known inherited syndrome as the cause for hormone over secretion (i.e. Carney Complex, McCune-Albright syndrome, MEN-1, AIP).

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk
www.medicinraadet.dk

Main study and patient characteristics (LINC-4)	
	• Patients with Cushing's syndrome due to ectopic ACTH secretion or ACTH independent (adrenal) Cushing's syndrome. Pregnant or nursing (lactating) women. 8. Women of child-bearing potential. defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 1 week after completion of dosing.
Intervention	**Study period 1:** The initial study drug dose was 2 mg BID. The dose escalation sequence was: 5 mg BID, 10 mg BID and 20 mg BID. Osilodrostat could be up titrated to the next dose in the sequence, based on the mUFC value until mUFC is normalized **Study period 2**: Allowing for further dose titration as needed by the investigator. All patients on doses of ≥2 mg BID at the Week 12 visit received open-label osilodrostat at a starting dose of 2 mg BID at the beginning of Period 2, regardless of treatment assignment in Period 1. Patients on <2 mg BID at the Week 12 visit continued the same dose they were on at the end of Period 1, regardless of treatment assignment during Period 1 **Optional extension phase:** During the optional extension phase, the dose of osilodrostat was maintained at the established effective dose unless a change was required based on mUFC results collected at Week 48, and if applicable, at Weeks 60, 72, and 84.

Baseline characteristics

FAS population			
Patient Characteristics, n (%)	**Osilodrostat N=48**	**Placebo N=25**	**All Patients N=73**
Age, years			
Mean (SD)	42.3 (13.82)	38.9 (12.33)	41.2 (13.35)
Median (range)	41.0 (21.0–67.0)	37.0 (19.0–63.0)	39.0 (19.0–67.0)
Sex - n (%)			
Female	43 (89.6)	18 (72.0)	61 (83.6)
Male	5 (10.4)	7 (28.0)	12 (16.4)
Race - n (%)			
Caucasian	34 (70.8)	15 (60.0)	49 (67.1)
Asian	9 (18.8)	8 (32.0)	17 (23.3)
Black or African American	2 (4.2)	0	2 (2.7)
Unknown	2 (4.2)	1 (4.0)	3 (4.1)
American Indian or Alaska Native	1 (2.1)	0	1 (1.4)
Other	0	1 (4.0)	1 (1.4)
Weight, kg			
Mean (SD)	78.8 (17.46)	77.3 (16.90)	78.3 (17.17)
Median (range)	80.1 (46.9–113.7)	74.0 (53.5–114.5)	77.0 (46.9–114.5)

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk
www.medicinraadet.dk

Main study and patient characteristics (LINC-4)

Time (months) to first osilodrostat dose since diagnosis			
Median (range)	69.9 (6.0–257.7)	65.0 (11.2–215.9)	67.4 (6.0–257.7)
CD status - n (%)			
De novo	3 (6.3)	0	3 (4.1)
Persistent/recurrent	45 (93.8)	25 (100)	70 (95.9)
Any previous surgery, n (%)			
Yes	41 (85.4)	23 (92.0)	64 (87.7)
No	7 (14.6)	2 (8.0)	9 (12.3)
Any previous treatments for Cushing's disease: n (%)			
Yes	26 (54.2)	19 (76.0)	45 (61.6)
No	22 (45.8)	6 (4.0)	28 (38.4)
Any previous pituitary irradiation: n (%)			
Yes	6 (12.5)	3 (12.0)	9 (12.3)
No	42 (87.5)	22 (88.0)	64 (87.7)
Baseline mUFC, nmol/day			
Mean (SD)	421.3 (291.3) 3.1xULN	451.5 (535.1) 3.3xULN	431.7 (388.6) 3.1xULN
Median (interquartile range)	342.2 (252.6-519.9) 2.5xULN	297.6 (211.2-518.8) 2.2xULN	340.3 (221.3-518.8) 2.5xULN

Abbreviations: CD, Cushing's disease; FAS: full analysis set; mUFC, mean urinary free cortisol; SD, standard deviation.

*Key: * Pituitary adenomas <10mm in size are defined as microadenomas, ≥10mm in size are defined as macroadenomas.*

Note: Data cut-off is 25 February 2020.

Primary and secondary endpoints

Primary endpoint: The proportion of randomized patients with a complete response, i.e. mUFC ≤ ULN, at Week 12.

Key secondary endpoint: The proportion of patients with mUFC ≤ ULN at Week 36 for combined randomized patients who received osilodrostat treatment.

Secondary endpoints:

- To assess the proportion of patients with a complete response (mUFC ≤ ULN) or a partial response (mUFC decrease ≥50.0% from baseline and >ULN) at Week 12, Week 36, and Week 48.
- To assess the change in mUFC during the Core and Extension periods.
- To compare the time-to-first control of mUFC during the placebo-controlled period (Weeks 1-12) between the randomized treatment arms.
- To assess the time-to-escape during osilodrostat treatment up to Week 48.
- To assess cardiovascular and metabolic related parameters associated with CD (fasting plasma glucose, HbA1c, fasting lipid profile, blood pressure, weight and waist circumference) by assessing actual and percent change from baseline and shift table at Weeks 12, 36, and 48.
- To assess the change from baseline at Weeks 12, 36, and 48 in physical features of CD
- To assess the change from baseline in BMD by DXA scan at the lumbar spine and total hip at Week 48.
- To determine the safety and tolerability of osilodrostat in the study population.

Main study and patient characteristics (LINC-4)	
	• To assess the change from baseline in HRQoL, as measured by the CushingQoL, BDI-II, and EQ-5D-5L, by randomized treatment arm and overall. • To evaluate pharmacokinetic exposure of osilodrostat in the study population. • To assess the change from baseline in serum, salivary and hair cortisol levels
Method of analysis	• Full Analysis Set (FAS): comprised all randomized patients who received at least one dose of study drug (osilodrostat or placebo). FAS is the default analysis set for efficacy. The randomization was stratified by history of pituitary irradiation (yes/no) • Safety Analysis Set (SAS): Comprised all patients who received at least one dose of study drug (osilodrostat or placebo). Patients were analyzed according to the study drug received, where treatment received was defined as the randomized/assigned treatment if the patient took at least one dose of that treatment or the first treatment received if the randomized/assigned treatment was never received • Per-Protocol Set (PPS): Comprised a subset of the patients in the FAS who were compliant (e.g. did not have any protocol deviations that would lead to exclusion from PPS) with the requirements of the Clinical Study Protocol
Subgroup analyses	None

8.4.3 LINC-2 study characteristics

Table 70 Study characteristics: LINC-2 (Fleseriu, 2016) (5)

Main study and patient characteristics (Fleseriu, 2016)	
Trial name	LINC-2; C2201 (part II)
NCT number	NCT01331239
Objective(s)	**Primary**: To assess the effects of 10 weeks' treatment of osilodrostat on 24-hour UFC in patients with Cushing's Disease (same objective as in LINC-1) **Secondary:** (Follow-up and Expansion cohorts):

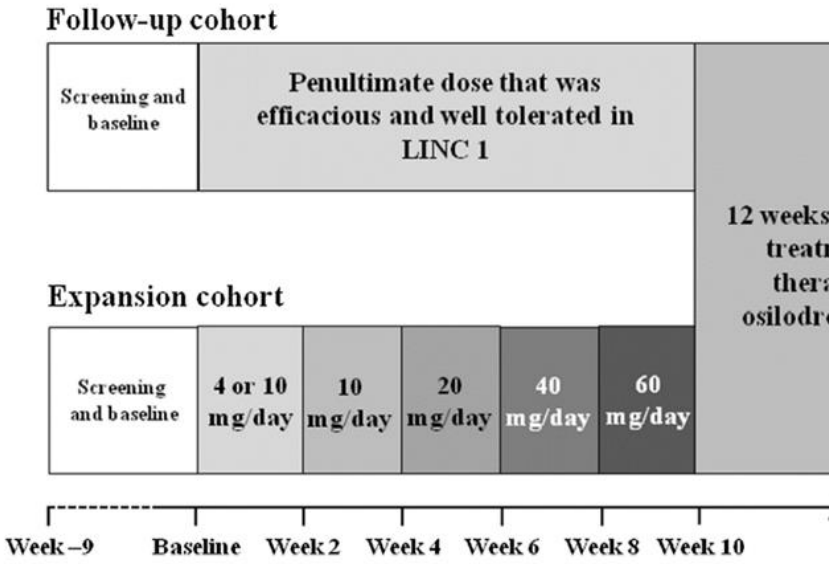
Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk
www.medicinraadet.dk

Main study and patient characteristics (Fleseriu, 2016)	

	• To assess the effects of 10 weeks' treatment of osilodrostat on 24-hour UFC in patients with Cushing's Disease
	• To assess the 10-week and 22-week safety and tolerability of multiple doses of osilodrostat
	• To assess the effect of osilodrostat on steroid hormones of the HPA-axis in plasma, urine and saliva
	• To assess the effects of osilodrostat on improving the metabolic abnormalities (hypertension, dyslipidemia, obesity, insulin sensitivity, glycosylated hemoglobin [HbA1c] and fasting plasma glucose [FPG]) of Cushing's disease
	• To assess the steady state pharmacokinetics of osilodrostat in patients with Cushing's Disease
	• To assess the effect of 22-weeks of treatment with osilodrostat monotherapy on 24-hour UFC in patients with Cushing's Disease. The proportion of patients controlled or partially controlled was determined as follows:
	  • Controlled UFC: defined as a mUFC level≤ ULN
	  • Partially controlled UFC: defined as a mUFC level >ULN but with ≥ 50.0% reduction from baseline
	• To assess escape. Escape is defined as loss of UFC control (i.e. UFC >ULN) on at least 2 consecutive visits at the highest tolerated dose after previously attaining UFC normalization
	
	Objectives of the extensions-1 and -2 (optional beyond the 22 weeks) were to provide long-term efficacy and safety data.

Publications – title, author, journal. year	**Osilodrostat, a potent oral 11β-hydroxylase inhibitor: 22-week, prospective, Phase II study in Cushing's disease.** Fleseriu M, Pivonello R, Young J, Hamrahian AH, Molitch ME, Shimizu C, Tanaka T, Shimatsu A, White T, Hilliard A, Tian C, Sauter N, Biller BM, Bertagna X. Pituitary. 2016
Study type and design	The LINC-2 study was a 22-week, prospective, open-label, multicenter, phase II study that enrolled patients (aged 18–75 years) with a confirmed diagnosis of CD. Patients were enrolled in two cohorts: • The '**follow-up cohort'** comprised patients who completed LINC 1 and • The '**expansion cohort'** which comprised newly enrolled patients who were naïve to osilodrostat. **Extension phase (optional)** At the End of Week 22, patients were evaluated for clinical benefit and had the option to enter the 12-month long term Extension Phase at the Investigators discretion provided they did not meet discontinuation criteria. This is not part of the Fleseriu, 2016 article, but is described. The optional extension phase consists of two extensions: **Long-term extension 1** At Day 154 (Week 22), patients had the option to enter the 12-month extension phase at the Investigators discretion, provided they did not meet any discontinuation criteria. Dosing titration during the extension 1 was based on efficacy (UFC control) and safety. Patients were to come for monthly visits for the first 6 months (Day 154-Day 322) and then every 3 months from month 6 through 12 (Day 322 - Day 490) of long-term extension 1 (extension-1). **Long term extension 2** At Day 490, patients had the option to enter a second long-term extension phase

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk
www.medicinraadet.dk

	(extension-2) at the Investigator's discretion, provided they did not meet any of the study discontinuation criteria. Dose adjustment during extension-2 was based on efficacy (UFC control) and safety. Patients were to visit every 3 months during the first 18 months of extension-2 (approximately 3 years into the study), and every 6 months thereafter. This additional long-term extension (extension-2) was planned to provide long-term safety and efficacy data of osilodrostat in patients with Cushing's disease.  *Note: Patients in the Follow-up cohort could re-enter the study if their current UFC level was above the upper limit of normal (ULN; i.e.>1 x ULN). Patients were off osilodrostat treatment for 15–19 months before enrolment in LINC-2 (administrative time between the end of LINC 1 and initiation of LINC-2)* *Note: An amendment to the protocol was conducted to allow the total treatment duration with osilodrostat to extend to 22 weeks. This amendment led to the expansion of the LINC-1 trial into LINC-2. In addition, at Day 154 visit or End of Treatment Core visit (Week 22), two optional long-term extension phases (Extension-1 and Extension-2) were planned to evaluate long-term safety and efficacy data of* osilodrostat *in patients with CD. The study duration was subsequently extended several times*
Follow-up time	19 months (optional extension)
Population (inclusion and exclusion criteria)	The eligibility criteria for LINC-2 are the same as LINC-1. In addition, patients should complete the 22-week study and if they responded to osilodrostat or were considered by the investigator to be receiving clinical benefit could enter the extension phase. **Inclusion criteria:** • Patients could be included once they had given written informed consent and had confirmed CD and were willing to complete the prescribed washout periods prior to baseline efficacy assessments • Male or female patients aged 18 – 75 years • Patients must have confirmed CD (including de novo patients) **Exclusion criteria:** • Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of enrollment, whichever is longer; or longer if required by local regulations, and for any other limitation of participation in an investigational trial based on local regulations

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk
www.medicinraadet.dk

Main study and patient characteristics (Fleseriu, 2016)

- History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases
- Patients who have been treated with mitotane during the last 6 months prior to Visit 1
- Patients who have a known inherited syndrome as the cause for hormone over secretion (i.e. Carney Complex, McCune-Albright syndrome, MEN-1, AIP)
- Patients with CS due to ectopic ACTH secretion or adrenal CS
- Patients with pseudo-Cushing's syndrome
- Patients with renal impairment

Intervention

Osilodrostat

Expansion cohort: Patients in the Expansion cohort started osilodrostat treatment at Day 1 with 2 mg BID (if baseline UFC ≤ 3xULN) or 5 mg BID (if baseline UFC >3xULN). The dose was then escalated every 2 weeks according to the escalation sequence 10, 20, 40, and 60 mg/day until UFC was ≤ULN.

Follow-up cohort: Patients in the Follow-up cohort started at the penultimate osilodrostat dose that was efficacious and well tolerated for them. The dose was up titrated from the penultimate dose according to the escalation sequence 10, 20, 40, and 60 mg/day until UFC was ≤ULN. This titration was continued up to Week 10 as needed based on efficacy and tolerability.

If UFC normalized before Week 10 in either cohort, dose was maintained at the effective level until Week 10; if UFC normalized but subsequently increased to >ULN, dose escalation was resumed.

Extension phase (optional): Patients continued on the same dose of osilodrostat as at Week 22; however, dose adjustments were permitted during the extension (min/max, 1 mg once daily/30 mg BID). (n=16 in long-term extension-1 and n=13 in long-term extension-2)

Baseline characteristics

Factor	Expansion Cohort N=15	Follow-up Cohort N=4	All Patients N=19
Mean age ±SD, years	37.5±9.0	34.3±5.5	36.8±8.4
Female:male, n	11:4	3:1	14:5
Race, n (%)			
Caucasian	11 (73.3)	4 (100.0)	15 (78.9)
Other	4 (26.7)	0	4 (21.1)
Mean (SD) BMI (kg/m^2)	30.6 (7.46)	31.3 (5.5)	30.7 (7.0)
Median time since diagnosis (range), months	63.4 (12–155.2)	82.5 (57.6–100.3)	70.2 (12.2–155.2)
Previous treatment for CD	12 (80.0)	4 (100)	16 (84.2)
Previous surgery, n (%)	13 (86.7)	4 (100.0)	17 (89.5)
Mean baseline UFC ± SD, nmol/24 hours*	1630±3043	398±176[l]	1371±2734

Primary and secondary endpoints

Objectives of the extensions-1 and -2 were to provide long-term efficacy (response rate of [partially] controlled UFC) and safety data.

Method of analysis

The analysis sets were as follows:

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk
www.medicinraadet.dk

Main study and patient characteristics (Fleseriu, 2016)	
	• Full Analysis Set (FAS): all patients who re-entered the study in the Follow-up cohort, and who were newly enrolled in the study in the Expansion cohort • Safety Analysis Set (SAS): all patients that received at least 1 dose of osilodrostat in each patient cohort • Pharmacokinetic Analysis Set (PAS): all patients with at least 1 dose of osilodrostat and at least 1 post-dose pharmacokinetic assessment
Subgroup analyses	NA

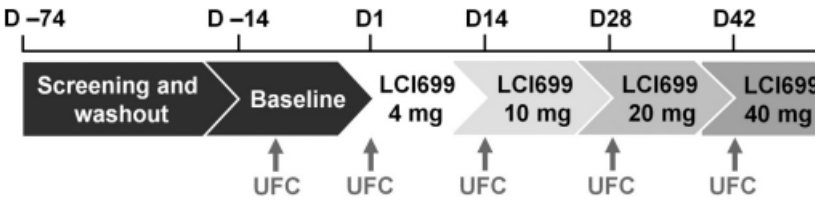
Abbreviations: ACTH, adrenocorticotropic hormone; BID, twice daily; CD, Cushing's disease; CS, Cushing's syndrome; HRQoL, health-related quality of life; LLN=lower limit of normal; ULN, upper limit of normal; UFC=urinary free cortisol

8.4.4 LINC-1 study characteristics

Table 71 Study characteristics: LINC-1 (Bertagna, 2014) (6)

Main study and patient characteristics (Bertagna, 2014)	
Trial name	LINC-1; C2201 (part I)
NCT number	NCT01331239
Objective	**Primary:** To assess the effects of 10 weeks' treatment of osilodrostat on 24-hour UFC in patients with Cushing's Disease **Secondary:** • To assess the safety and tolerability of multiple doses of osilodrostat in patients with Cushing's Disease • To assess the effect of osilodrostat on steroid hormones of the HPA-axis in plasma, urine and saliva • To assess the effects of osilodrostat on improving the metabolic abnormalities (hypertension, dyslipidemia, obesity, insulin sensitivity) of Cushing's Disease • To determine steady-state through plasma concentrations of osilodrostat
Publications – title, author, journal. year	**LCI699, a potent 11β-hydroxylase inhibitor, normalizes urinary cortisol in patients with Cushing's disease: results from a multicenter, proof-of-concept study.** Bertagna X, Pivonello R, Fleseriu M, Zhang Y, Robinson P, Taylor A, Watson CE, Maldonado M, Hamrahian AH, Boscaro M, Biller BM. J Clin Endocrinol Metab. 2014
Study type and design	A proof-of-concept, single-arm, open-label, multicenter study, designed to assess the efficacy, safety and tolerability of 10 weeks (70 days) of sequentially increasing doses of osilodrostat treatment in patients with Cushing's disease LINC-1 comprised of the following periods: • A **screening period** of up to 60 days (to allow an adequate washout period for any medications that modified cortisol levels) • A 10–14-day **baseline period** • A 10-week **treatment period** (Days 1–70); and • A 14-day **washout period** (Days 71–84) followed by the end of study evaluation

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk
www.medicinraadet.dk

Main study and patient characteristics (Bertagna, 2014)	
	
Follow-up time	12 weeks (see LINC-2)
Population (inclusion and exclusion criteria)	**Inclusion criteria:** • Patients could be included once they had given written informed consent and had confirmed CD and were willing to complete the prescribed washout periods prior to baseline efficacy assessments • Male or female patients aged 18 – 75 years • Patients must have confirmed Cushing's disease (including de novo patients) **Exclusion criteria:** • Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of enrollment, whichever is longer; or longer if required by local regulations, and for any other limitation of participation in an investigational trial based on local regulations • History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases • Patients who have been treated with mitotane during the last 6 months prior to Visit 1 • Patients who have a known inherited syndrome as the cause for hormone over-secretion (i.e. Carney Complex, McCune-Albright syndrome, MEN-1, AIP) • Patients with Cushing's syndrome due to ectopic ACTH secretion or adrenal Cushing's syndrome • Patients with pseudo-Cushing's syndrome • Patients who had undergone major surgery within 1 month before screening • Patients who had poorly controlled diabetes mellitus *Patients with moderate-to-severe Cushing's disease were enrolled.*
Intervention	Osilodrostat; 2 mg BID starting dose for the first 2 weeks. The dose was escalated every 14 days to 5, 10, 20 and 50 mg bid until UFC normalized, whereupon the dose was maintained until treatment ended (day 70). If UFC normalized during the escalation period, the dose was maintained at the effective level until the end of active treatment (Day 70). If a patient's UFC had normalized but subsequently increased to above the ULN, dose escalation was resumed.

Main study and patient characteristics (Bertagna, 2014)	
Baseline characteristics	Patient Demographics and Baseline Characteristics (SAS)

Patient demographics	All patients (N=12)
Mean (SD) age, years	39 (10.3)
Female, n (%)	8 (66.7)
Weight, mean (SD), kg	95.6 (30.95)
Height, mean (SD) cm	167 (7.7)
BMI, mean (SD), kg/m^2	33.8 (8.54)

Abbreviations: SAS, safety analysis set; SD, standard deviation.

Primary and secondary endpoints	**Primary** The primary endpoint was UFC ≤ULN or a ≥50% decrease from baseline at day 70. *Mean UFC level from at least two 24-hour urine samples collected at baseline and within the 10th week of treatment was used. Otherwise, UFC was assessed from a single 24-hour urine sample taken on the penultimate day of each 14-day treatment period. Responders were classed as patients whose mean UFC level from three 24-hour urine samples collected at Week 10 was ≤ULN (as defined by the local laboratories) or represented a ≥50.0% decrease from baseline.*
Method of analysis	Patient analysis sets were as follows: • Primary variable: All patients with evaluable UFC data (at least two 24-hour measurements for both baseline and Week 10) were included in the analysis of the primary variable • Safety analysis set (SAS): All patients that received at least one dose of study drug • PK/PD data analysis: Comprised all patients with evaluable PK/PD data
Subgroup analyses	NA

Abbreviations: ACTH, adrenocorticotropic hormone; BID, twice daily; CD, Cushing's disease; CS, Cushing's syndrome; HRQoL, health-related quality of life; LLN=lower limit of normal; ULN, upper limit of normal; UFC=urinary free cortisol

8.4.5 C1201 study characteristics

Table 72 Study characteristics: C1201 (Tanaka, 2020) (7)

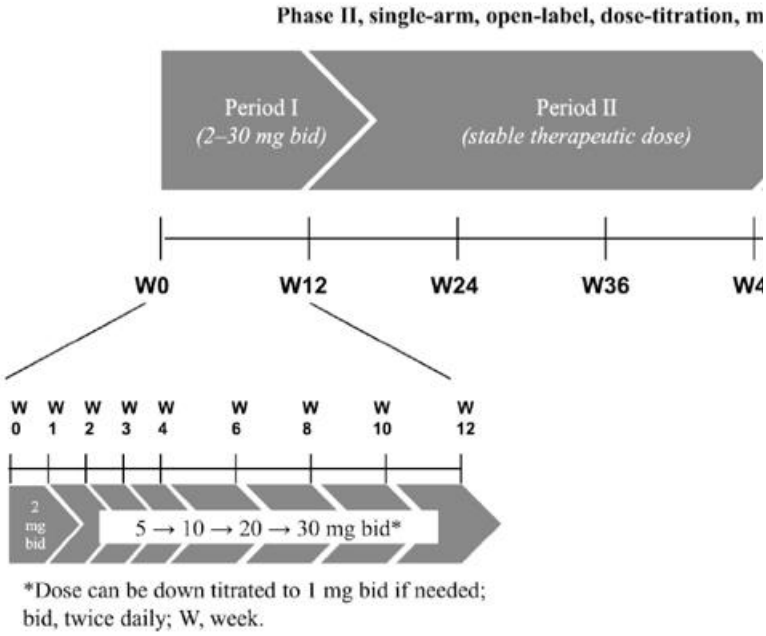
Main study and patient characteristics (Tanaka 2020)	
Trial name	C1201
NCT number	NCT02468193
Objective	**Primary:** To assess the percentage change from baseline in the mUFC at the individual patient level at Week-12

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk
www.medicinraadet.dk

Main study and patient characteristics (Tanaka 2020)	
	Secondary: • To assess the percentage change from baseline in the mUFC at the individual patient level at Week 24 and Week 48 • To assess the absolute and percentage change from baseline in mUFC at Week 12, Week 24 and Week 48 • To assess the complete, partial. and overall response rate at Week 12, Week 24 and Week 48 • To assess the absolute and percentage change from baseline in morning serum cortisol at the individual patient level at Week 12, Week 24 and Week 48 • To assess the absolute and percentage change from baseline in steroid hormones at the individual patient level at Week 12, Week 24 and Week 48 • To assess the change from baseline in cardiovascular-related metabolic parameters associated with Cushing's syndrome at Week 12, Week 24 and Week 48 • To assess the general safety of osilodrostat • To assess the change from baseline in Patient-Reported Outcomes (HRQoL) at individual patient level at Week 12, Week 24 and Week 48 using the CushingQoL and Beck Depression Inventory-II instruments • To evaluate osilodrostat PK in patients with CS
Publications – title, author, journal. year	**A multicenter, phase 2 study to evaluate the efficacy and safety of osilodrostat, a new 11β-hydroxylase inhibitor, in Japanese patients with endogenous Cushing's syndrome other than Cushing's disease.** Tanaka T, Satoh F, Ujihara M, Midorikawa S, Kaneko T, Takeda T, Suzuki A, Sato M, Shimatsu A. Endocr J. 2020
Study type and design	Phase II, single-arm, open-label, dose titration, multi-center study to assess osilodrostat in Japanese patients with all types of endogenous Cushing's syndrome except Cushing's disease caused by adrenal tumor/hyperplasia or ectopic adrenocorticotropic hormone syndrome. The study comprised three distinct study periods: • **Study Period I** (Week 0 [Day 1]) to Week-12): In this study period, the aim was to achieve a stable therapeutic dose of osilodrostat. • **Study Period II** (After Week-12 to Week-48): In this period, the aim was to assess efficacy and long-term safety, on the stable therapeutic dose of osilodrostat achieved in Study Period I. During this period, only patients who tolerated and agreed to continue osilodrostat treatment continued the study. • **Extension phase (optional)** (After Week 48): Patients who entered the extension period were to be continued to be treated with the study drug without interruption to be assessed for efficacy and safety. Patients who continued to benefit from study treatment as assessed by the study investigator and who completed Week 72 were to be invited to participate in a separate long-term safety follow-up study. The optional extension period ended after all patients had completed Week 72 or had discontinued early.

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk
www.medicinraadet.dk

Main study and patient characteristics (Tanaka 2020)



Follow-up time	Optional **extension period** (After Week-48): Patients were re-consented at Week-48 to participate in the extension period. Patients who entered the extension period were to be continued to be treated with the study drug without interruption to be assessed for efficacy and safety. • **Post-treatment Follow-up**: All patients had 30 days safety follow-up after the last dose of study treatment
Population (inclusion and exclusion criteria)	**Inclusion criteria:** • Patients with confirmed Cushing's Syndrome [i.e. ectopic corticotropin syndrome, adrenal adenoma, adrenal carcinoma, ACTH-Independent Macronodular Adrenal Hyperplasia (AIMAH), or Primary Pigmented Nodular Adrenal Dysplasia (PPNAD)] • Patients who were expected to remain in stable condition for at least 5 months • For patients on medical treatment for hypercortisolism due to Cushing's syndrome, the washout periods were completed prior to baseline efficacy assessments • Patients (both genders) aged 18–85 years **Exclusion criteria:** • Patients with Cushing's Disease • History of hypersensitivity to osilodrostat or to drugs of similar chemical classes • History of malignancy of any organ system (with the exception of: a) malignancy causing ectopic corticotropin syndrome, or b) localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases • Patients receiving treatment for malignancy (e.g., cytotoxic chemotherapy, molecular targeting drugs, somatostatin analogue) within 4 weeks or ≤ 5 x

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk
www.medicinraadet.dk

Main study and patient characteristics (Tanaka 2020)	
	half-life of the agent (whichever was longer) before first dose of osilodrostat • Patients with risk factors for QTc prolongation or Torsades de Pointes
Intervention	Osilodrostat; 2 mg BID starting dose, with titration up to a maximum of 30 mg bid **Study period I**: The titration schedule was 2 mg bid, 5 mg bid, 10 mg bid, 20 mg bid, and 30 mg bid. The maximum dose was 30 mg BID. • **Study period II**: The stable therapeutic dose of osilodrostat achieved in Study Period I • **Optional Extension Period**
Baseline characteristics	See table below
Primary and secondary endpoints	**Primary endpoint:** • The percentage change from baseline in the mUFC at the individual patient level at Week-12 **Secondary endpoints:** • The percentage change from baseline in the mUFC at the individual patient level at Week-24 and Week-48 • The absolute and percentage change from baseline in mUFC at Week-12, Week-24 and Week-48 • The complete, partial. and overall response rate at Week-12, Week-24 and Week-48 • The absolute and percentage change from baseline in morning serum cortisol at the individual patient level at Week-12, Week-24 and Week-48 • The absolute and percentage change from baseline in steroid hormones at the individual patient level at Week-12, Week-24 and Week-48 • The change from baseline in cardiovascular-related metabolic parameters associated with Cushing's Syndrome at Week-12, Week-24 and Week-48 • The general safety of osilodrostat • The change from baseline in Patient-Reported Outcomes (HRQoL) at individual patient level at Week-12, Week-24 and Week-48 using the CushingQoL and Beck Depression Inventory-II instruments • Osilodrosat PK in patients with Cushing's Syndrome

Patient demographics	**All patients (N=9)**
Median (range) age, years	46.0 (20–75)
≥65 years, n (%)	3 (33.3)
Female, n (%)	7 (77.8)
Weight, median (range), kg	59.30 (47.0–106.5)
Height, median (range), cm	156.00 (145.0–170.0)
BMI, median (range), kg/m^2	23.876 (19.31–38.19)
Type of disease, n (%)	
AIMAH	1 (11.1)
Adrenal adenoma	5 (55.6)
Ectopic corticotropin syndrome	3 (33.3)
Previous treatment, n (%)*	
Surgery	1 (11.1)
Medication†	5 (55.6)
Radiotherapy	0 (0.0)
Median mUFC	841.80

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk
www.medicinraadet.dk

Main study and patient characteristics (Tanaka 2020)	
Method of analysis	The analysis sets were as follows: • Full Analysis Set (FAS): Comprises all enrolled patients who received at least one dose of osilodrostat • Safety Analysis Set (SAS): Comprises all patients who received at least one dose of osilodrostat and had at least one valid post-baseline safety assessment • Pharmacokinetic Analysis Set (PAS): Comprises all patients who received at least one dose of osilodrostat and had at least one evaluable PK concentration at any visit (post-first-dose) *Due to the limited sample size and patients enrolled with various disease types, no statistical hypothesis was set up for this study. Given the small sample size, data were primarily described on an individual basis or by disease type (ectopic corticotropin syndrome, adrenal adenoma, adrenal carcinoma, AIMAH, and PPNAD)*
Subgroup analyses	NA

Abbreviations: ACTH, adrenocorticotropic hormone; BID, twice daily; CD, Cushing's disease; CS, Cushing's syndrome; HRQoL, health-related quality of life; LLN=lower limit of normal; ULN, upper limit of normal; UFC=urinary free cortisol

8.4.6 Castinetti et al 2014 study characteristics

Table 73 Study characteristics (Castinetti 2014) (8)

Main study and patient characteristics (Castinetti 2014)	
Trial name	Castinetti 2014
NCT number	NA
Objective	To evaluate efficacy and tolerance, particularly hepatic tolerance, to clarify whether this drug should still be considered in therapeutic algorithms of hypercortisolism.
Publications – title, author, journal. year	**Ketoconazole in Cushing's disease: is it worth a try?** Castinetti F, Guignat L, Giraud P, Muller M, Kamenicky P, Drui D, Caron P, Luca F, Donadille B, Vantyghem MC, Bihan H, Delemer B, Raverot G, Motte E, Philippon M, Morange I, Conte-Devolx B, Quinquis L, Martinie M, Vezzosi D, Le Bras M, Baudry C, Christin-Maitre S, Goichot B, Chanson P, Young J, Chabre O, Tabarin A, Bertherat J, Brue T. J Clin Endocrinol Metab. 2014
Study type and design	Retrospective, multicenter (France), cohort study (year 1995-2012) reviewing data from patients treated by ketoconazole as a single agent for Cushing's Disease The studied population was divided in three groups: • Pre-surgical • Primary treatment (treatment naïve) • Second-line treatment (treatment after either a non successful operation or radiotherapy)
Follow-up time	Up to 135 months
Population (inclusion and exclusion criteria)	**Inclusion:** • Treatment of ketoconazole as only treatment for active Cushing's disease • Diagnosis of Cushing based on current guidelines **Exclusion**:

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk
www.medicinraadet.dk

Main study and patient characteristics (Castinetti 2014)

- Not applicable due to retrospective study design

Intervention

Ketoconazole; 200mg p.o., 2-3 times daily

Starting dose 400-600mg/day, max dose 1200mg/day

- Ketoconazole dose was increased by 200 mg/day every 7 to 28 days until normalization was achieved.

Baseline characteristics

N=200

Patient demographics	All patients (N=200)
Median ± SD (range) age, years	41.9 ±15.8 (8 – 87)
Male, n (%)	44 (22)
Female, n (%)	156 (78)
Type of disease, n (%)	
Microadenoma	156 (78)
Macroadenoma	106 (53.4)
Lack of obvious adenoma	36 (18.2)
Previous treatment, n (%)	
Transsphenoidal surgery, n (%)	144 (72)
Radiotherapy, n (%)	47 (23.6)
Second surgery, n (%)	16 (8)
Mean baseline UFC ± SD, nmol/24 hours (range)	4.1±5.3 x ULN (1.1-40

Primary and secondary endpoints

- UFC level at the final assessment
- Controlled, partial and non-responder rate at the final assessment
- Assessment of clinical signs of hypercortisolism including blood pressure, plasma potassium and glucose tolerance at the final assessment
- Assessment of liver status including aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), and gamma-glutamyl transpeptidase
- Adverse events
- Discontinuation rate at final assessment including reason discontinuation

Patients were considered:

- *Controlled if they had normal 24-hour UFC at 2 consecutive evaluations.*
- *Partial control was defined as a decrease in UFC of more than 50% without normalization.*
- *Not controlled was defined by a decrease in UFC of less than 50% and/or immediate clinical or biological intolerance leading to ketoconazole discontinuation.*

Improvement in hypertension was defined as a decrease of at least 10 mm Hg of systolic and/or diastolic blood pressure in patients with hypertension.

Improved glycemic control was defined as 1 or more of the following: a decrease of insulin dose (>10% of the total dose), a decrease in the number of antidiabetic drugs, and an improvement of hemoglobin A1c (>0.5% when available) without addition of other antidiabetic drugs

Final assessment could vary from patient to patient.

For each patient final UFC, final dose, length of ketoconazole treatment, length of follow-up period, and reason for withdrawal were recorded.

Method of analysis

NR

Subgroup analyses

NA

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk
www.medicinraadet.dk

Abbreviations: ACTH, adrenocorticotropic hormone; BID, twice daily; CD, Cushing's disease; CS, Cushing's syndrome; HRQoL, health-related quality of life; LLN=lower limit of normal; ULN, upper limit of normal; UFC=urinary free cortisol

In additon to the available studies for ketoconazole, is should be noted that the EMA reported in the special warnings of the smpc the need for monitoring of liver function in all patients receiving ketoxonazole. Close follow-up of patients is required due to the risk of serious hepatic toxicity. (16)

8.4.7 Castinetti et al 2008 study characteristics

Table 74 Study characteristics (Castinetti 2008) (9)

Main study and patient characteristics (Castinetti 2008)	
Trial name	Castinetti 2008
NCT number	NA
Objective	To analyze the long-term hormonal effects and tolerance of ketoconazole in patients with Cushing's disease
Publications – title, author, journal. year	**Ketoconazole revisited: a preoperative or postoperative treatment in Cushing's disease.** Castinetti F, Morange I, Jaquet P, Conte-Devolx B, Brue T. Eur J Endocrinol. 2008
Study type and design	Retrospective, single centre (France), cohort study (year 1995-2005) reviewing data from patients treated by ketoconazole as a single agent for Cushing's Disease The studied population was divided in two groups: • No pituitary surgery group - those who were not treated surgically before ketoconazole • After pituitary surgery group – those who had ketoconazole as an adjunctive treatment
Follow-up time	Between 6 to 72 months (mean of 23 months)
Population (inclusion and exclusion criteria)	**Inclusion:** • Treatment of ketoconazole as only treatment for active Cushing's disease **Exclusion:** • Not applicable due to retrospective study design
Intervention	Ketoconazole Starting dose was 200–400 mg/day, max dose1200 mg/day The dose of ketoconazole was increased by 200 mg per day every 10–15 days until biochemical remission
Baseline characteristics	N= 38

Patient demographics	No pituitary surgery group (N=16)	After pituitary surg (N=)
Median (range) age, years	44 (24-73)	42 (18-66)
Male, n	2	3
Female, n	14	14
Previous treatment, n (%)		
Transsphenoidal surgery, n		

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk
www.medicinraadet.dk

Main study and patient characteristics (Castinetti 2008)			
	Unsuccessful pituitary surgery			15
	Mean baseline UFC, nmol/24 hours (range)	1792 (275-16700)	2124 (248-12500)	
	**The 5 patients with immediate cessation of treatment because of intolerance have been excluded*			
Primary and secondary endpoints	• UFC level • Controlled and non controlled rate • Assessment of clinical signs of hypercortisolism, weight, blood pressure • Assessment of blood glucose • Assessment of liver status including aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), and gamma-glutamyl transpeptidase *Note:* *Patients were considered controlled if they had normal 24-hour UFC at 2 consecutive evaluations.* *Final assessment could vary from patient to patient.* *For each patient final UFC, final dose, length of ketoconazole treatment, length of the follow-up period were recorded.*			
Method of analysis	NR			
Subgroup analyses	NA			

8.4.8 Daniel et al 2015 study characteristics

Table 75 Study characteristics Daniel et al 2015 (10)

Main study and patient characteristics (Daniel et al 2015)	
Trial name	Daniel et al. 2015
NCT number	NA
Objective	To assess the effectiveness of metyrapone therapy in a contemporary series of patients with CS, by performing a retrospective study of patients treated in the United Kingdom.
Publications – title, author, journal. year	**Effectiveness of Metyrapone in Treating Cushing's Syndrome: A Retrospective Multicenter Study in 195 Patients.** Daniel E, Aylwin S, Mustafa O, Ball S, Munir A, Boelaert K, Chortis V, Cuthbertson DJ, Daousi C, Rajeev SP, Davis J, Cheer K, Drake W, Gunganah K, Grossman A, Gurnell M, Powlson AS, Karavitaki N, Huguet I, Kearney T, Mohit K, Meeran K, Hill N, Rees A, Lansdown AJ, Trainer PJ, Minder AE, Newell-Price J. J Clin Endocrinol Metab. 2015
Study type and design	Multicenter, retrospective study was performed across 13 University hospital centers in England and Wales, members of the United Kingdom Endocrine Neoplasia Collaboration. Patients treated with metyrapone were identified through pharmacy records and electronic databases. Patients with a diagnosis of CS and treated with metyrapone between 1997 and 2013 were included.
Follow-up time	NA
Population (inclusion and exclusion criteria)	Patients with a diagnosis of Cushing's Syndrome

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk
www.medicinraadet.dk

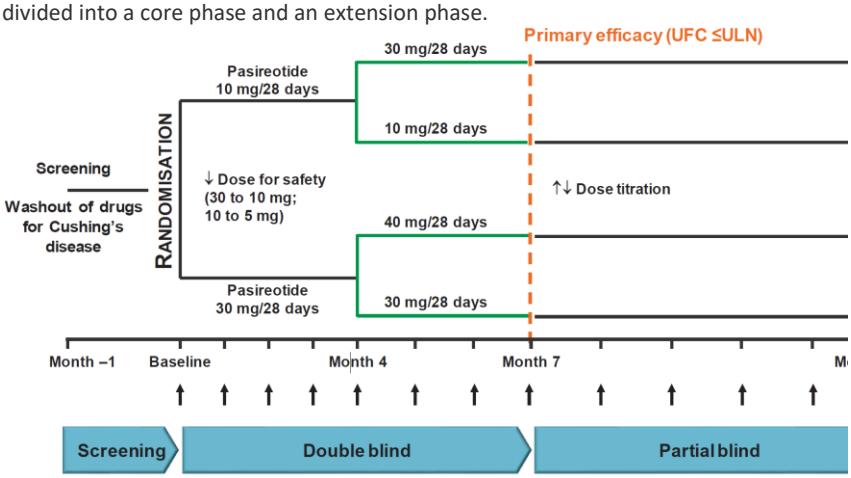
Main study and patient characteristics (Daniel et al 2015)	
Intervention	Metyrapone, Patients were treated either with a dose titration regimen, i.e. metyrapone dose was up-titrated according to response to achieve a biochemical target for cortisol, or a block-and-replace regimen, where the dose of metyrapone was quickly up-titrated to achieve blockade of cortisol synthesis and a replacement dose of glucocorticoid was added to provide background physiological levels. Table 3 of the Daniels et al article shos the different otal daily dosage of metyrapone for patients treated with a dose titration regimen.
Baseline characteristics	A total of 195 patients were treated with metyrapone across the 13 centers. Most patients had CD (115 patients, of which 37 with macroadenoma) with the remainder having ectopic ACTH syndrome (EAS) (37), adrenocortical carcinoma (ACC) (10), and benign adrenal disease (30 adrenal adenoma [AA], ACTH-independent macronodular adrenal hyperplasia [2] and primary pigmented nodular adrenal hyperplasia [1]) There was a female predominance in all causes of CS except EAS (female patients:74% CD, 49% EAS, 86% AA, and 80% ACC). At initiation of treatment, there was a wide age distribution, with 76% of patients aged 30–69 years (age range 1–81, median age 48, average age 49.6 ± 15.7 y), and 32% of patients (n = 63) were women in the reproductive ages 18–45. (N=195) Comorbidities at presentation included hypertension (64.6%) and diabetes mellitus (35.3%) (N=195)
Primary and secondary endpoints	Biochemical targets for treatment (eucortisolemia) were defined as a mean CDC value of 150–300 nmol/L (10.9 µg/dL), which has been shown to equate to a normal cortisol production rate as assessed by stable isotopic methodology (11), a UFC level below the upper limit of normal (ULN) for the assay used or a 9 AM serum cortisol within target. Although 9 AM serum cortisol is occasionally being used as a sole test for evaluating patients' response to treatment, there is currently no standardized agreement for what values of this test represent appropriate control. Two different levels of target 9 AM cortisol weretherefore assessed: 1) below the ULN for the assay used, or less than 600 nmol/L (21.7 µg/dL) if the ULN was higher than this value; and 2) a recommended value of 331 nmol (12.0 µg/dL) (12). Cortisol levels were reported in nmol/L and divided by 27.59 to calculate the equivalent value in µg/dL. There was a wide range of UFC assays used with variable reference range of normal values; therefore, UFC values were converted to multiples of the ULN for the assay and this value was used for statistical comparisons
Method of analysis	NR
Subgroup analyses	NA

8.4.9 G2304 study characteristics

Table 76 Study characteristics: G2304 trial (11, 17)

Main study characteristics (G2304 trial)	
Trial name	G2304
NCT number	NCT01374906

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk
www.medicinraadet.dk

Main study characteristics (G2304 trial)	
Objective	To describe results of the first Phase 3 trial of long-acting pasireotide in patients with Cushing's disease.
Publications – title, author, journal. year	**Efficacy and safety of once-monthly pasireotide in Cushing's disease: a 12 month clinical trial.** Lacroix A, Gu F, Gallardo W, Pivonello R, Yu Y, Witek P, Boscaro M, Salvatori R, Yamada M, Tauchmanova L, Roughton M, Ravichandran S, Petersenn S, Biller BMK, Newell-Price J; Pasireotide G2304 Study Group. Lancet Diabetes Endocrinol. 2018 **Long-term efficacy and safety of once-monthly pasireotide in Cushing's disease: A Phase III extension study.** Fleseriu M, Petersenn S, Biller BMK, Kadioglu P, De Block C, T'Sjoen G, Vantyghem MC, Tauchmanova L, Wojna J, Roughton M, Lacroix A, Newell-Price J. Clin Endocrinol (Oxf). 2019
Study type and design	Study G2304 is a global, multi-center, randomized, double-blind, Phase 3 study evaluating the efficacy and safety of pasireotide LAR in patients with CD. The study is divided into a core phase and an extension phase.  In the core phase, patients first underwent a 30-day screening period, after which there was randomization 1:1 into a starting dose of either 10 mg or 30 mg pasireotide LAR once every 28 days for 4 months. Doses could be titrated at Months 4, 7, and 9 depending on the patient's mUFC levels. The total duration of treatment in the core phase was 12 months. Patients who completed the core phase, showed acceptable tolerability to treatment, achieved/maintained ≤1.0 x ULN at Month 12, or were deemed to have received clinical benefit by the investigator, and met additional extension phase inclusion criteria were able to continue treatment in the extension phase based on ending treatment dosage.
Follow-up time	Core study: Up to 12 months Extension study: Up to 36 months
Population (inclusion and exclusion criteria)	**Inclusion criteria:** A confirmed pituitary source of Cushing's disease was defined as: • Magnetic resonance imaging (MRI) confirmation of a pituitary adenoma >6 mm with positive dynamic test (eg, corticotrophin-releasing hormone [CRH] or high-dose dexamethasone test); or • Inferior petrosal sinus sampling gradient ≥3 after CRH/desmopressin stimulation or ≥2 at baseline for patients with a pituitary adenoma ≤6 mm; or

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk
www.medicinraadet.dk

Main study characteristics (G2304 trial)	
	• Histopathology confirming an adrenocorticotropic hormone (ACTH)-staining adenoma (in patients who had prior pituitary surgery) **Exclusion criteria:** Patients who were candidates for surgery; pituitary irradiation within 10 years, previous pasireotide therapy, or mitotane therapy within 6 months; compression of the optic chiasm causing any visual field defect requiring surgical intervention; poorly controlled diabetes on antidiabetic medication (defined as glycated haemoglobin [HbA1c] >8%); symptomatic cholelithiasis at study entry; liver disease such as cirrhosis, chronic active hepatitis, or chronic persistent hepatitis, or patients with alanine aminotransferase and/or aspartate aminotransferase >2x the upper limit of normal (ULN) or serum bilirubin >1·5xULN; risk factors for torsades de pointes, congestive heart failure, unstable angina, 4 sustained ventricular tachycardia, ventricular fibrillation, advanced heart block, or a history of acute myocardial infarction within 1 year of study entry.
Intervention	Pasireotide, suspension for intramuscular injection, once every 28 days Starting dose 10 or 30 mg Max dose 40 mg Four dose levels available
Baseline characteristics	

Factor	10 mg group N=74	30 mg group N=76	All Patients N=150
Mean age, (SD) years	38,3 (12,5)	38,6 (13,0)	38,5 (12,7)
Female sex – n (%)	58 (78)	60 (79)	118 (79)
Pituitary adenoma – n (%)			
Microadenoma	34 (46)	34 (45)	68 (45)
Macroadenoma	20 (27)	29 (38)	49 (33)
Mean time since diagnosis (range), months	22,3 (9,5–53,7)	22,4 (5,0–64,3)	22,3 (6,6–62,5)
Mean baseline UFC, nmol/24 hours	2,8 (1,5)	2,9 (2,0)	2,8 (1,8)
Previous treatment – n (%)			
Surgery	59 (80)	64 (84)	123 (82)
Medical therapy	32 (43)	30 (39)	62 (41)
Cushing's disease status - n (%)			
Persistent or recurrent	59 (80)	64 (84)	123 (82)
De novo*	15 (20)	12 (16)	27 (18)

**27 (18%) patients did not have pituitary surgery before study entry for the following reasons: 15 (10%) refused surgery, 11 (7%) were poor candidates for surgery, and one (1%) could not access a surgical facility*

Primary and secondary endpoints	Primary objective – percentage of patients that attained a mUFC concentration of less than or equal to the ULN at month 7, regardless of dose titration. Key secondary objective – percentage of patients that attained a mUFC concentration of less than or equal to the ULN at month 7 and without dose uptitration at month 4
Method of analysis	Efficacy analyses using the intention-to-treat principle (based on randomised dose).
Subgroup analyses	NA

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk
www.medicinraadet.dk

8.4.10 B2305 study characteristics

Table 77 Study characteristics: B2305 trial (12, 18-20)

Main study characteristics (B2305 trial)	
Trial name	B2305 trial
NCT number	NCT00434148
Objective	To evaluate the safety and efficacy of two different doses of Pasireotide in patients with de novo or recurrent/persistent Cushing's Disease.
Publications – title, author, journal. year	**A 12-month phase 3 study of pasireotide in Cushing's disease.** Colao A, Petersenn S, Newell-Price J, et al.; A 12-month phase 3 study of pasireotide in Cushing's disease. N Engl J Med 2012 **Long-term treatment of Cushing's disease with pasireotide: 5-year results from an open-label extension study of a Phase III trial.** Petersenn S, Salgado LR, Schopohl J, Portocarrero-Ortiz L, Arnaldi G, Lacroix A, Scaroni C, Ravichandran S, Kandra A, Biller BMK. Endocrine. 2017 **Pasireotide can induce sustained decreases in urinary cortisol and provide clinical benefit in patients with Cushing's disease: results from an open-ended, open-label extension trial.** Schopohl J, Gu F, Rubens R, Van Gaal L, Bertherat J, Ligueros-Saylan M, Trovato A, Hughes G, Salgado LR, Boscaro M, Pivonello R. Pituitary. 2015 **Treatment effectiveness of pasireotide on health-related quality of life in patients with Cushing's disease.** Webb SM, Ware JE, Forsythe A, Yang M, Badia X, Nelson LM, Signorovitch JE, McLeod L, Maldonado M, Zgliczynski W, de Block C, Portocarrero-Ortiz L, Gadelha M. Eur J Endocrinol. 2014
Study type and design	Multicenter, randomized, double-blind
Follow-up time	Core study: Up to 12 months Extension study: Up to 76.6 months
Population (inclusion and exclusion criteria)	**Inclusion criteria:** Patients (aged ≥18 years) with a confirmed diagnosis of persistent/recurrent or de novo (if not surgical candidates) Cushing's disease, defined as: mean 24-hour urinary free cortisol (UFC), calculated from four 24-hour urine samples collected within 2 weeks, ≥1.5x the upper limit of normal (ULN) and morning plasma adrenocorticotropic hormone (ACTH) ≥5ng/L (≥1.1nmol/L). A pituitary source of the Cushing's syndrome was confirmed by at least one of the following: pituitary macroadenoma on magnetic resonance imaging (MRI), bilateral inferior petrosal sinus sampling central-to-peripheral ACTH gradient >2 basally, or >3 after corticotropin releasing hormone stimulation in patients with a microadenoma, or histopathology confirming an ACTH staining adenoma. For patients on medical treatment for Cushing's disease, the following washout periods must have been completed before baseline efficacy assessments were performed: • Inhibitors of steroidogenesis (ketoconazole, metyrapone): 1 week • Dopamine agonists (bromocriptine, cabergoline): 4 weeks • Rosiglitazone: 1 week • Octreotide LAR and Lanreotide Autogel: 8 weeks

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk
www.medicinraadet.dk

Main study characteristics (B2305 trial)	
	• Lanreotide SR: 4 weeks • Octreotide (immediate release formulation): 1 week **Exclusion criteria:** Pituitary irradiation within the last 10 years; mitotane within the last 6 months; optic chiasm compression causing any visual-field defect; Cushing's syndrome due to non-pituitary sources or an inherited syndrome; glucocorticoid-remediable aldosteronism; uncontrolled hypothyroidism; symptomatic cholelithiasis; HbA1C >8%; abnormal coagulation; significantly impaired cardiovascular function; QTc >480ms; liver disease; Karnofsky performance status <60; an immunocompromised state.
Intervention	Pasireotide, subcutaneous injection, twice daily Starting dose 600 µg (82 patients) or 900 µg (80 patients) per injection Max dose 1200 µg per injection

Baseline characteristics

Factor	600 µg group N=82	900 µg group N=80	All Patients N=162
Mean age, years	41	40	40
Female sex – n (%)	62 (76)	64 (80)	126 (78)
Race, n (%)			
Caucasian	65 (79)	62 (78)	127 (78)
Asian	10 (12)	10 (12)	20 (12)
Mean time since diagnosis (range), months	53.4 (0.1–341.8)	54.7 (0.1–372.1)	54.0 (0.1–372.1)
Previous medication treatment, n (%)	36 (44)	42 (52)	78 (48)
Previous surgery, n (%)	64 (78)	64 (80)	128 (79)
Previous pituitary irradiation, n (%)	3 (4)	4 (5)	7 (4)
Mean baseline UFC ± range, nmol/24 hours	1156 (220-22,944)	782 (195-6123)	970 (195-22,944)
Severity of hypercortisolism - n (%)			
Mild	12 (15)	14 (18)	26 (16)
Moderate	26 (32)	40 (50)	66 (41)
Severe	28 (34)	13 (16)	41 (25)
Very severe	11 (13)	9 (11)	20 (12)

Primary and secondary endpoints

Primary endpoint: number of UFC ≤ ULN responders at month 6 without a prior dose increase

Secondary endpoints:

- a urinary free cortisol level at or below the upper limit of the normal range at months 3, 6, and 12, regardless of dose adjustment;
- partial control of hypercortisolism (a urinary free cortisol level above the upper limit of the normal range but reduced by ≥50% from baseline);
- levels of plasma corticotropin, urinary free cortisol, and serum and salivary cortisol over time;
- changes in clinical signs and symptoms;
- quality of life;
- safety.

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk
www.medicinraadet.dk

Main study characteristics (B2305 trial)	
Method of analysis	Intention-to-treat population at all time points for efficacy and safety analysis.
Subgroup analyses	*NA*

8.4.11 SEASCAPE study characteristics

Table 78 Study characteristics SEASCAPE (13)

Main study characteristics (SEASCAPE)	
Trial name	SEASCAPE
NCT number	NCT01582061
Objective	To describe safety and efficacy results of an international. real-world study of pasireotide subcutaneous in a large population of patients with Cushing's disease in clinical practice.
Publications – title, author, journal. year	**Safety and efficacy of subcutaneous pasireotide in patients with Cushing's disease: results from an open-label, multicenter, single-arm, multinational. expanded-access study** Fleseriu M, Iweha C, Salgado L, Mazzuco TL, Campigotto F, Maamari R, Limumpornpetch P. *Frontiers in endocrinology,* 10, p. 436. 2019
Study type and design	An Open-label, Multi-center international. Expanded Access Study of Pasireotide s.c. in Patients With Cushing's Disease Non-RCT single arm
Follow-up time	Patients received treatment until pasireotide s.c. was approved for commercial use and reimbursed in each respective country or until December 31, 2015 (December 31, 2016 for sites in South Korea and Brazil), whichever occurred first.
Population (inclusion and exclusion criteria)	**Inclusion**: Adult patients (>18 years old) with persistent or recurrent Cushing's disease, or de novo patients not considered candidates for surgery, were recruited. Patients must have had active disease, as evidenced by: mean of three 24 h UFC samples collected during a 3-week screening period above the upper limit of normal (ULN; 137.95 nmol/24 h), which was determined from a central laboratory reference; morning plasma ACTH within or above the normal range; and confirmed pituitary source of the disease. For patients on previous medical treatment for Cushing's disease, the following washout periods were required prior to screening assessments: mitotane, 6 months; long-acting octreotide, lanreotide Autogel, 8 weeks; dopamine agonists (bromocriptine, cabergoline), mifepristone, lanreotide sustained release, 4 weeks; steroidogenesis inhibitors (ketoconazole, metyrapone, rosiglitazone), octreotide immediate release, 1 week **Exclusion**: Patients were excluded from the study if they had any of the following criteria: prior exposure to pasireotide sc; radiotherapy <4 weeks before screening; tumor compressing the optic chiasm, causing visual field defects; symptomatic cholelithiasis; diabetes with poorly controlled blood glucose levels (glycated hemoglobin [HbA1c] >8%); QTcF >450ms at screening and any other clinically significant impairment of cardiovascular function; pregnancy.

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk
www.medicinraadet.dk

Main study characteristics (SEASCAPE)

Intervention

After a 21-day screening period, enrolled patients in EU countries received pasireotide sc starting doses of 900 µg bid; the study protocol was amended in 2013 (patient enrollment began in 2011) so that all EU patients received starting doses of 600 µg bid to align with the recommendation by the Committee for Medicinal Products for Human Use and the European Medicines Agency that the starting dose of pasireotide sc should be 600 µg bid (21). Patients in non-EU countries received starting doses of 900 µg bid (600 µg bid in patients with impaired glucose metabolism). The dose could be increased (after >2 months' treatment if UFC was not controlled) or decreased (for sustained UFC normalization/tolerability issues) in 300 µg increments or decrements to a maximum of 900 µg bid or a minimum of 300µg bid.

Baseline characteristics

	Pasireotide 600 µg bid *N* = 49	Pasireotide 900 µg bid *N* = 55	
Mean age, years (SD)	45.5 (13.1)	39.9 (12.6)	
Female, *n* (%)	37 (75.5)	47 (85.5)	
Race, *n* (%)			
Caucasian	39 (79.6)	36 (65.5)	
Black or African American	3 (6.1)	2 (3.6)	
Asian	6 (12.2)	15 (27.3)	
Other	1 (2.0)	2 (3.6)	
Median time from diagnosis to first pasireotide dose, months(range)	60.3 (0.7–309.0)	34.3 (1.0–298.0)	
Cushing's disease status, *n* (%)			
De novo	8 (16.3)	5 (9.1)	
Persistent/recurrent	41 (83.7)	50 (90.9)	
Previous pituitary surgery, *n* (%)			
Yes	38 (77.6)	46 (83.6)	
No	3 (6.1)	4 (7.3)	
Missing	8 (16.3)	5 (9.1)	
Median time from previous surgery to first pasireotide dose,months (range)	44.8 (4.1–306.1)	30.5 (1.9–294.1)	
Prior pituitary irradiation, *n* (%)			
Yes	12 (24.5)	15 (27.3)	
No	37 (75.5)	40 (72.7)	
Median time from last pituitary irradiation to first pasireotide dose, months (range)	56.9 (8.5–169.9)	29.0 (3.1–205.8)	

Primary and secondary endpoints

The primary objective of the study was to document the safety of pasireotide s.c.; the primary endpoint was the proportion of patients with drug-related grade 3/4 AEs or drug-related SAEs.

Key secondary endpoints, which were assessed at weeks 12, 24, and 48, included: proportion of patients with mUFC≤ULN; proportion of patients achieving at least 50% reduction from baseline in mUFC; changes from baseline in clinical signs and symptoms; and changes from baseline in health-related QoL (HRQoL).

Method of analysis

The analysis populations were defined as follows: Safety assessments were performed on all patients who received at least one dose of pasireotide s.c. and had at least one post-baseline safety assessment and are summarized descriptively.

Secondary efficacy assessments were performed on all patients who received at least one dose of pasireotide s.c. and are summarized descriptively with corresponding two-sided 95% exact confidence intervals (CIs) for weeks 12, 24, and 48.

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk
www.medicinraadet.dk

Main study characteristics (SEASCAPE)	
Subgroup analyses	Diabetic vs non-diabetic patients Shift in fasting plasma glucose, fasting plasma glucose and HbA1c levels from baseline to last post-baseline value according to diabetic status.

8.4.12 B2208 study characteristics

Table 79 Study characteristics B2208 study (14)

Main study characteristics (B2208)	
Trial name	CSOM230B2208
NCT number	NCT00088608
Objective	The objective of this study was to evaluate the efficacy and safety of extended treatment with pasireotide.
Publications – title, author, journal. year	**Extended treatment of Cushing's disease with pasireotide: results from a 2-year, Phase II study.** Boscaro M, Bertherat J, Findling J, Fleseriu M, Atkinson AB, Petersenn S, Schopohl J, Snyder P, Hughes G, Trovato A, Hu K, Maldonado M, Biller BM. *Pituitary.* 2014
Study type and design	Open-ended, single-arm extension study and a planned extension to the 15-day core study
Follow-up time	Core study: 15 days Extension study: 6 months
Population (inclusion and exclusion criteria)	**Inclusion:** <u>Core study:</u> • Eligible patients were at least 18 yr of age and had clinically and biochemically confirmed ACTH-dependent Cushing's disease within 2 months of study entry. Patients were required to have a Karnofsky performance status of at least 60 and either have de novo Cushing's disease and be candidates for pituitary surgery or have persistent or recurrent Cushing's disease after surgery without having received any prior pituitary irradiation. <u>Extension phase:</u> • Patients with Cushing's disease (aged≥18 years) who had completed the 15-day, proof-of-concept, Phase II core study were eligible to enter this extension phase if they had normal 24-h UFC levels at the end of the core study and/or, in the opinion of the investigator, obtained significant clinical benefit with pasireotide. • Patients were included if they did not experience any unacceptable AEs or tolerability issues during the original 15-day treatment period. Female patients of childbearing potential who had not undergone clinically documented total hysterectomy and/or ovariectomy, or tubal ligation, had to agree to use barrier contraception throughout the course of the extension study and for 1 month after the study had ended.

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk
www.medicinraadet.dk

Main study characteristics (B2208)	
	Exclusion: Core study: • Key exclusion criteria included Cushing's syndrome due to ectopic ACTH secretion, hypercortisolism secondary to adrenal tumors or nodular (primary) bilateral adrenal hyperplasia, a known inherited syndrome as a cause forACTHhypersecretion (e.g. Carney complex,MEN-1), and McCune-Albright syndrome. Patients who were not euthyroid, had received octreotide LAR or any other long-acting somatostatin analogue within 8 wk of study entry, had poorly controlled diabetes mellitus (presence of ketoacidosis or a glycosylated hemoglobin level >10%), liver disease, or active gallbladder disease were also ineligible. Extension phase: • Patients could not enrol in the extension study if they experienced any of the following during the core study: development of poorly controlled diabetes mellitus (as indicated by ketoacidosis or HbA1c >10%); persistent alanine aminotransferase/aspartate aminotransferase or alkaline phosphatase levels >2.5 x ULN; serum creatinine >2.0 x ULN and/or serum bilirubin >2 x ULN; abnormal coagulation (prothrombin time and partial thromboplastin time elevated by 30% above normal limits) or white blood cell (<3.0 x 10^9/L), hemoglobin (<12.0 g/dL for females, <13.0 g/dL for males) or platelet count (<100 x 10^9/L); or any other unacceptable AEs or tolerability problems.
Intervention	Patients self-administered pasireotide 600 µg sc twice daily (bid) for 15 d at 09:00 and 21:00 h. Dose adjustments were permitted for patients unable to tolerate the protocol-specified dosage. Patients who achieved normalized UFC levels at the end of the core study continued at a dose of 600 µg sc bid. If UFC levels increased, the pasireotide dose could be increased to 900 µg sc bid. The dose of pasireotide could be reduced by 150 µg per injection at any time if the investigator believed that a drug-related AE was present. One patient had a dose decrease to 450 µg sc bid and subsequent increase back to 600 µg. Seven patients had a dose increase to pasireotide 900 µg sc bid at some point before month 6.
Baseline characteristics	Of 38 patients who completed 15 days' pasireotide therapy, 19 entered this extension phase, 17 women and two men, all Caucasian, mean age 43 years (range 22–73, standard deviation [SD]: 11.6).
Primary and secondary endpoints	**Outcomes for core study:** • Primary outcome: Normalization of mean UFC levels after 15 day treatment* • Changes in plasma ACTH and serum cortisol • Safety assessments **Outcomes of the extended study:** • Primary outcome: The proportion of patients with normalized UFC levels after 6 months of treatment (normal UFC range: 55–276 nmol/24 h;20–100 µg/24 h).

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk
www.medicinraadet.dk

Main study characteristics (B2208)	
	• Mean percentage change from core baseline in body weight, systolic BP and diastolic BP. Improvement in HB1AC and fasting plasma glucose, Electrocardiogram intervals • Secondary objectives included assessment of the safety and tolerability of multiple doses of pasireotide and trough plasma concentrations of pasireotide after chronic dosing.
Method of analysis	The analysis populations were defined as follows: the intention-to-treat (ITT) and safety populations consisted of patients who received at least one pasireotide dose in the extension period. The primary efficacy population consisted of those ITT patients whose mean UFC at core baseline, based on at least two UFC samples, was (ULN). No formal statistical comparisons were performed for this study because of the small sample size.
Subgroup analyses	NA

8.4.13 'Italian pasireotide real-world evidence' study characteristics

Table 80 Study characteristics: Italian pasireotide real-world evidence study (15)

Main study characteristics (Italian real-world evidence study)	
Trial name	NR
NCT number	NR
Objective	The objective of this study was to evaluate the efficacy and safety of pasireotide treatment according to the real-world evidence
Publications – title, author, journal. year	**The medical treatment with pasireotide in Cushing's disease: an Italian multicentre experience based on "real-world evidence".** Pivonello R, Arnaldi G, Scaroni C, Giordano C, Cannavò S, Iacuaniello D, Trementino L, Zilio M, Guarnotta V, Albani A, Cozzolino A, Michetti G, Boscaro M, Colao A. *Endocrine*. 2019
Study type and design	Real-world evidence-study
Follow-up time	24 weeks Converted from months (6 months) to weeks
Population (inclusion and exclusion criteria)	**Inclusion:** Confirmation of a diagnosis of CD in active phase of disease, based on the presence of average (mean of two or three determinations performed in different days along one week) UC > ULN and/or late night salivary cortisol (LNSC) > ULN and/or increase in midnight serum cortisol (> 1.8 µg/dl), together with lack of suppression (≥ 1.8 µg/dl) in serum cortisol after low-dose (overnight 1-mg and/or 2-days 2-mg dexamethasone) suppression test and a clinical picture suggestive of CD. The diagnosis of CD needed to be confirmed by one of the following evidence: histological confirmation of corticotroph pituitary tumour at a previous surgery for patients who already had surgery before starting pasireotide or the presence of a pituitary macroadenoma or large (maximal diameter > 5 mm) microadenoma, or

Main study characteristics (Italian real-world evidence study)	
	positive gradient at the inferior petrosal sinus sampling, performed anytime before starting pasireotide treatment. **Exclusion:** Pituitary or adrenal surgery performed less than three months before entering the study, pituitary radiotherapy performed less than three years for stereotactic radiotherapy and less than five years for conventional radiotherapy before entering the study, history of intolerance to somatostatin analogues, risk conditions for prolonged QT syndrome, uncontrolled DM, with glycated haemoglobin (HbA1c) > 9%, severe liver or renal insufficiency and pregnancy.
Intervention	Pasireotide Initial dose: 600 µg sc bid twice daily Patients with persistently increased UC received an up-titration of the drug dose to 900 µg bid. In case of occurrence of adrenal insufficiency, diagnosed on the basis of clinical or hormonal picture, as well as in case of drug intolerance during the first period of treatment, pasireotide was reduced to 450 or 300 µg bid. During the following period of treatment, clinical and hormonal evaluation was performed every three months and pasireotide dose was adjusted on the basis of UC levels and/or clinical picture, as well as drug intolerance, according to the physician judgement, considering 300 µg bid as the minimal dose and 900 µg bid as the maximal dose.
Baseline characteristics	

Characteristics	**Patients no. (%)**
Females	21 (80.8)
Males	5 (19.2)
Age - years	
Mean	47
Range	21-71
Time since diagnosis – years	
Mean	7.5
Range	0–17
Previous treatment	
Pituitary Surgery	21 (80.8)
Adrenalectomy	2 (7.7)
Medication	16 (61.5)
Pituitary irradiation	8 (30.8)
Urinary Cortisol - ULN	
Mean	1.55
Median	1.39
Range	0.48–2.71

Primary and secondary endpoints	• Disease responsiveness, in terms of normalization or significant decrease of UC levels after six months of treatment • Proportion of patients who normalized UC after three months of treatment, Change in plasma ACTH and morning serum cortisol after three and six months, change in clinical and metabolic parameters after three and six months, Change in tumor size after six months of treatment; • Clinical parameters included the measurement of weight, body mass index (BMI), waist circumference, blood pressure and heart rate; • Metabolic evaluation included the measurement of fasting plasma glucose (FPG), HbA1c, total cholesterol (Total-C), lowdensity lipoprotein-

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk
www.medicinraadet.dk

Main study characteristics (Italian real-world evidence study)	
	cholesterol (LDL-C) and high density lipoprotein-cholesterol (HDL-C), triglycerides (TG) and liver enzymes; • Hormonal evaluation included UC, plasma ACTH and serum cortisol levels; • Safety and tolerability.
Method of analysis	The efficacy analysis was performed considering the totality of patients entering the study and starting pasireotide treatment, and particularly the 32 patients with any degree of disease, and the 31 patients with very mild to moderate disease, which is the main focus of the current study, as well as the 28 patients with very mild to moderate disease, and increase UC at baseline, according to an "intention-to-treat" and a "per-protocol" approaches.
Subgroup analyses	NA

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk
www.medicinraadet.dk

8.5 Results per study

8.5.1 LINC-4

LINC-4 is a randomized study with an initial 12-week placebo-controlled period (study period 1). During study period 2, which was a single arm open label treatment (weeks 13-48), and the optional extension (weeks 48-96) all patients received osilodrostat. Given this study design, a comparison between the treatment arms can only be interpreted during the placebo-controlled period. Statistical comparisons of treatment arms after week 12 virtually means comparing osilodrostat with osilodrostat, and can therefore not be conducted. For study period after week 12, rates for specific end points for different treatment arms can be presented, but no comparison can be made.

Results of study LINC-4											
Trial name:	LINC-4										
NCT number:	NCT02697734										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Proportion of patients with complete response at 4 weeks	Osilodrostat Placebo		NA	NA	NA	NA	NA	NA	NA		No data was collected during the trial at week 4
	Osilodrostat	48	58.3%	0.423	[0.223;0.624]	<.0001	3.65	[1.44;9.24]	0.0064	Full analysis set	Data on file

Results of study LINC-4										
Proportion of patients with complete response at 5 weeks	Placebo	25	16.0%						2-sided 95% Confidence Intervals (CIs) for proportions are based on the exact (Clopper-Pearson) method The effect measure for the comparison of the two groups is assessed by means of the ARR (absolute risk reduction) and the RR (relative risk) and the 2-sided 95% Confidence Intervals are based on the asymptotic continuity correct (Wald) method	
Proportion of patients with complete response at 12 weeks	Osilodrostat	48	77.1% (62.7-88.0)	0.691	[0.531;0.850]	<.0001	9.64	[2.53; 36.73]	0.0010	Full analysis set 2-sided 95% Confidence Intervals (CIs) for proportions are based on the exact (Clopper-Pearson) method The effect measure for the comparison of the two groups is assessed by means of the ARR (absolute risk reduction) and the RR (relative risk) and the 2-sided 95% Confidence Intervals are based on the asymptotic continuity correct (Wald) method	Gadelha 2022
	Placebo	25	8.0% (1.0-26.0)								

Results of study LINC-4										
Proportion of patients with complete response at the longest follow up (72 weeks)	Osilodrostat Placebo	48 25	61.0% (44.5, 75.8) 62.5% (40.6, 81.2)	XX	XX	XX	XX	XX	XX	Full analysis set 2-sided 95% Confidence Intervals (CIs) for proportions are based on the exact (Clopper-Pearson) method Note that placebo patients were on osilodrostat since week 12 so no interpretable comparison between arms is possible for this timepoint	Data on file
HRQoL Cushings (Actual change from baseline at Week 48)	Osilodrostat Placebo	48 25	11.7 (6.6-16.7) 12.8 (6.5-19.1)	XX	XX	XX	XX	XX	XX	Full analysis set Note that placebo patients at week 48 have also been treated with osilodrostat since week 12 so no interpretable comparison between arms is possible.	Gadelha 2022
Proportion of patients who experience treatment-requiring side effects (during overall period including both RW and OL)	Osilodrostat Placebo	48 25	95.8% (85.7-99.5) 84.0% (63.9-95.5)	NA	NA	NA	NA	NA	NA	Percentage of patients who experience treatment-requiring side effects Safety set 2-sided 95% Confidence Intervals (CIs) for proportions are based on the exact (Clopper-Pearson) method	Data on file

8.5.2 LINC-3

Results of study LINC-3											
Trial name:	LINC-3										
NCT number:	NCT02180217										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Proportion of patients with complete response at 4 weeks	Osilodrostat Placebo		NA	NA	NA	NA	NA	NA	NA		
Proportion of patients with	Osilodrostat	36	86.1% (70.50-95.33)	-0.053	[-0.199;0.093]	0.4854	0.94	[0.80;1.11]	0.4885	FAS population	Pivonello 2020

Results of study LINC-3					
complete response at 12 weeks	Placebo	35	91.4% (76.94-98.20)		95% Cis is based on Clopper-Pearson method (exact method). Full analysis set (non-randomized patients) Note that at week 12 all patients are on osilodrostat, they are split to placebo at a later stage (see trial design). Thus, this information should be considered with caution. The effect measure for the comparison of the two groups is assessed by means of the ARR (absolute risk reduction) and the RR (relative risk) and the 2-sided 95% Confidence Intervals are based on the asymptotic continuity correct (Wald) method

Results of study LINC-3										
Proportion of patients with complete response at the longest follow up (72 weeks)	Osilodrostat Placebo	35 30	82.9% (66.35-93.44) 83.3% (65.28-94.36)	-0.005	[-0.187;0.178]	0.9630	0.99	[0.80;1.24]	0.9630	FAS population Please note that patients at week 72 are all on osilodrostat, however have been in split in study period 3 where they were either on placebo or osilodrostat. Therefore these results should be considered with caution. The effect measure for the comparison of the two groups is assessed by means of the ARR (absolute risk reduction) and the RR (relative risk) and the 2-sided 95% Confidence Intervals are based on the asymptotic continuity correct (Wald) method	Pivonello 2020
	Osilodrostat	36	16.1 (10.9-21.3)	5.9		0.1327	19.9		0.4407	Change from	Data on file

Results of study LINC-3										
HRQoL Cushings (change from baseline at Week 48)	Placebo	35	10.2 (4.2-16.1)		[-1.84 to 13.64]		[-31.33 to 71.13]		baseline in CushingQoL in the FAS population The absolute and relative difference in effect were estimated using a two-sided t-test based on a t-test calculator ("MedCalc Software Ltd. Comparison of means calculator. https://www.medcalc.org/calc/comparison_of_means.php (Version 20.027)). The software imputing the values of mean changes and mean percentage changes from baseline, std and n for each group, returns the difference between the two groups with the CI 95 and the p value	
	Osilodrostat	36	91.7%	-0.027	0.5813	0.97	[0.88;1.07]	0.5830		Data on file

Results of study LINC-3						
Proportion of patients who experience treatment-requiring side effects	Placebo	35	97.1%	[-0.120;0.066]	Percentage of patients with adverse events requiring additional treatment at data cut off in the safety analysis set The effect measure for the comparison of the two groups is assessed by means of the ARR (absolute risk reduction) and the RR (relative risk) and the 2-sided 95% Confidence Intervals are based on the asymptotic continuity correct (Wald) method	

8.5.3 LINC-2

Results of study LINC-2	
Trial name:	LINC-2
NCT number:	NCT01331239 (PART-II)

Results of study LINC-2											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Proportion of patients with complete response at 4 weeks	Osilodrostat		NA	NA	NA	NA	NA	NA	NA		
Proportion of patients with complete response at 12 weeks	Osilodrostat		NA	NA	NA	NA	NA	NA	NA		
Proportion of patients with complete response at the longest follow up (22 weeks)	Osilodrostat	19	78.9% (54.4-94.0)	NA	NA	NA	NA	NA	NA		Fleseriu et al 2016

Results of study LINC-2										
Proportion of patients with complete response at the longest follow up (84 weeks- Month 19) in the extension study	Osilodrostat	16	81.3%	NA	NA	NA	NA	NA	NA	Data on file
HRQoL Cushings (change from baseline)	Osilodrostat	NA		NA	NA	NA	NA	NA	NA	
Proportion of patients who experience treatment-requiring side effects	Osilodrostat	NA		NA	NA	NA	NA	NA	NA	

8.5.4 LINC-1

Results of study LINC-1	
Trial name:	LINC-1

Results of study LINC-1											
NCT number:	NCT01331239 (PART I)										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Proportion of patients with complete response at 4 weeks	Osilodrostat		NA	NA	NA	NA	NA	NA	NA		
Proportion of patients with complete response at 12 weeks	Osilodrostat		NA	NA	NA	NA	NA	NA	NA		
Proportion of patients with complete response at the longest follow up (see LINC-2)	Osilodrostat	NA	NA	NA	NA	NA	NA	NA	NA		

Results of study LINC-1									
HRQoL Cushings (change from baseline)	Osilodrostat	NA	NA	NA	NA	NA	NA	NA	NA	
Proportion of patients who experience treatment-requiring side effects	Osilodrostat	NA	NA	NA	NA	NA	NA	NA	NA	

8.5.5 C1201

Results of study C1201											
Trial name:	C1201										
NCT number:	NCT02468193										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		

Results of study C1201										
Proportion of patients with complete response at 4 weeks	Osilodrostat		NA	NA	NA	NA	NA	NA	NA	
Proportion of patients with complete response at 12 weeks	Osilodrostat	9	66.7 % (29.9-92.5)	NA	NA	NA	NA	NA	NA	Full analysis set Due to the limited sample size and patients enrolled with various disease type, no statistical hypotheses was set up for this study.	Tanaka 2020
Proportion of patients with complete response at the longest follow up (48 weeks)	Osilodrostat	2	50.0 % (1.3-98,7)	NA	NA	NA	NA	NA	NA	Full analysis set Due to the limited sample size and patients enrolled with various disease type, no statistical hypotheses was set up for this study.	Tanaka 2020

Results of study C1201										
HRQoL Cushings (change from baseline)	Osilodrostat	NA	NA	NA	NA	NA	NA	NA	NA		
Proportion of patients who experience treatment-requiring side effects	Osilodrostat	9	89.9%	NA	NA	NA	NA	NA	NA	Safety analysis set	Tanaka 2020

8.5.6 Castinetti et al. 2014

Table A3b Results of study Castinetti 2014	
Trial name:	Castinetti 2008 and 2014
NCT number:	NA

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Proportion of patients with complete response at 4 weeks	Ketoconazole		NA	NA	NA	NA	NA	NA	NA		
Proportion of patients with complete response at 12 weeks	Ketoconazole		NA	NA	NA	NA	NA	NA	NA		
Proportion of patients with complete response at the longest follow up (variable timing)	Ketoconazole	200	48.5%	NA	NA	NA	NA	NA	NA		

HRQoL Cushings (change from baseline at Week 48)	Ketoconazole	NA	NA	NA	NA	NA	NA	NA	
Proportion of patients who experience treatment-requiring side effects	Ketoconazole	NA	NA	NA	NA	NA	NA	NA	

8.5.7 Daniel et al. 2015

Results of study Daniel et al. 2015	
Trial name:	Daniel et al. 2015
NCT number:	NA

Results of study Daniel et al. 2015											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Proportion of patients with complete response at 4 weeks	Metyrapone		NA	NA	NA	NA	NA	NA	NA		
Proportion of patients with complete response at 12 weeks	Metyrapoone		NA	NA	NA	NA	NA	NA	NA		

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Results of study Daniel et al. 2015										
Proportion of patients with complete response at the longest follow up (variable timing)	Metyrapone	195	43%	NA	NA	NA	NA	NA	NA	Daniel et al. 2015
HRQoL Cushings (change from baseline)	Metyrapone		NA	NA	NA	NA	NA	NA	NA	
Proportion of patients who experience treatment-requiring side effects	Metyrapone		NA	NA	NA	NA	NA	NA	NA	

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

8.5.8 PROMPT

Results of study PROMPT											
Trial name:	PROMPT										
NCT number:	NCT02297945										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Proportion of patients with complete response at 4 weeks	Metyrapone		NA	NA	NA	NA	NA	NA	NA		
Proportion of patients with complete response at 12 weeks	Metyrapone		NA	NA	NA	NA	NA	NA	NA		

Results of study PROMPT									
Proportion of patients with complete response at the longest follow up (variable timing)	Metyrapone	%	NA	NA	NA	NA	NA	NA	Daniel et al. 2015
HRQoL Cushings (change from baseline)	Metyrapone	NA	NA	NA	NA	NA	NA	NA	
Proportion of patients who experience treatment-requiring side effects	Metyrapone	NA	NA	NA	NA	NA	NA	NA	

8.5.9 G2304

Results of study G2304											
Trial name:	G2304										
NCT number:	NCT01374906										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Proportion of patients with complete response at 4 weeks (one month)	Pasireotide 10 mg	74	29.7%	-0.071	[-0.221;0.079]	0.3597	0.81	[0.51;1.28]	0.3642	*Figure 4 : Error bars represent IQRs.* The effect measure for the comparison of the two groups is assessed by means of the ARR (absolute risk reduction) and the RR (relative risk) and the 2-sided 95% Confidence Intervals are based on the asymptotic continuity correct (Wald) method	Lacroix 2018
	Pasireotide 30 mg	74	37.3%								
Proportion of patients	Pasireotide 10 mg	68	27,9%	-0.085	[-0.231;0.061]	0.2543	0.75	[0.46;1.23]	0.2612	*Figure 4 : Error bars represent IQRs.*	Lacroix 2018

Results of study G2304											
with complete response at 12 weeks (month 3)	Pasireotide 30 mg	74	35,1%							The effect measure for the comparison of the two groups is assessed by means of the ARR (absolute risk reduction) and the RR (relative risk) and the 2-sided 95% Confidence Intervals are based on the asymptotic continuity correct (Wald) method	
Proportion of patients with complete response at the longest follow up (12 months)	Pasireotide 10 mg	74	35.1% (24.4-47.7)	0.101	[-0.045;0.247]	0.1744	1.41	[0.85;2.31]	0.1810	The effect measure for the comparison of the two groups is assessed by means of the ARR (absolute risk reduction) and the RR (relative risk) and the 2-sided 95% Confidence Intervals are based on the asymptotic continuity correct (Wald) method	Lacroix 2018
	Pasireotide 30 mg	76	25.0% (15.8-36.6)								
	Pasireotide 10 mg	NR	6.4 (1.3-11.6)	*-0.4*	*-6.75 to 5.95*	*0.9008*	*-2.0*		*0.8769*	The absolute and relative difference in effect were	Lacroix 2018 appendix

Results of study G2304										
Quality of Life at Month 12	Pasireotide 30 mg	NR	7.0 (3.0-10.9)					*[-27.55 to 23.55]*	estimated using a two-sided t-test based on a t-test calculator ("MedCalc Software Ltd. Comparison of means calculator. https://www.medcalc.org/calc/comparison_of_means.php (Version 20.027)). The software imputing the values of mean changes and mean percentage changes from baseline, std and n for each group, returns the difference between the two groups with the CI 95 and the p value	
Proportion of patients who experience treatment-requiring side effects	Overall patient population	150	96.7%	NA	NA	NA	NA	NA	NA	

8.5.10 B2305

Results of study B2305												
Trial name:	B2305 trial											
NCT number:	NCT00434148											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Proportion of patients with complete response at 4 weeks	Pasireotide 600 Pasireotide 900		NA	NA	NA	NA	NA	NA	NA		
Proportion of patients with complete response at 12 weeks	Pasireotide 600	NR	16% (8-24)	-0.116	[-0.242;0.009]	0.0692	0.58	[0.31;1.06]	0.0776	Given the availability on the Danish market, the 600g is used as the primary intervention The effect measure for the comparison of the two groups is assessed by means of the ARR (absolute risk reduction) and the RR (relative risk) and the 2-sided 95% Confidence Intervals are based on the asymptotic continuity correct (Wald) method	Colao 2012
	Pasireotide 900	NR	28% (18-37)								

Results of study B2305											
Proportion of patients with complete response at longest possible follow-up time (Month 24)	Pasireotide 600	26	30.8%	-0.052	[-0.154;0.049]	0.3145	0.65	[0.28;1.51]	0.3202	Given the availability on the Danish market, the 600g is used as the primary intervention The effect measure for the comparison of the two groups is assessed by means of the ARR (absolute risk reduction) and the RR (relative risk) and the 2-sided 95% Confidence Intervals are based on the asymptotic continuity correct (Wald) method	Schopohl 2015
	Pasireotide 900	32	37.5%								
Quality of Life at Month 12	Overall population (Pasireotide 600 and Pasireotide 900)	39	11.1 (6.8-15.5)	NA	NA	NA	NA	NA	NA		Colao 2012 appendix
Proportion of patients who experience treatment-	Pasireotide 600	82	86.6%	-0.059	[-0.153;0.035]	0.2177	0.94	[0.84;1.04]	0.2220	Safety analysis set The effect measure for the comparison of the two groups	Data on File

Results of study B2305											
requiring side effects	Pasireotide 900	80	92.5%							is assessed by means of the ARR (absolute risk reduction) and the RR (relative risk) and the 2-sided 95% Confidence Intervals are based on the asymptotic continuity correct (Wald) method	

8.5.11 SEASCAPE

Results of study SEASCAPE											
Trial name:	SEASCAPE										
NCT number:	NCT01582061										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Proportion of patients with complete response at 4 weeks	Pasireotide 600		NA	NA	NA	NA	NA	NA	NA		
	Pasireotide 900										

Results of study SEASCAPE										
Proportion of patients with complete response at 12 weeks	Pasireotide 600	27	77.8% (57.7-91.4)	0.393	[0.174;0.612]	0.0005	2.02	[1.30;3.16]	0.0020	Given the availability on the Danish market, the 600g is used as the primary intervention The effect measure for the comparison of the two groups is assessed by means of the ARR (absolute risk reduction) and the RR (relative risk) and the 2-sided 95% Confidence Intervals are based on the asymptotic continuity correct (Wald) method	Fleseriu et al. 2019
	Pasireotide 900	39	38.5% (23.4-55.4)								
Proportion of patients with complete response at longest possible follow-up time (week 48)	Pasireotide 600	10	70% (34.8-93.3)	0.518	[0.154;0.882]	0.0053	3.85	[1.03;14.38]	0.0446	Given the availability on the Danish market, the 600g is used as the primary intervention The effect measure for the comparison of the two groups is assessed by means of the ARR (absolute risk reduction) and the RR (relative risk) and the 2-sided 95% Confidence Intervals are based on the asymptotic continuity correct (Wald) method	Fleseriu et al. 2019
	Pasireotide 900	11	18.2% (2.3-51.8)								
Quality of Life at week 48	Pasireotide 600	49	24.0 (6.8-41.1)	-	-	-	*-18.3*	*- [54.61 to 18.01]*	*0.3126*	The elative difference in effect was estimated using a two-sided t-test based on a t-test calculator (“MedCalc Software Ltd. Comparison of means	Fleseriu et al. 2019

Results of study SEASCAPE										
	Pasireotide 900)	55	42.3 (18.8-65.8)							calculator. https://www.medcalc.org/calc/comparison_of_means.php (Version 20.027)). The software imputing the values of mean changes from baseline, std and n for each group, returns the difference between the two groups with the CI 95 and the p value
Proportion of patients who experience treatment-requiring side effects	Pasireotide 600	15	89.8%	0.043	[-0.083;0.169]	0.5095	1.05	[0.91;1.21]	0.5109	The effect measure for the comparison of the two groups is assessed by means of the ARR (absolute risk reduction) and the RR (relative risk) and the 2-sided 95% Confidence Intervals are based on the asymptotic continuity correct (Wald) method
	Pasireotide 900	20	85.5%							

8.5.12 B2208

Results of study B2208	
Trial name:	B2308 trial
NCT number:	NCT00088608

Results of study B2208											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Proportion of patients with complete response at 4 weeks	Pasireotide		NA	NA	NA	NA	NA	NA	NA		
Proportion of patients with complete response at 12 weeks	Pasireotide	NA	NA	NA	NA	NA	NA	NA	NA		
Proportion of patients with complete response at longest possible follow-up time (Month 6)	Pasireotide	18	22.2% (6.4-47.6)	NA	NA	NA	NA	NA	NA		Boscaro et al 2014
Quality of Life at	Pasireotide		NA	NA	NA	NA	NA	NA	NA		

Results of study B2208											
Proportion of patients who experience treatment-requiring side effects	Pasireotide	19	5.35%	NA	NA	NA	NA	NA	NA		Boscaro et al 2014

8.5.13 Italian pasireotide RWE study

Results of study 'Italian pasireotide RWE study'											
Trial name:	Italian pasireotide RWE study										
NCT number:	NR										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
	Pasireotide		NA	NA	NA	NA	NA	NA	NA		

Results of study 'Italian pasireotide RWE study'											
Proportion of patients with complete response at 4 weeks											
Proportion of patients with complete response at 12 weeks	Pasireotide	32	59.37%	NA	NA	NA	NA	NA	NA	ITT population	Pivonello 2019
Proportion of patients with complete response at the longest follow up (6 monts)	Pasireotide	32	62.5%	NA	NA	NA	NA	NA	NA	ITT population	Pivonello 2019
	Pasireotide	NA	NA	NA	NA	NA	NA	NA	NA		

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Results of study 'Italian pasireotide RWE study'									
HRQoL Cushings (change from baseline)									
Proportion of patients who experience treatment-requiring side effects	Pasireotide	NA	NA	NA	NA	NA	NA	NA	NA

8.6 Results per PICO (clinical question)

8.6.1 PICO question 1

Not feasible to perform meta-analysis due to the differences in trial design (retrospective cohort study and RCTs).

Results referring to question 1: What is the value of osilodrostat compared to ketoconazole in adult patients with endogenous Cushing's syndrome?								
Results per outcome:	*Attach forest plots and statistical results as a separate file.* *Results from the comparative analysis should be given in the table below, if possible.*							
		Absolute difference in effect			**Relative difference in effect**			**Methods used for quantitative synthesis**
	Studies included in the analysis	**Difference**	**CI**	***P* value**	**Difference**	**CI**	***P* value**	
Complete response at Week 4	[3-6,8]	NA	NA	NA	NA	NA	NA	NA
Complete response at Week 12	[3-6,8]	NA	NA	NA	NA	NA	NA	NA
Complete response at longest FU	[3-6,8]	NA	NA	NA	NA	NA	NA	NA

Results referring to question 1: What is the value of osilodrostat compared to ketoconazole in adult patients with endogenous Cushing's syndrome?								
HRQoL Cushings Disease	[3-6,8]	NA	NA	NA	NA	NA	NA	NA
AEs requiring treatment	[3-6,8]	NA	NA	NA	NA	NA	NA	NA

8.6.2 PICO question 2

Not feasible to perform meta-analysis due to the differences in trial design (retrospective cohort study and RCTs).

Results referring to question 2: What is the value of osilodrostat compared to metyrapone in adult patients with endogenous Cushing's syndrome?								
Results per outcome:	*Attach forest plots and statistical results as a separate file. Details presented in section 8.8.* *Results from the comparative analysis should be given in the table below, if possible.*							
		Absolute difference in effect			**Relative difference in effect**			**Methods used for quantitative synthesis**
	Studies included in the analysis	**Difference**	**CI**	***P* value**	**Difference**	**CI**	***P* value**	
Complete response at Week 4	[3-6,10, (32)]	NA	NA	NA	NA	NA	NA	NA

Results referring to question 2: What is the value of osilodrostat compared to metyrapone in adult patients with endogenous Cushing's syndrome?								
Complete response at Week 12	[3-6,10, (32)]	NA	NA	NA	1.64	(1.12-1.93)	NA	Details on the MAIC of LINC-4 and PROMPT are presented in section 8.8
Complete response at longest FU (week 36)	[3-6,10, (32)]	NA	NA	NA	1.82	(1.37-1.98)	NA	Details on the MAIC of LINC-4 and PROMPT are presented in section 8.8
HRQoL Cushings Disease	[3-6,10,(32)]	NA	NA	NA	NA	NA	NA	NA
AEs requiring treatment	[3-6,10, (32)]	NA	NA	NA	NA	NA	NA	NA

8.6.3 PICO question 3

Results referring to question 3: What is the value of osilodrostat compared to pasireotide in adult patients with endogenous Cushing's syndrome?				
Results per outcome:	*Results based on LINC3 study vs pasireotide LAR*			
		Absolute difference in effect	**Relative difference in effect**	**Methods used for quantitative synthesis**

Results referring to question 3: What is the value of osilodrostat compared to pasireotide in adult patients with endogenous Cushing's syndrome?								
	Studies included in the analysis	**Difference**	**CI**	***P* value**	**Difference**	**CI**	***P* value**	
Complete response at Week 4	[3-6,11]	0.12	-0.09-0.26	NA	1.42	0.82-2.88	NA	Propensitiy weighted analysis based on patient level data, an abstract has already been published – see futher explanation on the results in section 8.7
Complete response at Week 12	[3-6,11]	0.48	0.27-0.62	NA	2.88	1.58-6.18	NA	Propensitiy weighted analysis based on patient level data – see futher explanation on the results in section 8.7
Complete response at longest FU	[3-6,11]	0.25	0.04-0.42	NA	1.65	1.07-3.01	NA	Propensitiy weighted analysis based on patient level data – see futher explanation on the results in section 8.7
HRQoL Cushings Disease	[3-6,11]	NA	NA	NA	NA	NA	NA	NA
AEs requiring treatment	[3-5,8,10,12,14-15]	NA	NA	NA	NA	NA	NA	NA

Results referring to question 3: What is the value of osilodrostat compared to pasireotide in adult patients with endogenous Cushing's syndrome?								
Results per outcome:	*Results based on LINC4 study vs pasireotide LAR*							
		Absolute difference in effect			**Relative difference in effect**			**Methods used for quantitative synthesis**
	Studies included in the analysis	**Difference**	**CI**	***P* value**	**Difference**	**CI**	***P* value**	
Complete response at Week 4[1]	[3,11]	0.09	-0.13-0.31	NA	1.18	0.81-2.13	NA	Propensitiy weighted analysis based on patient level data – see futher explanation on the results in section 8.7
Complete response at Week 12	[3,11]	0.41	0.16-0.60	NA	2.14	1.26-4.64	NA	Propensitiy weighted analysis based on patient level data – see futher explanation on the results in section 8.7
Complete response at longest FU	[3,11]	0.10	-0.09-0.35	NA	1.16	0.89-1.91	NA	Propensitiy weighted analysis based on patient level data – see futher explanation on the results in section 8.7
HRQoL Cushings Disease	[3-11]	NA	NA	NA	NA	NA	NA	NA
AEs requiring treatment	[3-11]	NA	NA	NA	NA	NA	NA	NA

[1] week 4 data are not available in LINC-4 so the analysis uses the closest time point of week 5

Results referring to question 3: What is the value of osilodrostat compared to pasireotide in adult patients with endogenous Cushing's syndrome?								
Results per outcome:	*Results based on LINC4 study vs pasireotide SC*							
		Absolute difference in effect			**Relative difference in effect**			**Methods used for quantitative synthesis**
	Studies included in the analysis	**Difference**	**CI**	***P* value**	**Difference**	**CI**	***P* value**	
Complete response at Week 4[2]	[3,11]	0.31	0.10-0.45	NA	2.13	1.21-4.38	NA	Propensitiy weighted analysis based on patient level data – see futher explanation on the results in section 8.7
Complete response at Week 12	[3,11]	0.58	0.37-0.69	NA	4.02	1.92-9.95	NA	Propensitiy weighted analysis based on patient level data – see futher explanation on the results in section 8.7
Complete response at longest FU	[3,11]	0.54	0.34-0.65	NA	3.82	1.85-9.27	NA	Propensitiy weighted analysis based on patient level data – see futher explanation on the results in section 8.7
HRQoL Cushings Disease	[3-11]	NA	NA	NA	NA	NA	NA	NA

[2] week 4 data are not available in LINC-4 so the analysis uses the closest time point of week 5

Results referring to question 3: What is the value of osilodrostat compared to pasireotide in adult patients with endogenous Cushing's syndrome?								
AEs requiring treatment	[3-11]	NA	NA	NA	NA	NA	NA	NA

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

8.7 Propensity score weighting results

Patient-level data were available for two osilodrostat trials (LINC-3, LINC-4), one pasireotide SC trial (PASSPORT) and one pasireotide LAR trial (G2304). A propensity score weighted analysis was performed to adjust the pasireotide trial populations to be similar to the LINC-3 and LINC-4 population in terms of the selected baseline characteristics (age, race, mean urinary free cortisol [mUFC], time since diagnosis, prior surgery and prior medications). The patient-level data and derived propensity score weights were used to conduct an unanchored indirect treatment comparison of osilodrostat versus pasireotide SC, and osilodrostat versus pasireotide LAR (48).

8.7.1 Propensity score weighting for LINC 3

To make an adjusted comparison between the different studies, individual patients were assigned a propensity score. The propensity score is the probability of study assignment as a function of a set of observable covariates. The propensity score logistic regression model estimates the odds of being enrolled into Colao 2012, Lacroix 2018 or LINC-3. From the propensity score, patients were assigned weights that adjust for differences in the distribution of prognostic factors (including sex, age, mUFC, prior surgery and prior medications). For more details please refer to Appendix section 8.7.

Given that PLD from three studies were used, weighting was performed for all pairwise study comparisons and each study was matched to the other two studies.

As the target population for the matching was the LINC-3 study, the average treatment effect for the treated (ATT) estimand was used for the weighting, which assigns all patients in LINC-3 a weight of 1 and patients in the other two studies are weighted to their under/overrepresentation in LINC-3, as defined in the equation below:

$$weight_{(LINC-3,\ Lacroix\ 2018\ /Colao\ 2012)} = \ (1,\ \frac{propensity\ score}{1 - \ propensity\ score})$$

The estimated weights for the other two studies were rescaled in the analysis to match the effective sample size (ESS) to prevent underestimating the uncertainty of parameter estimates. Where the ESS is the number of independent, non-weighted individuals that would be required to give an estimate with the same precision as the weighted sample estimate. In the analysis an ESS of 27.7 for pasireotide LAR was used.

A small ESS, relative to the original sample size is an indication that the weights are variable due to the lack of population overlap, and the result may be unstable. (49) The ESS is estimated using the following equation:

$$ESS = \frac{(\sum_{i=1}^{n} weight_i)^2}{\sum_{i=1}^{n} weight_i^2}$$

Following the estimation of weights and ESS, the weights were rescaled using the formula below such that the sum of the rescaled weights is equal to the ESS to prevent underestimation of the parameter estimates.

$$Analysis\ Rescaled\ weight_i = \frac{weight_i}{\sum_{i=1}^{n} weight_i} \times ESS$$

The rescaled weights were then applied to a logistic regression model to obtain weighted odds ratios (ORs). Note that the patients who are not being adjusted have a weight of 1 whereas the adjusted patients receive a weight based on their under/overrepresentation in the matched population. The method used for the rescaling is based on the method used for the TTCR and TTFPR analyses. The reason for rescaling the weights is due to the increase in sample size for pasireotide LAR after weighting (74 patients to 137 patients). Higher sample sizes lead to reduced uncertainty for inference which does not seem appropriate. Therefore the sample size has been rescaled to be equal to the ESS, allowing for additional uncertainty (i.e. wider confidence intervals) in subsequent analyses.

The 95% confidence interval around the ORs has been constructed using two methods:

- Standard error estimated directly from the regression equation.
- Robust sandwich variance estimator – this approach does not require the assumption that the residual errors have constant variance

Although it might not be needed to calculate the CI via two different methods, this reassured that the two methods give similar results and validated the chosen method of rescaling the weights. Therefore the approach is considered appropriate.

Derivation of data

Complete response (CR) analyses have been performed at three time points:

- Week 4
- Week 12
- Longest follow up (final observation)

In order to obtain the proportion of responders at week 4 and 12, the analyses considered observations 14 days either side of day 29 (for week 4) and day 85 (for week 12) from the studies data. This approach may be more appropriate for an ITC given the large range of study day observations reported in the study reports.
Only scheduled assessments were considered and patients who had discontinued or who had missing observations were considered non-responders.

Table 81 ITC results for complete response: osilodrostat versus pasireotide LAR

Time point	Target population	Intervention		Comparator		Weighted OR (95% CI)	Weighted RR (95% CI)
		Treatment	Proportion of patients with CR (%)	Treatment	Proportion of patients with CR (%)		
4 weeks	LINC-3	Osilodrostat	55/137 (40.1%)	Pasireotide LAR	21/74 (28.4%)	1.70 (0.69 to 4.14)	1.42 (0.82 to 2.88)
12 weeks	LINC-3	Osilodrostat	101/137 (73.7%)	Pasireotide LAR	18/74 (24.3%)	8.14 (3.20 to 20.72)	2.88 (1.58 to 6.18)
Longest follow up	LINC-3	Osilodrostat	86/137 (62.8%)	Pasireotide LAR	33/74 (44.6%)	2.76 (1.19 to 6.40)	1.65 (1.07 to 3.01)

Table 81 presents the results for the ITC analyses of complete response for osilodrostat relative to pasireotide LAR at 4 weeks, 12 weeks and at the longest follow-up. An OR greater than one provides evidence of improved complete response for patients receiving osilodrostat versus pasireotide. After adjusting for differences in patient characteristics, results show that a greater proportion of patients with osildrostat achieve complete response at 4 weeks compared with pasireotide (40.1% versus 28.4%, OR: 1.70 [95% CI: 0.69 to 4.15]). Moreover, significantly more patients on osildrostat achieved complete response at 12 weeks and at longest of follow-up versus those on pasireotide LAR (73.7% versus 24.3% at 12 weeks, OR: 8.14 [95% CI: 3.20 to 20.71]; 62.8% versus 44.6% at longest follow-up, OR: 2.76 [95% CI: 1.19 to 6.40] respectively).

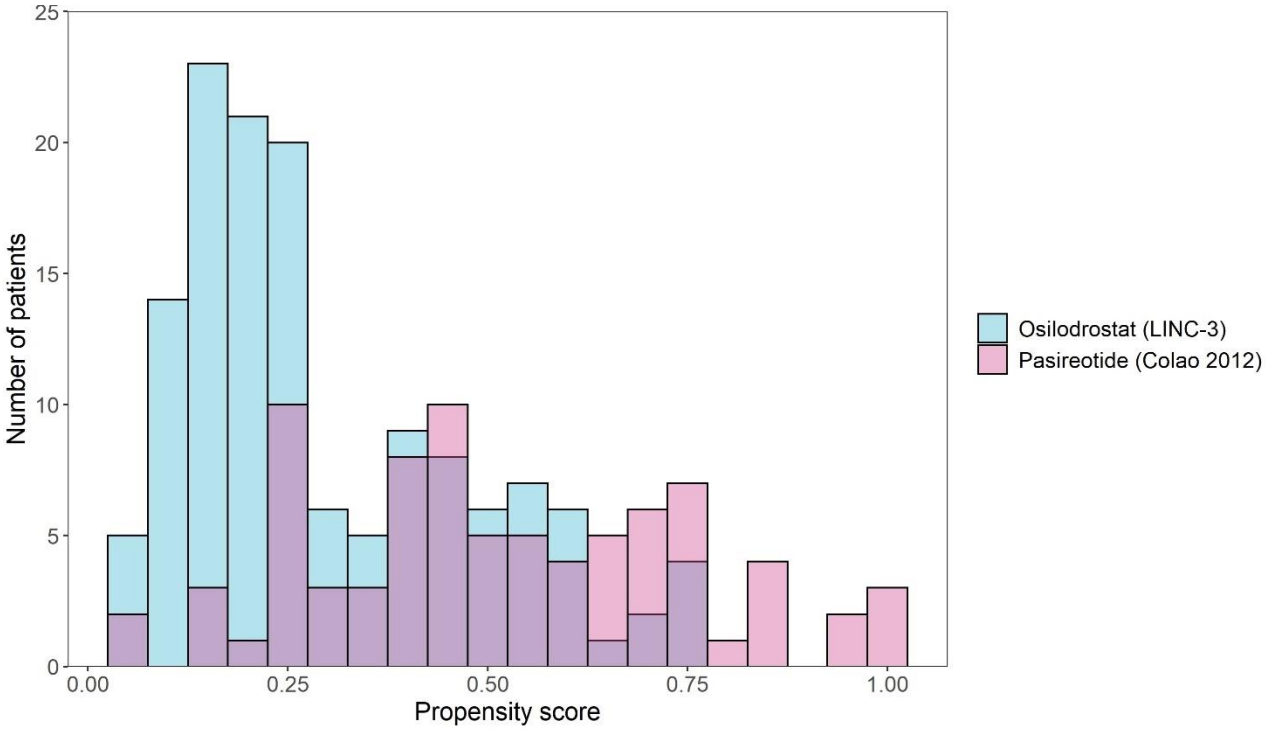
Methods

Six characteristics were adjusted for in the propensity model: age, race, mUFC, time since diagnosis, prior surgery and prior medications. Results are presented for the base case analysis, where the Colao 2012 and Lacroix 2018 populations are matched to LINC-3.

Figure 8 and Figure 9 present histograms of propensity scores for LINC-3 with Colao 2012 and Lacroix 2018, respectively. The estimated propensity score is the predicted probability of treatment assigned conditional on observed baseline characteristics. Values close to 0 indicate patients who have baseline characteristics more similar to LINC-3 (target population). In both cases, patients in LINC-3 tend to have lower scores whereas patients in Colao 2012 and Lacroix 2018 have a range of values from 0 to 1; there is some overlap in the distributions (shaded in purple in the plots).

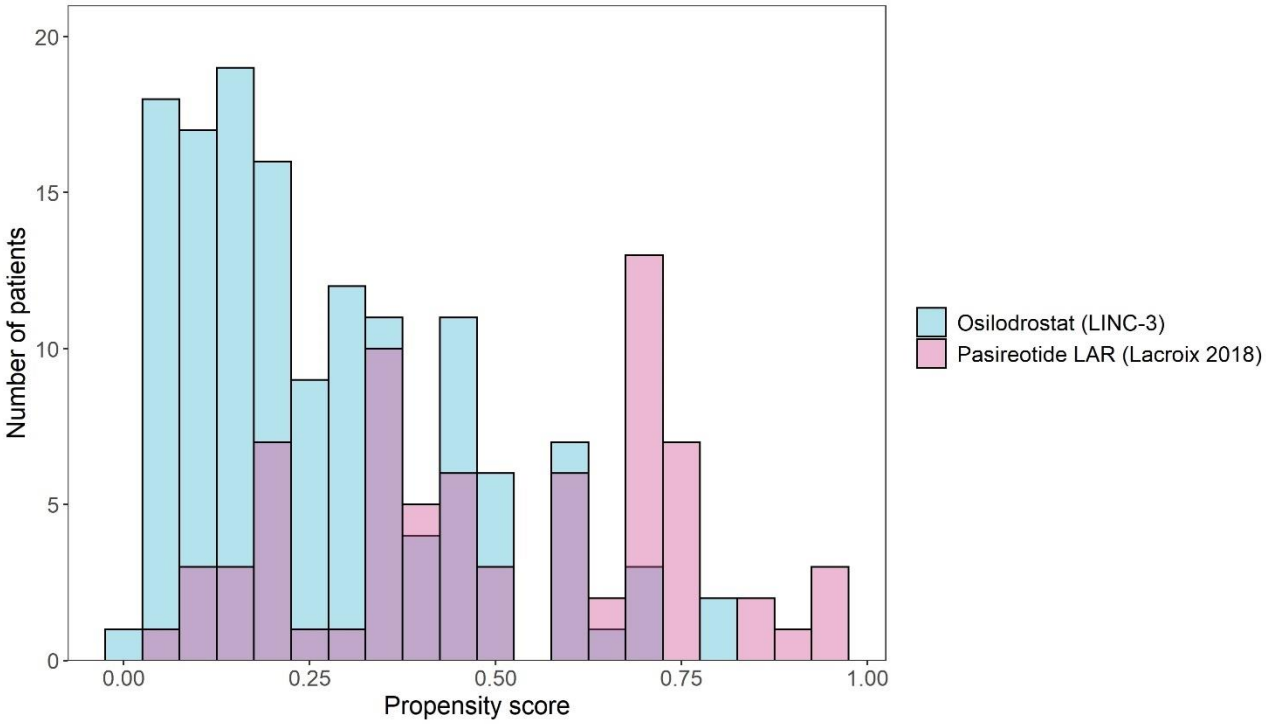
Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Figure 8 Histogram of propensity scores by study (LINC-3 and Colao 2102)



Notes: Colao 2012 data is for pasireotide subcutaneous. Bars shaded purple indicate overlap in the baseline patient characteristics within each study. Propensity score values close to 0 indicate patients who have baseline characteristics more similar to LINC-3 (target population), whereas propensity score values close to 1 indicate patients who have baseline characteristics which are less similar to LINC-3.

Figure 9: Histogram of propensity scores by study (LINC-3 and Lacroix 2018)

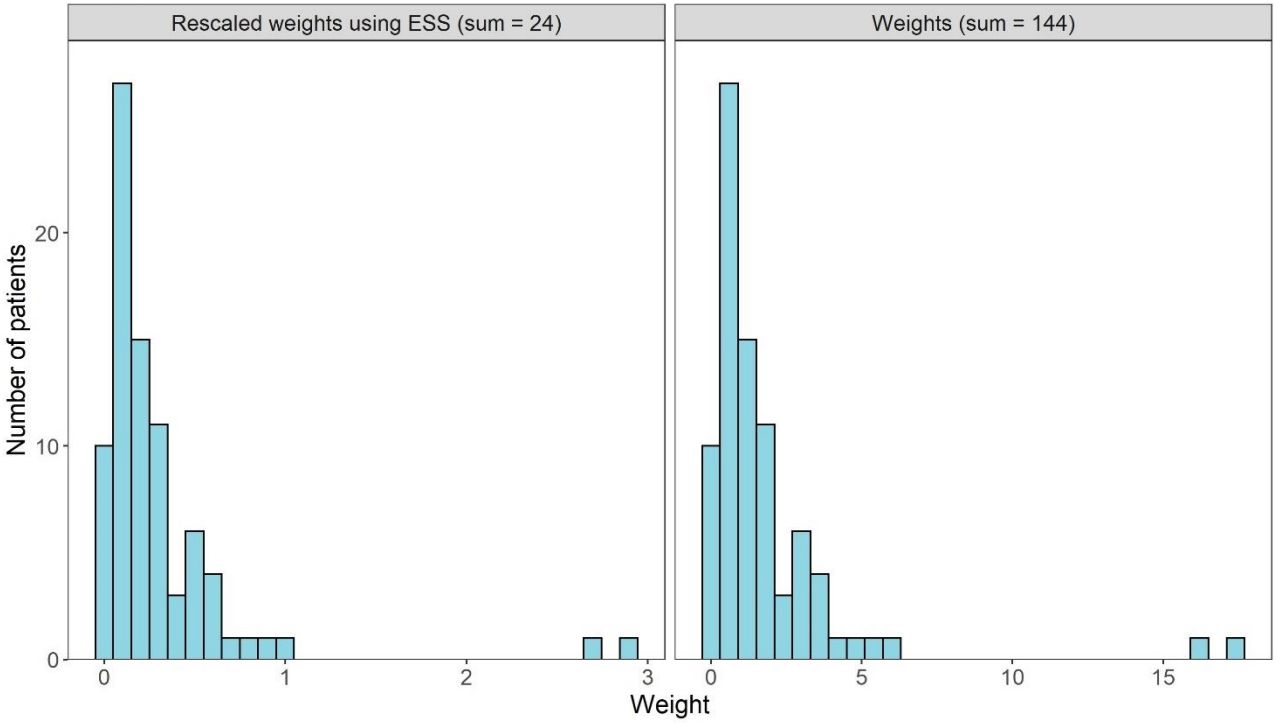


Key: LAR, long-acting release.
Notes: Bars shaded purple indicate overlap in the baseline patient characteristics within each study. Propensity score values close to 0 indicate patients who have baseline characteristics more similar to LINC-3 (target population), whereas propensity score values close to 1 indicate patients who have baseline characteristics which are less similar to LINC-3.

Figure 10 and Figure 11 present the derived weights for the Colao 2012 and Lacroix 2018 populations, respectively. Note that as the two populations were matched to LINC-3, all LINC-3 patients have a weight of 1. The sample size for

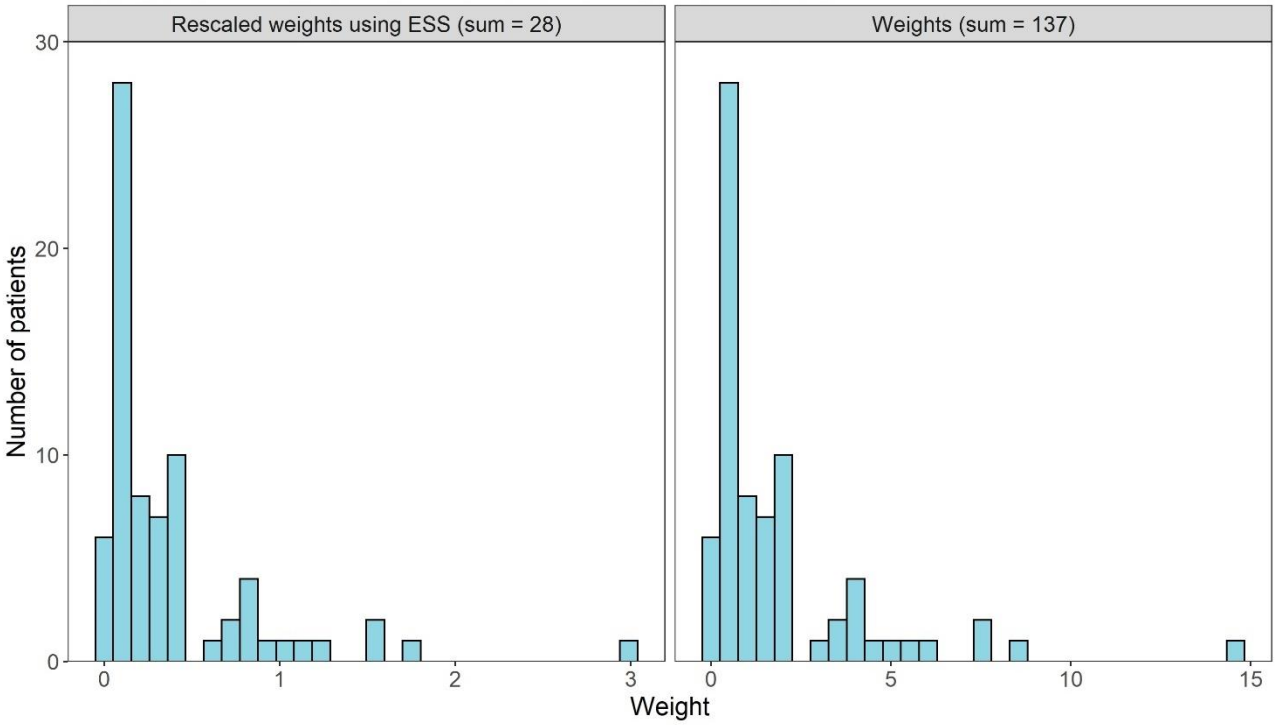
Colao 2012 before matching was 82; this increased to 144 after matching (as there are 137 LINC-3 patients). Similarly, the sample size for Lacroix before matching was 74 which increased to 137 after matching. The sum of the weights for Colao 2012 and Lacroix 2018 were rescaled to be equal to the corresponding ESS (24.4 in Colao 2012 and 27.7 in Lacroix 2018) to allow for greater uncertainty in the subsequent survival analysis. In both cases the ESS was less than half the observed sample size, suggesting there is limited population overlap.

Figure 10: Histogram of weights for Colao 2012 (pasireotide SC)



Key: SC, subcutaneous.

Figure 11: Histogram of weights for Lacroix 2018 (pasireotide LAR)



Key: LAR, long-acting release.

Table 82 presents the characteristics for the patients with the largest assigned weights in Colao 2012 and Lacroix 2018. For Colao 2012, each category listed had a lower proportion of patients compared to LINC-3 (e.g. 20.7% of patients were non-White in Colao 2012 compared to 35.0% of LINC-3 patients). For Lacroix 2018, four out of six characteristics listed had a lower proportion of patients compared to LINC-3 (age, race, mUFC and prior medications). These categories showed the largest differences in the selected characteristics before matching.

Table 82: Characteristics for the patient with the largest weight

Characteristic	Colao 2012 (pasireotide SC)	Lacroix 2018 (pasireotide LAR)
Age category	40 to <60 years	40 to <60 years
Race	Non-White	White
mUFC category	<2.0 x ULN	≥5.0 x ULN
Time since diagnosis	≥47 months	<47 months
Prior surgery	Yes (≥43 months ago)	Yes (<43 months ago)
Prior medications	Yes	Yes
Key: LAR, long-acting release; mUFC, mean urinary free cortisol; SC, subcutaneous; ULN, upper limit of normal.		

Table 83 presents a summary of the patient characteristics before and after matching for the covariates included in the propensity model. Characteristics are generally well balanced after matching, except for mUFC in Colao 2012 and time since diagnosis and prior surgery in Lacroix 2018. Figure 12 and Figure 13 present the associated absolute mean differences for Colao 2012 and Lacroix 2018, respectively. Note that raw mean differences are presented rather than standardized mean differences as raw mean differences are preferred when matching on categorical variables.(50) An absolute mean difference ≤0.1 suggests groups are well matched. For Colao 2012, all groups fall within this threshold after matching, except for mUFC (<2.0 x ULN). For Lacroix 2018, most groups fall within this threshold after matching, except for time since diagnosis (≥47 months) and prior surgery (≥43 months ago and <43 months ago).

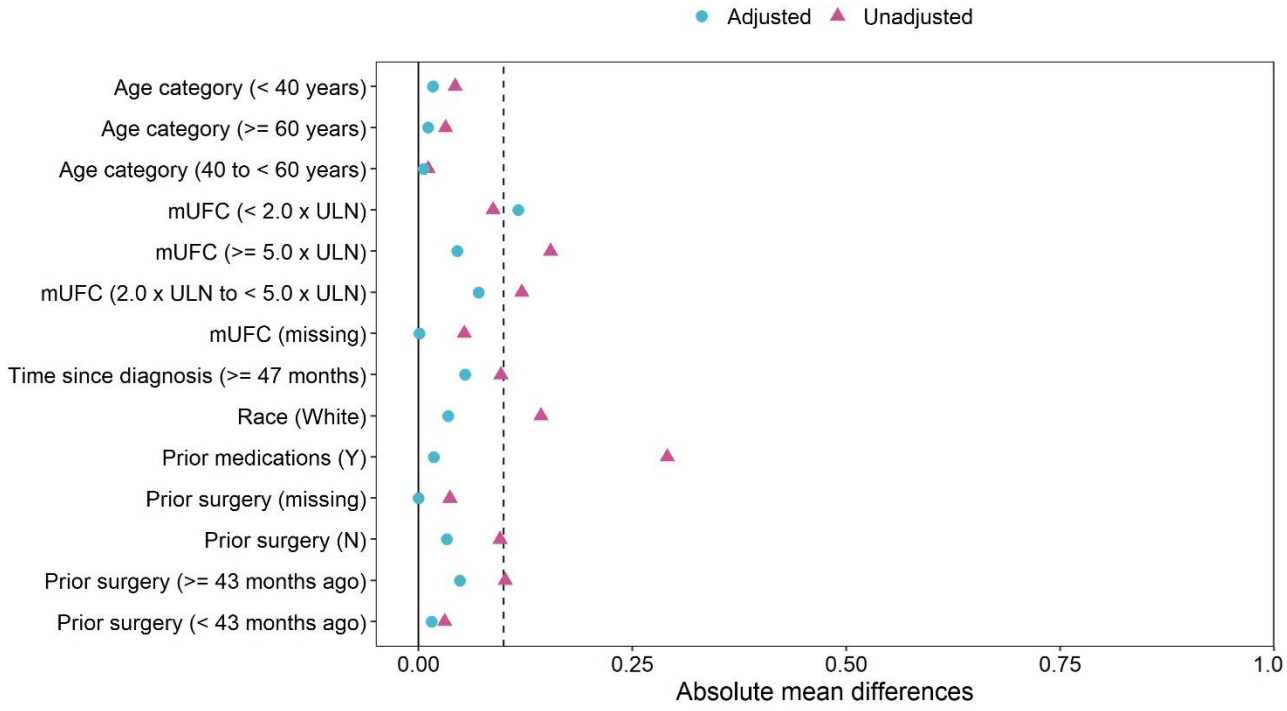
Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Table 83: Summary of patient characteristics before and after matching

Covariate	Before matching			After matching		
	Osilodrostat (N = 137)	Pasireotide SC (N = 82)	Pasireotide LAR (N = 74)	Osilodrostat (N = 137)	Pasireotide SC (N = 24.4)	Pasireotide LAR (N = 27.7)
Age (years)						
<40 years	48.2%	52.4%	60.8%	48.2%	49.9%	43.3%
40 to <60 years	40.1%	39.0%	31.1%	40.1%	39.6%	45.9%
≥60 years	11.7%	8.5%	8.1%	11.7%	10.6%	10.8%
Race – White	65.0%	79.3%	52.7%	65.0%	61.5%	70.7%
Baseline mUFC (nmol/24 h)						
<2.0 x ULN	23.4%	14.6%	36.5%	23.4%	35.0%	25.5%
2.0 x ULN to <5.0 x ULN	43.8%	47.6%	45.9%	43.8%	36.8%	40.4%
≥5.0 x ULN	31.2%	31.7%	9.5%	31.2%	27.6%	33.7%
Missing	0.7%	6.1%	8.1%	0.7%	0.6%	0.6%
Time since diagnosis (months)						
<47 months	48.9%	58.5%	75.7%	48.9%	43.4%	60.7%
≥47 months	51.1%	41.5%	24.3%	51.1%	56.6%	39.3%
Prior pituitary surgery						
No	12.4%	22.0%	20.3%	12.4%	9.1%	9.5%
Yes (<43 months ago)	44.5%	41.5%	54.1%	44.5%	43.0%	59.8%
Yes (≥43 months ago)	43.1%	32.9%	25.7%	43.1%	47.9%	30.7%
Missing	0%	3.7%	0%	0%	0%	0%
Prior medications – yes	73.0%	43.9%	43.2%	73.0%	74.8%	72.1%

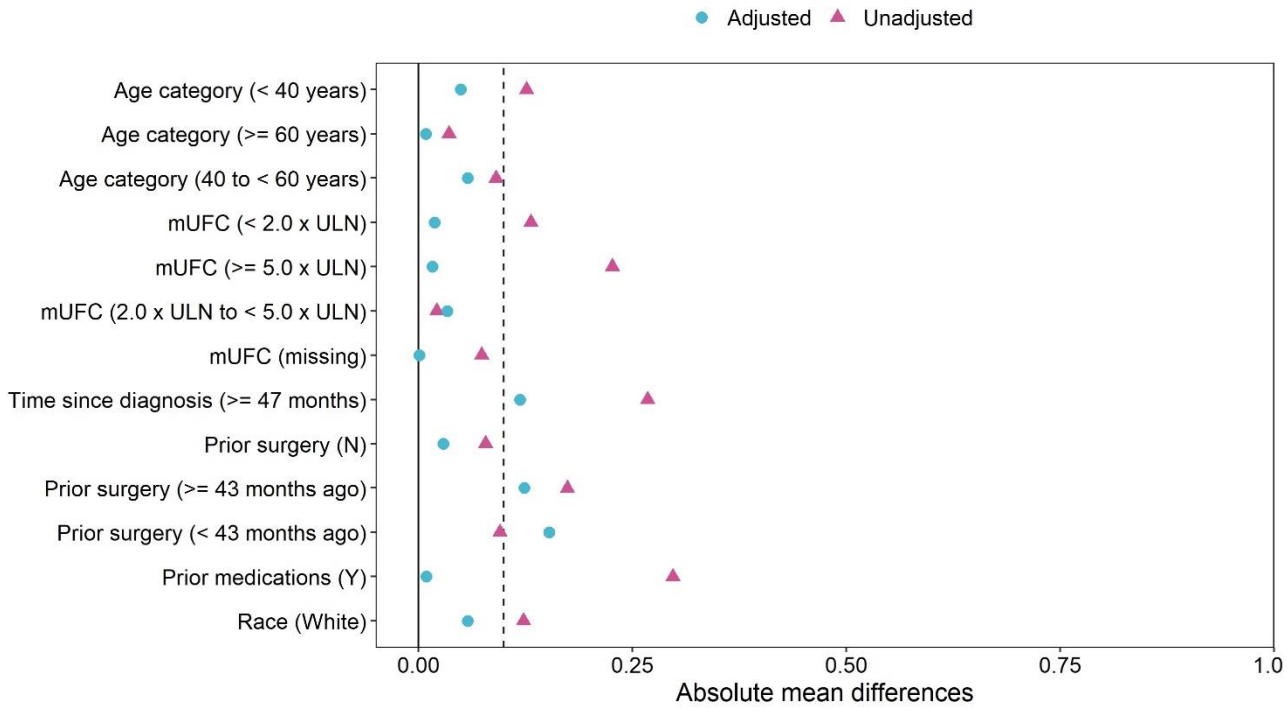
Key: LAR, long-acting release; mUFC, mean urinary free cortisol; SC, subcutaneous; ULN, upper limit of normal.
Notes: The ULN for mUFC was 138 nmol/24 h in LINC-3, 145 nmol/24h in Colao 2012 and 166 nmol/24 h in Lacroix 2018.

Figure 12: Mean differences for characteristics included in the model before and after matching – Colao 2012 (pasireotide SC) weighted to LINC-3 (osilodrostat)



Key: SC, subcutaneous; ULN, upper limit of normal.
Notes: An absolute mean difference ≤ 0.1 suggests groups are well matched.

Figure 13: Mean differences for characteristics included in the model before and after matching – Lacroix



Key: LAR, long-acting release; ULN, upper limit of normal.
Notes: An absolute mean difference ≤ 0.1 suggests groups are well matched.

8.7.2 Propensity score weighting for LINC 4

[redacted]

[redacted]

Table 84: ITC results for complete response: osilodrostat versus pasireotide LAR and SC

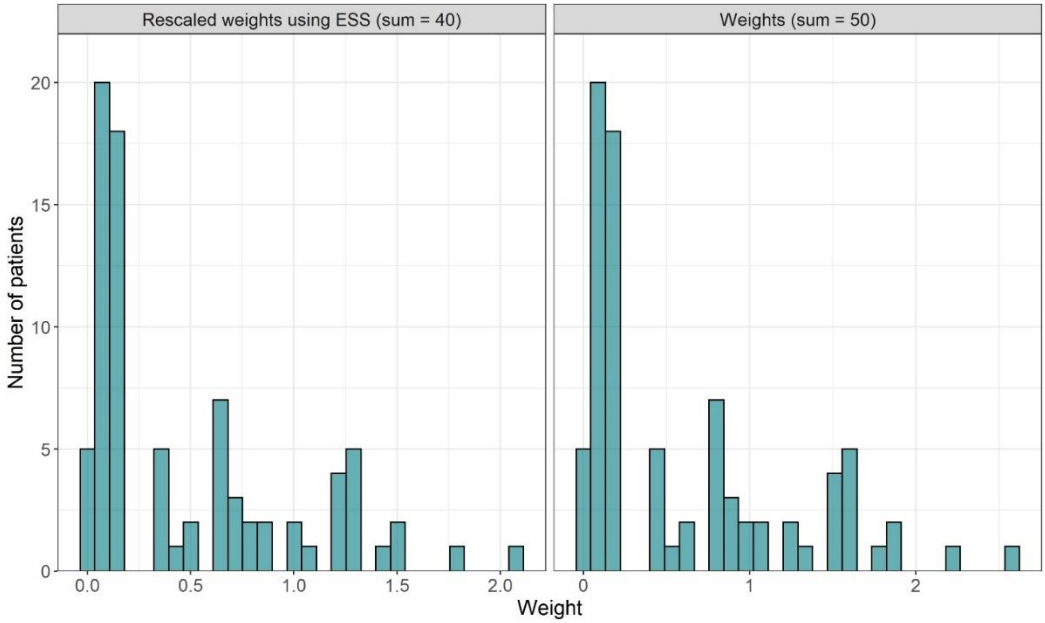
Time point	Target population	Intervention		Comparator		Weighted OR (95% CI)	Weighted RR (95% CI)
		Treatment	Proportion of patients with CR (%)	Treatment	Proportion of patients with CR (%)		
Osilodrostat versus pasireotide LAR							
4 weeks*	LINC-4	Osilodrostat	28/48 (58.3%)	Pasireotide LAR	21/74 (28.4%)	[redacted]	[redacted]
12 weeks	LINC-4	Osilodrostat	37/48 (77.1%)	Pasireotide LAR	18/74 (24.3%)	[redacted]	[redacted]
Longest follow up**	LINC-4	Osilodrostat	35/48 (72.9%)	Pasireotide LAR	33/74 (44.6%)	[redacted]	[redacted]
Osilodrostat versus pasireotide sc							
4 weeks*	LINC-4	Osilodrostat	28/48 (58.3%)	Pasireotide SC	22/82 (26.8%)	[redacted]	[redacted]
12 weeks	LINC-4	Osilodrostat	37/48 (77.1%)	Pasireotide SC	13/82 (15.9%)	[redacted]	[redacted]
Longest follow up**	LINC-4	Osilodrostat	35/48 (72.9%)	Pasireotide SC	13/82 (15.9%)	[redacted]	[redacted]

*Please note that the following data has been used for the week 4 time point when matching to the CSR: LINC-4 – 5 weeks (no week 4 data available), Colao 2012 – 30 days, Lacroix – 1 month

**Longest follow up as end of treatment visit

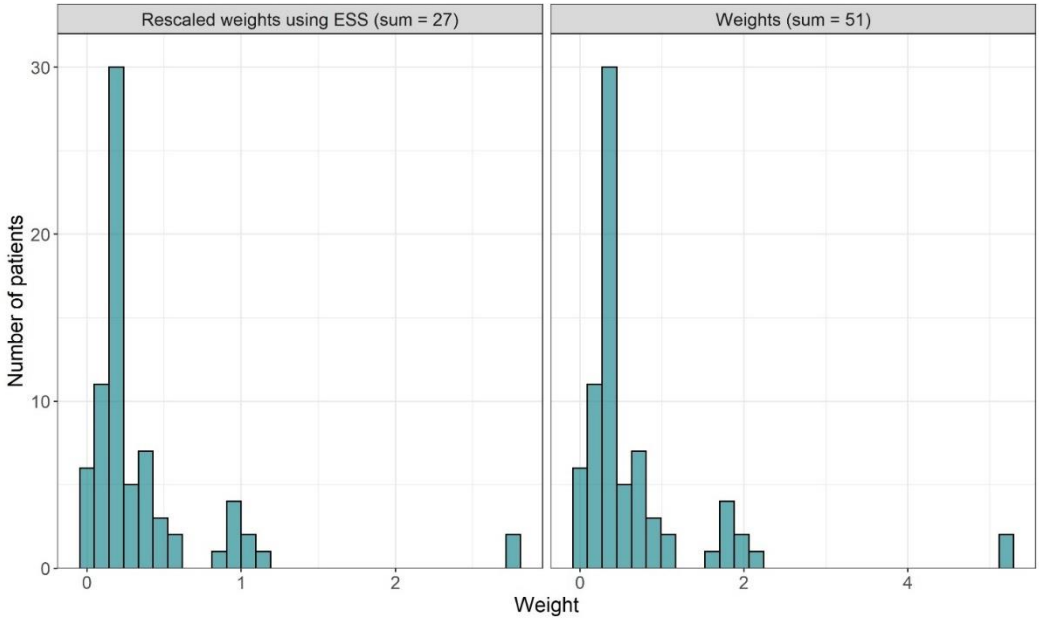
[redacted]

Figure 14: Histogram of weights for Colao 2012 (pasireotide SC)



Key: SC, subcutaneous.

Figure 15: Histogram of weights for Lacroix 2018 (pasireotide LAR)

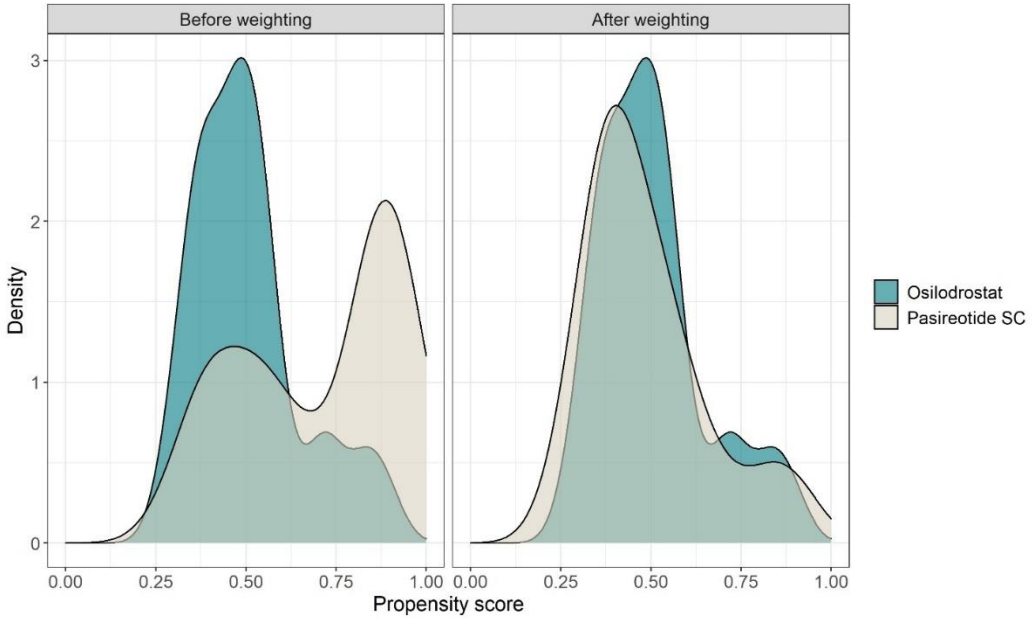


Key: LAR, long-acting release.

Distribution of propensity scores

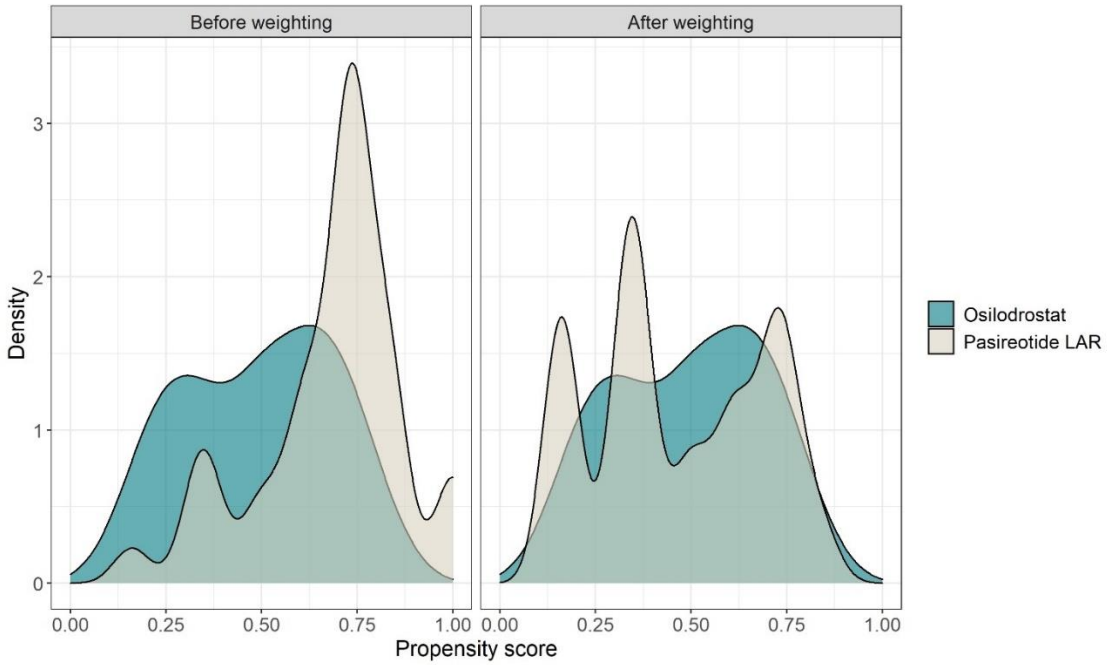
Propensity scores before and after weighting are compared in Figure 16 and Figure 17 versus Colao 2012 and Lacroix 2018, respectively. The estimated propensity score is the predicted probability of treatment assigned conditional on observed baseline characteristics. Overlapping distributions represent patients who could be assigned to either treatment based on their characteristics. In both cases, there is some overlap in the distributions prior to weighting. This suggests there is some population overlap but indicates there are observable differences which require adjustment. More overlap is seen in the distributions following the weighting which suggests the populations are reasonably similar.

Figure 16: Comparison of propensity scores for LINC-4 (osilodrostat) and Colao 2012 (pasireotide SC) before and after weighting



Key: SC, subcutaneous.
Notes: Overlapping distributions indicate populations are similar.

Figure 17: Comparison of propensity scores for LINC-4 (osilodrostat) and Lacroix 2018 (pasireotide LAR) before and after weighting



Key: LAR, long-acting release.
Notes: Overlapping distributions indicate populations are similar.

Comparison of patient characteristics before and after weighting

Table 85 below presents a summary of the patient characteristics before and after weighting for the covariates included in the propensity model. Characteristics are generally well balanced after weighting. Figure 18and Figure 19 present the associated absolute mean differences for Colao 2012 and Lacroix 2018, respectively. Note that raw mean differences are presented rather than standardized mean differences as raw mean differences are preferred when weighting on categorical variables. An absolute mean difference ≤ 0.1 suggests groups are well balanced. For Colao 2012, all groups fall within this threshold after weighting. For Lacroix 2018, most groups fall within this threshold after weighting; age (40 to < 60 years) is slightly over. These results suggest groups are sufficiently similar for performing ITCs.

Table 85: Summary of patient characteristics before and after weighting

Covariate	Before weighting			After weighting		
	Osilodrostat (N = 48)	Pasireotide SC (N = 82)	Pasireotide LAR (N = 74)	Osilodrostat (N = 48)	Pasireotide SC (N = 39.7)	Pasireotide LAR (N = 26.7)
Age						
< 40 years	48%	52%	61%	[redacted]	[redacted]	[redacted]
40 to < 60 years	35%	39%	31%	[redacted]	[redacted]	[redacted]
≥ 60 years	17%	9%	8%	[redacted]	[redacted]	[redacted]
Baseline mUFC (nmol/24 h)						
< 2.0 x ULN	29%	15%	36%	[redacted]	[redacted]	[redacted]
2.0 x ULN to < 5.0 x ULN	58%	32%	46%	[redacted]	[redacted]	[redacted]
≥ 5.0 x ULN	13%	48%	9%	[redacted]	[redacted]	[redacted]
Missing	0%	6%	8%	[redacted]	[redacted]	[redacted]
Time since diagnosis						
< 67 months	48%	67%	81%	[redacted]	[redacted]	[redacted]
≥ 67 months	52%	33%	19%	[redacted]	[redacted]	[redacted]
Prior pituitary surgery						
Yes	85%	78%	80%	[redacted]	[redacted]	[redacted]
No	15%	22%	20%	[redacted]	[redacted]	[redacted]
Prior medications						
Yes	54%	44%	43%	[redacted]	[redacted]	[redacted]
No	46%	56%	57%	[redacted]	[redacted]	[redacted]

Key: LAR, long-acting release; mUFC, mean urinary free cortisol; SC, subcutaneous; ULN, upper limit of normal.
Notes: Values may not sum to 100% due to rounding. The ULN for mUFC was 138 nmol/24 h in LINC-4, 145 nmol/24h in Colao 2012 and 166 nmol/24 h in Lacroix 2018.

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Figure 18: Mean differences for characteristics included in the model before and after weighting – Colao 2012 (pasireotide SC) weighted to LINC-4 (osilodrostat)

Key: SC, subcutaneous; ULN, upper limit of normal.
Notes: An absolute mean difference ≤ 0.1 suggests groups are well matched.

Figure 19: Mean differences for characteristics included in the model before and after weighting – Lacroix 2018 (pasireotide LAR) weighted to LINC-4 (osilodrostat)

Key: LAR, long-acting release; ULN, upper limit of normal.
Notes: An absolute mean difference ≤ 0.1 suggests groups are well matched.

Table presents the characteristics for the patients with the largest assigned weights in Colao 2012 and Lacroix 2018. For Colao 2012, all groups except time since diagnosis had a lower proportion of patients compared to LINC-4 (e.g. 9% of

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

patients were aged ≥ 60 years in Colao 2012 compared to 17% of LINC-4 patients). For Lacroix 2018, all categories had a lower proportion of patients compared to LINC-4.

Table 86: Characteristics for the patient with the largest weight

Characteristic	Colao 2012 (pasireotide SC)	Lacroix 2018 (pasireotide LAR)
Rescaled weight	2.06	2.73
Age category	≥ 60 years	≥ 60 years
mUFC category	2.0 x ULN to < 5.0 x ULN	2.0 x ULN to < 5.0 x ULN
Time since diagnosis	< 67 months	≥ 67 months
Prior surgery	Yes	Yes
Prior medications	Yes	Yes
Key: LAR, long-acting release; mUFC, mean urinary free cortisol; SC, subcutaneous; ULN, upper limit of normal.		

8.8 Matching adjusted indirect comparison LINC4 vs PROMPT

More robust comparisons were formed for osilodrostat versus metyrapone (using the PROMPT study) as ample patient characteristics were available in the literature.
Two methods for estimating comparative efficacy when a common treatment comparator is unavailable are discussed in the NICE DSU TSD 18 ('Methods for Population-Adjusted Indirect Comparisons in Submissions to NICE'). (49) The two population adjustment methods are:

- MAIC
- STC

Both MAIC and STC methods can be used to form estimates of relative efficacy between treatments by first adjusting for differences in patient characteristics between trials. MAICs produce weights for each patient depending on the similarity of the given patient to the aggregate characteristics of the comparator trial population. STC methods use predictive equations that model the relationship between the outcome and key baseline characteristics. MAIC is less complex and more intuitive then STCs. Therefore, for practicality, MAICs were preferred over STCs in this instance.

Identifying covariates

Multiple sources of evidence were used to identify prognostic factors and treatment effect modifiers that must be balanced when performing a population adjustment. Of note, ultimately, the choice of variables is conditional upon the individual-patient data that is available for LINC-4 and the availability of baseline characteristics for PROMPT.
The following methods were used to identify covariates to include in the matching:

- Assessment of treatment effect modifiers for complete response at Week 12 for LINC-4 (note, Week 36 not assessed as placebo patients switched to osilodrostat)
- Assessment of prognostic factors for complete response at Week 12 and 36 for LINC-4, Colao 2012 and Lacroix 2018 (note, Week 36 not assessed for Colao 2012 as time point is beyond the end of the core trial period)
- The stratification used for randomization in LINC-4, Colao 2012 and Lacroix 2018

To identify treatment effect modifiers, separate univariate logistic regressions including a treatment covariate only were fitted to each subset of patients within each characteristic of interest. For example, to investigate the impact of sex on the treatment effect for complete response at Week 12, a logistic regression (with treatment as the only covariate) was applied separately to the subgroup of data for male and female patients.
A similar approach is taken to identify prognostic factors; however, instead of splitting the data into subgroups based on the characteristic of interest, a covariate for the characteristic is included in the regression model and treatment is not

considered. For example, to assess whether sex has an impact on the prognosis of complete response at Week 12, a logistic regression (with characteristic as the only covariate) was applied to the whole dataset.
The results from these analyses are considered indicative and do not necessitate that all treatment effect modifiers or prognostic factors were identified, or for those that were to be clinically plausible. This is because subgroup data are not true randomized comparisons in cases where the randomization was not stratified for that subgroup. Furthermore, not all modifiers may be flagged as 'statistically significant' even if it is a known treatment effect modifier as the tests that underlie these may lack statistical power. Given the small sample size, a cut off of 0.1 in the p-value was used to detect statistical significance.

Estimation of the MAIC weights

To make an adjusted comparison between osilodrostat and metyrapone, individual LINC-4 were assigned statistical weights that adjust for their over- or under-representation relative to the average prognostic factors and treatment effect modifiers observed in PROMPT.
Weights were derived using a MAIC, a form of propensity score weighting. (51) The propensity score logistic regression model estimates the odds of being enrolled into LINC-4 or PROMPT. For this, a method of moments is used to allow a propensity score logistic regression model to be estimated without patient-level data for the comparative evidence source. The model was estimated based on patient-level data available for the osilodrostat-treated patients and the published summary data available for PROMPT.
Following estimation of the weights, it is necessary to explore their distribution. Re-scaled weights (specified in Equation below) were explored via the use of histograms to determine whether specific patient(s) or groups of patients (based on covariate values) are over- or under-represented in the analysis. The use of scaled weights aids interpretation; a scaled weight of > 1 means that an individual carries more weight in the re-weighted sample than in the original sample, and a scaled weight of < 1 means that an individual carries less weight.

$$Rescaled\ weight_i = \frac{weight_i}{\sum_{i=1}^{n} weight_i} \times N$$

The robustness of the analyses were also considered by approximating the effective sample size (ESS). For a weighted estimate, the ESS is the number of independent non-weighted individuals that would be required to give an estimate with the same precision as the weighted sample estimate. (52) The calculation of the ESS approximation is specified in equation below. A small ESS, relative to the original sample size, is an indication that the weights are highly variable due to a lack of population overlap, and that the estimate may be unstable. (52)

$$ESS = \frac{\left(\sum_{i=1}^{n} weight_i\right)^2}{\sum_{i=1}^{n} weight_i^2}$$

Application of the MAIC weights

As this endpoint is binary, the derived weights were applied to logistic regression models providing relative effect estimates in the form of (weighted) ORs. The logistic regression takes the following form:

$$\log\left(\frac{probability\ of\ event}{1 - probability\ of\ event}\right) = \beta_0 + \beta_1 \times treatment$$

where only one covariate is included (treatment). The weighted OR is found by exponentiating the treatment coefficient β_1.

Uncertainty estimation

To account for the fact that weights are estimated rather than fixed and known, uncertainty in the estimation of weights was included in the calculation of uncertainty around relative treatment effects.(52) Uncertainty was measured using robust standard errors via the sandwich estimator. Robust standard errors were used to prevent the analysis from

being sensitive to outlying observations. A heteroscedasticity-consistent estimation of the covariance matrix of the coefficient estimates in the regression was estimated using the vcovHC function from the 'sandwich' package (Version 3.0-2).(53) Using the covariance matrix, robust standard errors for the treatment coefficient were calculated and a confidence interval derived via a normal approximation.

8.8.1 Identifying covariates to include in the matching

Exploratory analyses were performed to determine which variables should be included in the MAIC analysis. This involved assessing the patient characteristics and identifying prognostic factors and/or treatment effect modifiers. In addition to those prognostic factors and effect modifiers identifiable through exploratory analyses, variables stratified for in LINC-4, Colao 2012 and Lacroix 2018 were also included in matching where possible.

Table 87 presents a comparison of patient characteristics for LINC-4 and PROMPT. Note that LINC-3 has not been considered here as analyses were based on LINC-4. Most characteristics were reported for PROMPT, except race, pituitary adenoma and Cushing's disease status. [redacted]

Table 87: Comparison of patient characteristics for LINC-4 and PROMPT

Characteristic	Osilodrostat	Metyrapone
	LINC-4 N = 48	PROMPT N = 49[c]
Age (years)		
Mean (SD)	42.3 (13.8)	46.8 (13.3)
Min	21.0	22.0
Median	41.0	47.0
Max	67.0	73.0
Male – n (%)	5 (10.4)	15 (30.6)
Race – n (%)		
White	34 (70.8)	NR
Asian	9 (18.8)	NR
Other	5 (10.4)	NR
Pituitary adenoma – n (%)	48 (100)	NR
BMI (kg/m²)		
Mean (SD)	29.9 (6.31)	30.5 (7.3)
Min	18.4	22.5
Median	29.1	27.7
Max	50.0	55.4

Characteristic	Osilodrostat	Metyrapone
	LINC-4 N = 48	PROMPT N = 49[c]
Baseline mUFC (nmol/24 h)		
Mean (SD)	421.4 (291.3)	1,041.7 (1,337.0)
Min	90.1	291.0
Median	342.2	570.3
Max	1,720.0	8,476.2
Baseline mUFC severity – n (%)		
< 1.5 x ULN	9 (18.8)	0
≥ 1.5 x ULN and ≤ 2 x ULN	5 (10.4)	2 (4.0)
> 2 x ULN and ≤ 5 x ULN	28 (58.3)	31 (63.0)
> 5 x ULN	6 (12.5)	16 (33.0)
Time since diagnosis (months)		
Mean (SD)	70.7 (55.9)	69.6 (67.2)
Min	6.0	3.6
Median	69.9	46.8
Max	257.7	261.6
Previous treatment for CD – n (%)		
Prior surgery	41 (85.4)	30 (61.2)
Prior medications	26 (54.2)	25 (51.0)
Prior irradiation	6 (12.5)	5 (10.2)
CD status – n (%)		
De novo	3 (6.3)	NR
Persistent/recurrent	45 (93.8)	NR

Key: BID, twice a day; BMI, body mass index; CD, Cushing's disease; ITC, indirect treatment comparison; mUFC, mean urinary free cortisol; NR, not reported; PLD, patient-level data; SD, standard deviation.

Prognostic factors

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Figure 20: Forest plot of possible prognostic factors for Week 12 complete response in LINC-4 (osilodrostat)

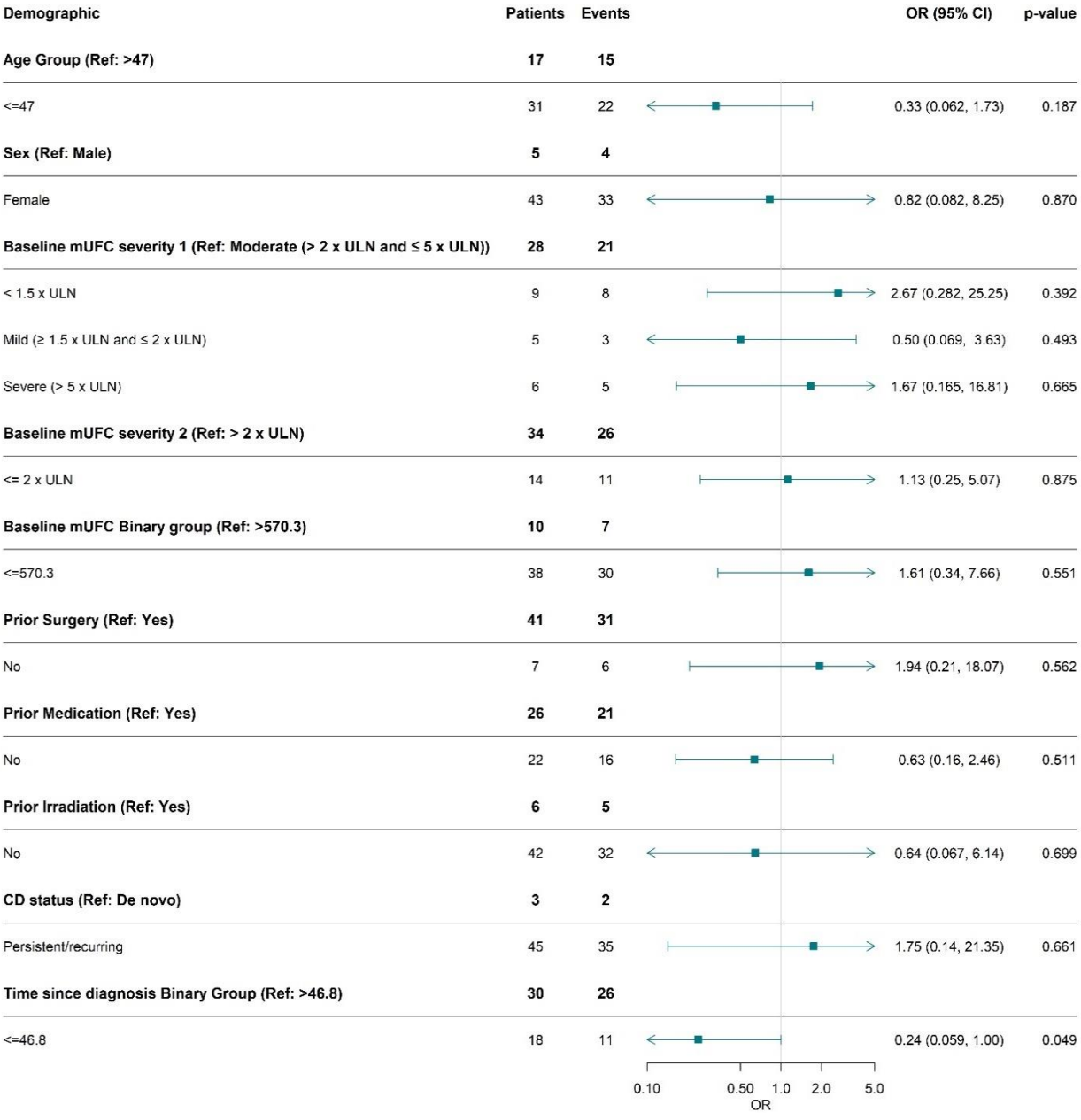


Figure 21: Forest plot of possible prognostic factors for Week 36 complete response in LINC-4 (osilodrostat)

Demographic	Patients	Events	OR (95% CI)	p-value
Age Group (Ref: >47)	**17**	**16**		
<=47	31	22	0.15 (0.018, 1.33)	0.089
Sex (Ref: Male)	**5**	**4**		
Female	43	34	0.94 (0.094, 9.53)	0.961
Baseline mUFC severity 1 (Ref: Moderate (> 2 x ULN and ≤ 5 x ULN))	**28**	**21**		
< 1.5 x ULN	9	7	1.2e+00 (0.19, 6.98)	0.866
Mild (≥ 1.5 x ULN and ≤ 2 x ULN)	5	4	1.3e+00 (0.13, 14.01)	0.811
Severe (> 5 x ULN)	6	6	3.9e+07 (0.00, Inf)	NA
Baseline mUFC severity 2 (Ref: > 2 x ULN)	**34**	**27**		
<= 2 x ULN	14	11	0.95 (0.21, 4.36)	0.948
Baseline mUFC Binary group (Ref: >570.3)	**10**	**8**		
<=570.3	38	30	0.94 (0.17, 5.31)	0.942
Prior Surgery (Ref: Yes)	**41**	**32**		
No	7	6	1.69 (0.18, 15.89)	0.647
Prior Medication (Ref: Yes)	**26**	**22**		
No	22	16	0.48 (0.12, 2.01)	0.318
Prior Irradiation (Ref: Yes)	**6**	**4**		
No	42	34	2.13 (0.33, 13.70)	0.428
CD status (Ref: De novo)	**3**	**2**		
Persistent/recurring	45	36	2.00 (0.16, 24.59)	0.588
Time since diagnosis Binary Group (Ref: >46.8)	**30**	**25**		
<=46.8	18	13	0.52 (0.13, 2.13)	0.363

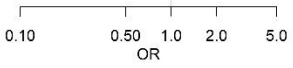


Figure 22: Forest plot of possible prognostic factors for Week 12 complete response in Colao 2012 (Pasireotide SC)

Demographic	Patients	Events	OR (95% CI)	p-value
Age Group (Ref: <=47 years)	**59**	**8**		
>47 years	23	5	1.77 (0.48, 6.04)	0.366
Sex (Ref: Female)	**62**	**13**		
Male	20	0	NA	NA
BMI (Ref: >=28 kg/m^2)	**49**	**10**		
<28 kg/m^2	33	3	0.39 (0.082, 1.41)	0.180
Baseline mUFC severity 1 (Ref: Severe (> 5 x ULN))	**39**	**5**		
Moderate (> 2 x ULN and ≤ 5 x ULN)	26	7	2.51 (0.705, 9.5e+00)	0.159
Mild (≥ 1.5 x ULN and ≤ 2 x ULN)	12	1	0.62 (0.031, 4.4e+00)	0.676
Missing	5	0	NA	NA
Baseline mUFC severity 2 (Ref: > 2 x ULN)	**68**	**12**		
<= 2 x ULN	9	1	0.58 (0.03, 3.6e+00)	0.626
Missing	5	0	NA	NA
Prior Surgery (Ref: Yes)	**64**	**10**		
No	18	3	1.08 (0.22, 4.08)	0.915
Prior Medication (Ref: No)	**46**	**5**		
Yes	36	8	2.34 (0.71, 8.46)	0.170
Prior Irradiation (Ref: No)	**79**	**10**		
Yes	3	3	2.9e+08 (1.8e-121, NA)	NA
Time since diagnosis (Ref: <=46.8 months)	**48**	**4**		
>46.8 months	34	9	3.96 (1.16, 15.85)	0.035
CD status (Ref: Persistent/recurrent)	**67**	**11**		
De novo	15	2	0.78 (0.11, 3.40)	0.768

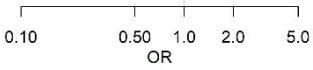


Figure 23: Forest plot of possible prognostic factors for Week 12 complete response in Lacroix 2018 (Pasireotide LAR)

Demographic	Patients	Events	OR (95% CI)	p-value
Age Group (Ref: <=47 years)	**55**	**14**		
>47 years	19	5	1.05 (0.30, 3.31)	0.941
Sex (Ref: Female)	**58**	**11**		
Male	16	8	4.27 (1.31, 14.27)	0.016
BMI (Ref: <28 kg/m^2)	**42**	**9**		
>=28 kg/m^2	32	10	1.67 (0.58, 4.85)	0.340
Baseline mUFC severity 1 (Ref: Moderate (> 2 x ULN and ≤ 5 x ULN))	**34**	**8**		
Mild (≥ 1.5 x ULN and ≤ 2 x ULN)	14	3	0.89 (0.170, 3.75)	0.875
< 1.5 x ULN	13	5	2.03 (0.497, 8.05)	0.311
Severe (> 5 x ULN)	7	1	0.54 (0.027, 3.88)	0.595
Missing	6	2	1.62 (0.199, 10.09)	0.611
Baseline mUFC severity 2 (Ref: > 2 x ULN)	**54**	**11**		
<= 2 x ULN	14	6	2.93 (0.82, 10.32)	0.091
Missing	6	2	1.95 (0.25, 11.46)	0.471
Prior Surgery (Ref: Yes)	**59**	**16**		
No	15	3	0.67 (0.14, 2.46)	0.575
Prior Medication (Ref: No)	**42**	**10**		
Yes	32	9	1.25 (0.43, 3.60)	0.674
Time since diagnosis (Ref: <=46.8 months)	**51**	**9**		
>46.8 months	23	10	3.59 (1.21, 11.00)	0.022
CD status (Ref: persistent/recurrent)	**59**	**16**		
de novo	15	3	0.67 (0.14, 2.46)	0.575

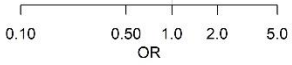
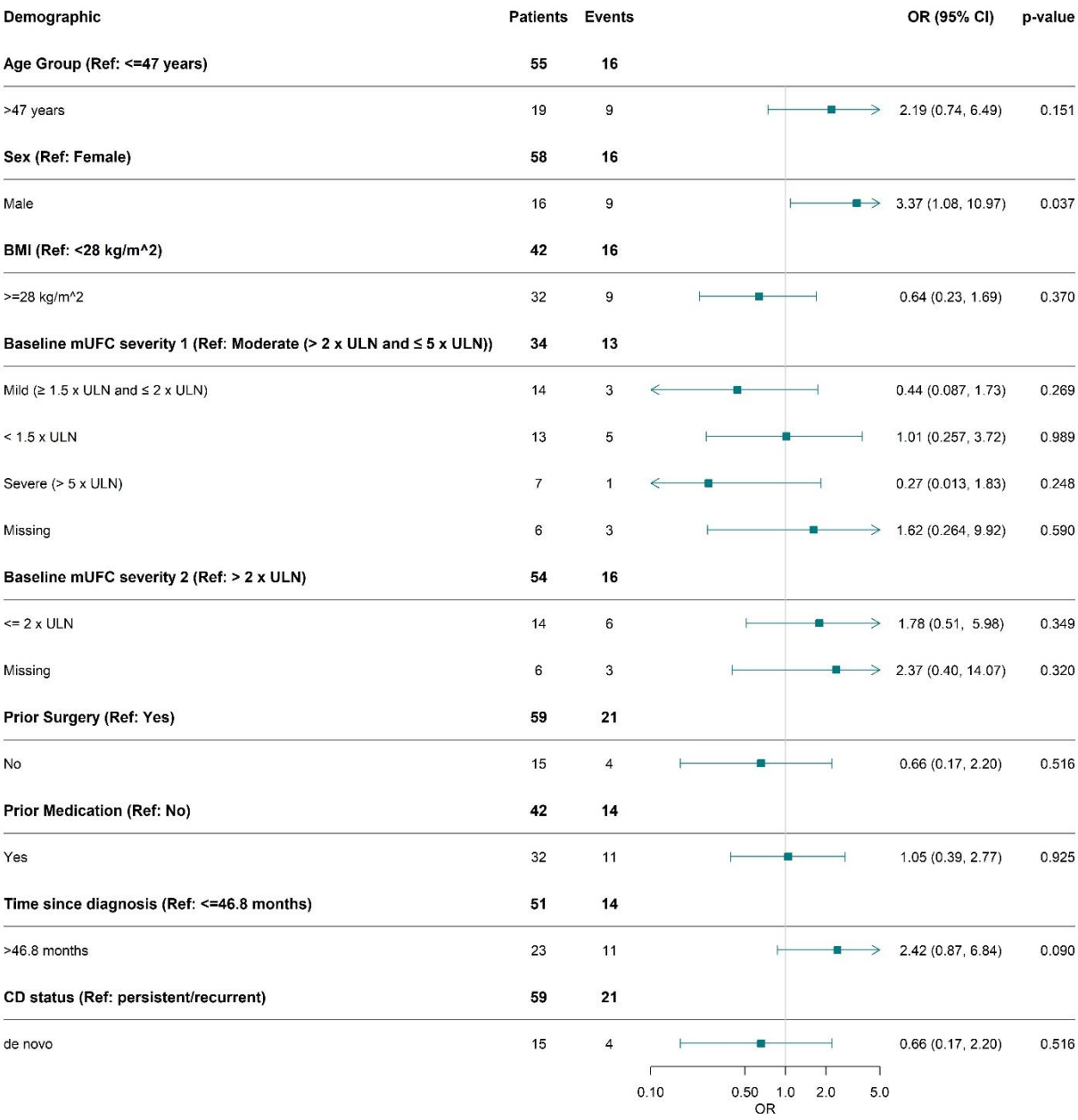


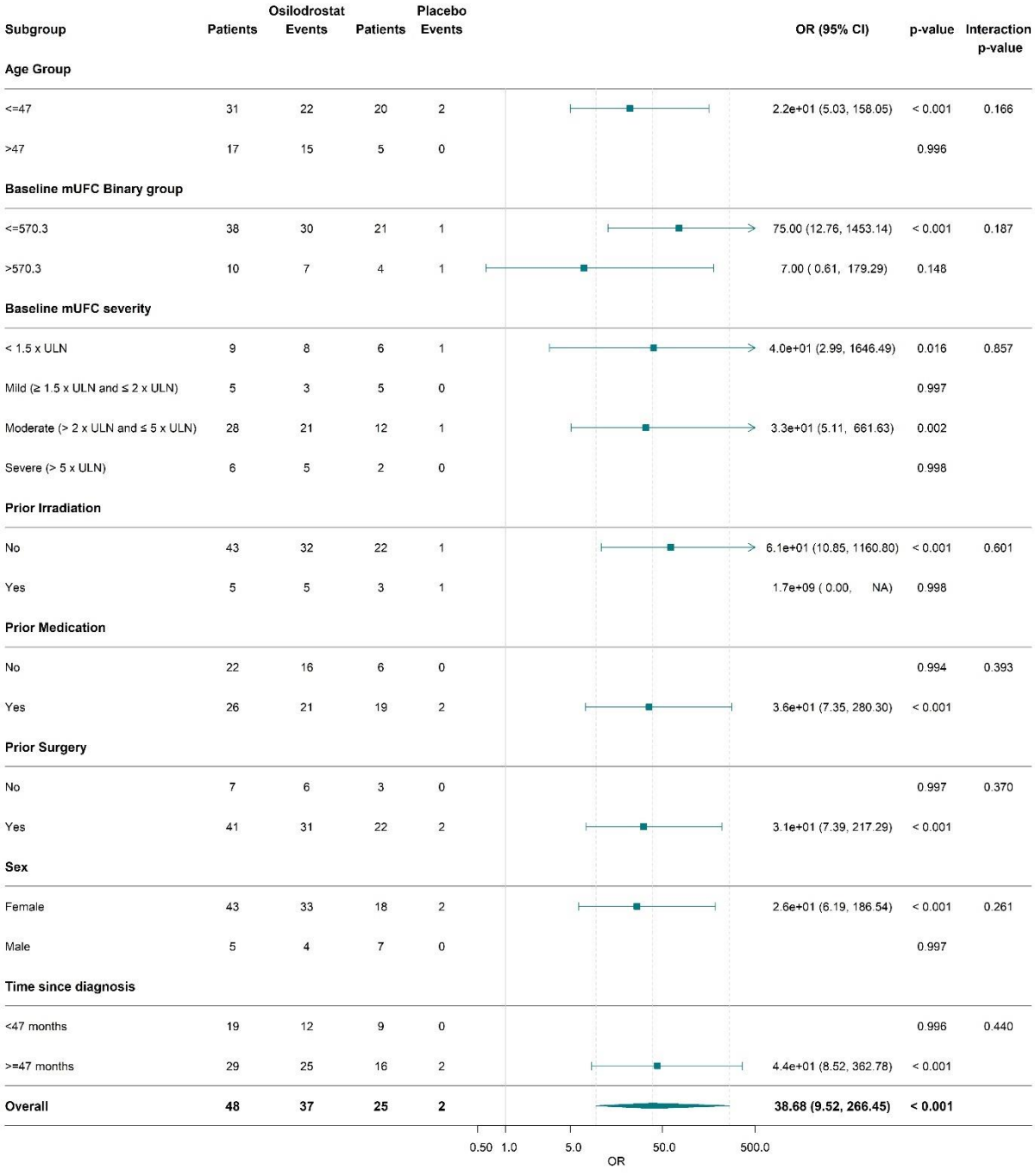
Figure 24: Forest plot of possible prognostic factors for Week 36 complete response in Lacroix 2018 (Pasireotide LAR)



Treatment effect modifiers

[redacted]

Figure 25: Forest plot of possible treatment effect modifiers for Week 12 complete response in LINC-4



Variables considered for MAIC analyses

[redacted]

[redacted]

[redacted]

Table 88: Summary of selection of baseline characteristics for inclusion as matching covariates in MAIC analyses

Characteristic	PROMPT data availability	Selected for matching	Rationale for inclusion/exclusion
Age	[redacted]	[redacted]	[redacted]
Sex	[redacted]	[redacted]	[redacted]
Time since diagnosis	[redacted]	[redacted]	[redacted]

Characteristic	PROMPT data availability	Selected for matching	Rationale for inclusion/exclusion
		[redacted]	
Baseline mUFC	[redacted]	[redacted]	[redacted]
Prior pituitary irradiation	[redacted]	[redacted]	[redacted]
Prior surgery	[redacted]	[redacted]	[redacted]
Prior medication	[redacted]	[redacted]	[redacted]
Race	[redacted]	[redacted]	[redacted]
BMI	[redacted]	[redacted]	[redacted]
CD status	[redacted]	[redacted]	[redacted]
Pituitary adenoma	[redacted]	[redacted]	[redacted]

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Characteristic	PROMPT data availability	Selected for matching	Rationale for inclusion/exclusion
			[redacted]

Key: BMI, body mass index; CD, Cushing's disease; CS, Cushing's syndrome; mUFC, mean urinary free cortisol; SD, standard deviation; ULN, upper limit of normal.

Scenario analyses considered

[redacted]

Table 89: Matching-adjusted indirect comparison – scenario analyses

Endpoint	Time point	mUFC included/excluded	Response derivation
Complete response	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]
		[redacted]	[redacted]
		[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]
		[redacted]	[redacted]
		[redacted]	[redacted]

Key: LOCF, last observation carried forward.

8.8.2 Matching-adjusted indirect treatment comparison results

Patient characteristics before and after matching

Table 90 presents a summary of the baseline patient characteristics before and after matching. For the analyses that did not adjust for baseline mUFC, the ESS for the weighted osilodrostat population was 30.2. When mUFC was included in the analysis, the ESS was reduced to 25.0. Characteristics are generally well-balanced after matching.

Table 90: Baseline characteristics before and after matching

Characteristic	Osilodrostat (LINC-4)			Metyrapone PROMPT N = 49
	Before matching (N = 48)	After matching		
		Incl baseline mUFC (ESS = 25)	Excl baseline mUFC (ESS = 30)	
Age (years)				
> 47 (%)	35.4	[redacted]	[redacted]	50.0
≤ 47 (%)	64.6	[redacted]	[redacted]	50.0
Sex				
Male	10.4	[redacted]	[redacted]	30.6
Female	89.6	[redacted]	[redacted]	69.4
Race				
White (%)	70.8	[redacted]	[redacted]	NR
Asian (%)	18.8	[redacted]	[redacted]	NR
Other (%)	10.4	[redacted]	[redacted]	NR
Pituitary adenoma (%)	100	[redacted]	[redacted]	NR
BMI (kg/m²)				
> 30.5 (%)	41.7	[redacted]	[redacted]	50.0
≤ 30.5 (%)	58.3	[redacted]	[redacted]	50.0
Baseline mUFC severity				
> 2 x ULN (%)	70.8	[redacted]	[redacted]	96.0
≤ 2 x ULN (%)	29.2	[redacted]	[redacted]	4.0
Time since diagnosis (months)				
> 46.8 (%)	62.5	[redacted]	[redacted]	50.0
≤ 46.8 (%)	37.5	[redacted]	[redacted]	50.0
Previous treatment for CD – n (%)				
Prior surgery	85.4	[redacted]	[redacted]	61.2
Prior medications	54.2	[redacted]	[redacted]	51.0
Prior irradiation	12.5	[redacted]	[redacted]	10.2
CD status				
De novo (%)	6.3	[redacted]	[redacted]	NR
Persistent/recurrent (%)	93.8	[redacted]	[redacted]	NR

Key: BMI, body mass index; CD, Cushing's disease; mUFC, mean urinary free cortisol; NR, not reported; ESS, effective sample size.

Derived patient weights

Figure 26 and Figure 27 show the distributions of weights and rescaled weights estimated by the MAIC scenarios including and excluding baseline mUFC as a matching characteristic, respectively. Some large weights were applied in both scenarios, this reflects the small number of osilodrostat patients and the limited overlap in LINC-4 and PROMPT populations with respect to some matching covariates.

Figure 26: Histogram of weights and rescaled weights for MAICs including baseline mUFC as a matching characteristic

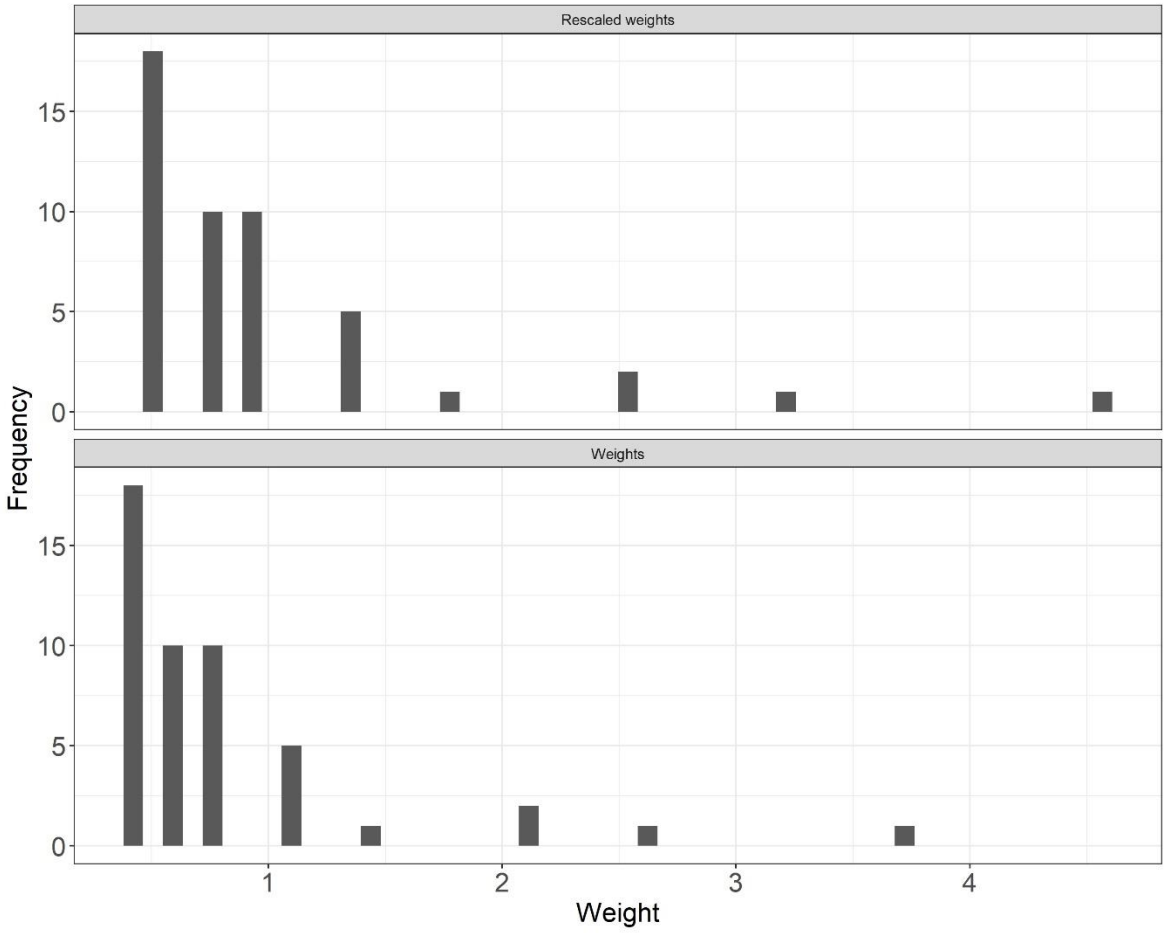
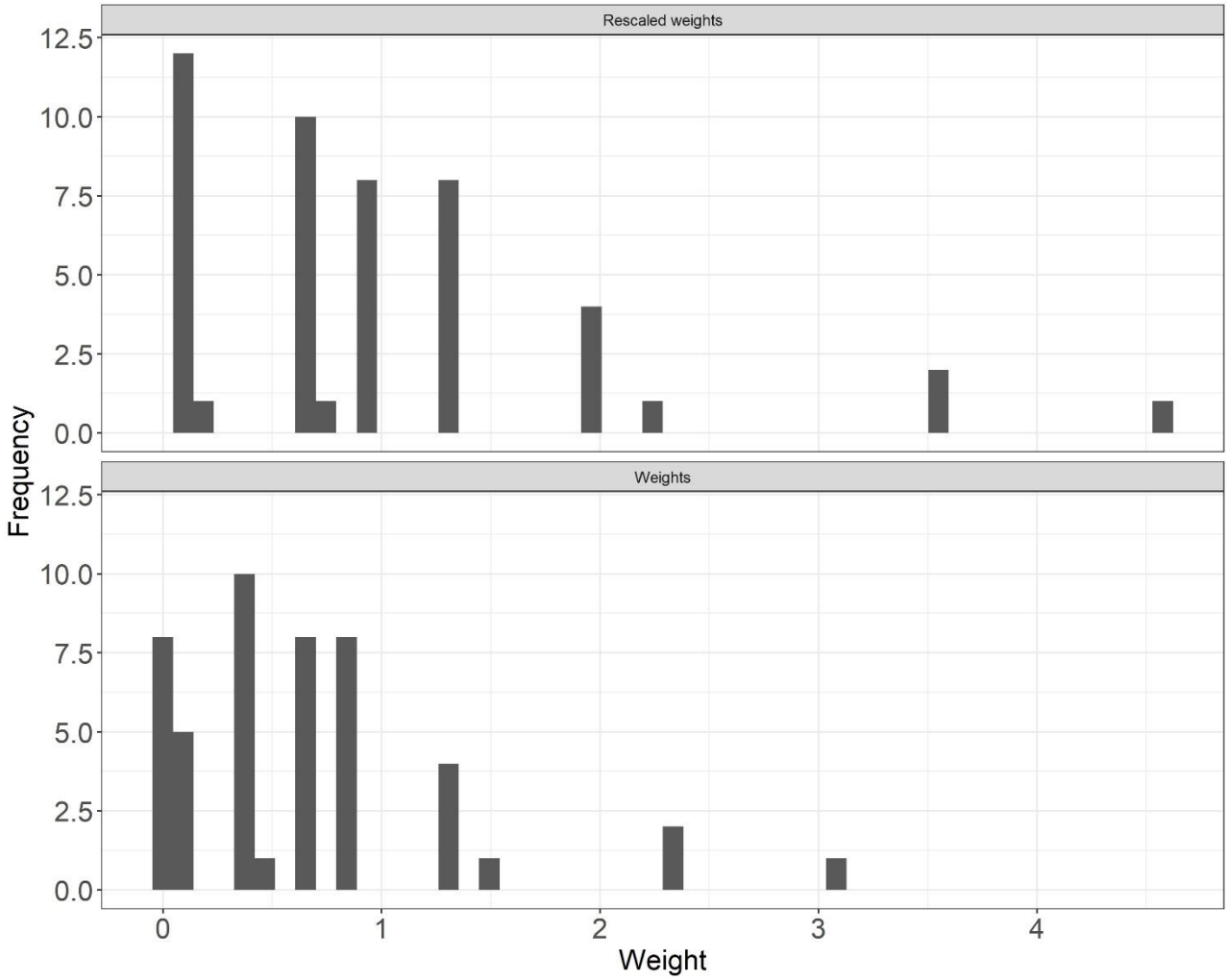


Figure 27: Histogram of weights and rescaled weights for MAICs excluding baseline mUFC as a matching characteristic



Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Cost-analysis and budget impact for the assessment of Isturisa® (osilodrostat) for endogenous Cushing's Syndrome

Submitted on: 22-12-2021

Validation update on: 21-04-2022

Abbreviations

Abbreviation	Definition
ACTH	Adrenocorticotropic hormone
AE	Adverse event
AIC	Akaike information criterion
BIC	Bayesian information criterion
BID	Twice a day
BLA	Bilateral adrenalectomy
CD	Cushing’s disease
CS	Cushing’s syndrome
EMA	European Medicines Agency
HR	Hazard ratio
HRQL	Health-related quality of life
HTA	Health technology assessment
INMB	Incremental net monetary benefit
ITC	Indirect treatment comparison
KM	Kaplan–Meier
LAR	Long-acting release
mUFC	Mean urinary free cortisol
PLD	Patient-level data
QoL	Quality of life
SC	Subcutaneous
SD	Standard deviation
SMR	Standardized mortality ratio
TSS	Transsphenoidal surgery
TTCR	Time to complete response
TTFPR	Time to treatment failure post-response
UFC	Urinary free cortisol
ULN	Upper limit of normal
VAS	Visual analogue scale

1. Background

1.1 Osilodrostat

Osilodrostat (Isturisa®) is a novel potent steroidogenesis inhibitor, blocking the activity of an enzyme involved in the production of cortisol called 11-beta-hydroxylase (CYP11B1). This reduces cortisol production and cortisol levels in the body, thereby relieving the symptoms of the disease. In January 2020, the EMA approved osilodrostat for the treatment of endogenous CS in adults.(1)

Evaluated in a robust Phase III randomized controlled study, osilodrostat has demonstrated compelling efficacy in terms of rapidly decreasing and sustaining control of cortisol levels compared with placebo while improving patient symptoms. In addition, as osilodrostat is an oral drug with a favourable safety profile, it offers an attractive new option for the treatment of CS.

1.2 Cost-effectiveness model

A global model was developed to support Recordati Rare's submissions to health technology assessment (HTA) bodies worldwide. This global model was adapted to the Danish setting. In accordance with the Danish guidelines a cost analysis with a budget impact model was developed.

2. Decision problem

2.1 Patient population

To follow the DMC protocol, the patient population are adult patients with endogenous Cushing's syndrome.

2.2 Market share

According to and using the DMC protocol between 20 to 30 new patients are expected to be treated annually for CS in Denmark. For the simplicity of the calculations, we have used an average of 25 new patients per year. Given that patients are treated up to two years on medical treatment, this has been used in the calculations. Therefore, in the first year it is expected that 25 CS patients are treated and the following years 50 patients per year. Assuming 25 new and 25 patients from the previous year. Using the estimated market shares (Table 1 and Table 2, respectively), creates Table 3 which shows the expected patients numbers in the scenario when osilodrostat is introduced, and Table 4 which shows the expected patient number in the scenario when osilodrostat is not introduced in the following five year time horizon.

The basis for the estimated market shares include internal documentation received from Pharma insights and Recordati internal assumptions. For simplification and given that pasireotide is also used for the treatment of acromegaly, there is a combined market share used including of pasireotide s.c. and pasireotide LAR together for the calculations in the budget impact.

Table 1: Estimated market shares when osilodrostat is introduced

Treatment	*Year 1*	*Year 2*	*Year 3*	*Year 4*	*Year 5*
Ketoconazole	23%	22%	21%	18%	17%
Metyrapone	32%	27%	25%	22%	20%
Pasireotide sc + LAR	37%	35%	34%	30%	29%
Osilodrostat	8%	16%	20%	30%	34%

Table 2: Estimated market shares when osilodrostat is not introduced

Treatment	*Year 1*	*Year 2*	*Year 3*	*Year 4*	*Year 5*
Ketoconazole	35%	31%	29%	27%	25%
Metyrapone	40%	42%	43%	44%	45%
Pasireotide sc + LAR	25%	27%	28%	29%	30%

Table 3: Patient numbers in the scenario when osilodrostat is introduced

Treatment	Year 1	Year 2	Year 3	Year 4	Year 5
Ketoconazole	8	14	13	11	10
Metyrapone	9	18	17	15	15
Pasireotide sc + LAR	6	11	11	9	9
Osilodrostat	2	8	10	15	17

Table 4: Patient numbers in the scenario when osilodrostat is not introduced

Treatment	Year 1	Year 2	Year 3	Year 4	Year 5
Ketoconazole	9	16	15	14	13
Metyrapone	10	21	22	22	23
Pasireotide sc + LAR	6	14	14	15	15
Osilodrostat	0	0	0	0	0

2.3 Intervention

The intervention considered in the cost analysis is osilodrostat.

Osilodrostat is available as tablets (1, 5 and 10 mg). The recommended starting dose is 2 mg osilodrostat twice daily, and the usual maintenance dose in clinical studies varied between 2 and 7 mg twice daily. The maximum recommended dose is 30 mg twice daily.(1)

2.4 Comparators

The medical therapies that are relevant comparators for this cost-analysis according to the DMC protocol are:

- Ketoconazole
- Metyrapone
- Pasireotide LAR
- Pasireotide SC

2.5 Analyses and outcomes

A cost and budget impact model were developed for the evaluation of the added cost of introducing osilodrostat for the treatment of CS. The cost analysis estimates to total cost per patient based on published unit costs and resource usage cost. The budget impact analysis employs the results of the cost analysis and estimates the annual cost difference in a five-year time horizon of two scenarios: when osilodrostat is introduced as a treatment of CS, and when osilodrostat is not introduced as a treatment of CS.

2.6 Perspective

To align with DMC guidelines all relevant costs associated with treatment and illness should be evaluated. Hence the model uses a societal perspective, accounting for lost productivity and carer costs. It was chosen not to include the travel costs to the hospital as it is assumed to be equal across the different treatments.

3. Model structure and settings

To inform the optimum modelling approach, a review of previously published economic models in CD and CS was conducted. This targeted search resulted in one poster available on the cost-effectiveness analysis of ketoconazole versus metyrapone from a Swedish perspective.(2) This study used a simple Markov model with health states describing the management and control of CD in terms of uncontrolled or controlled disease as measured by the level of urinary free cortisol.

In addition, a previous submission for pasireotide in CD in Finland was identified, but it was not possible to access this submission. No other relevant modelling studies were found.

3.1 Model structure

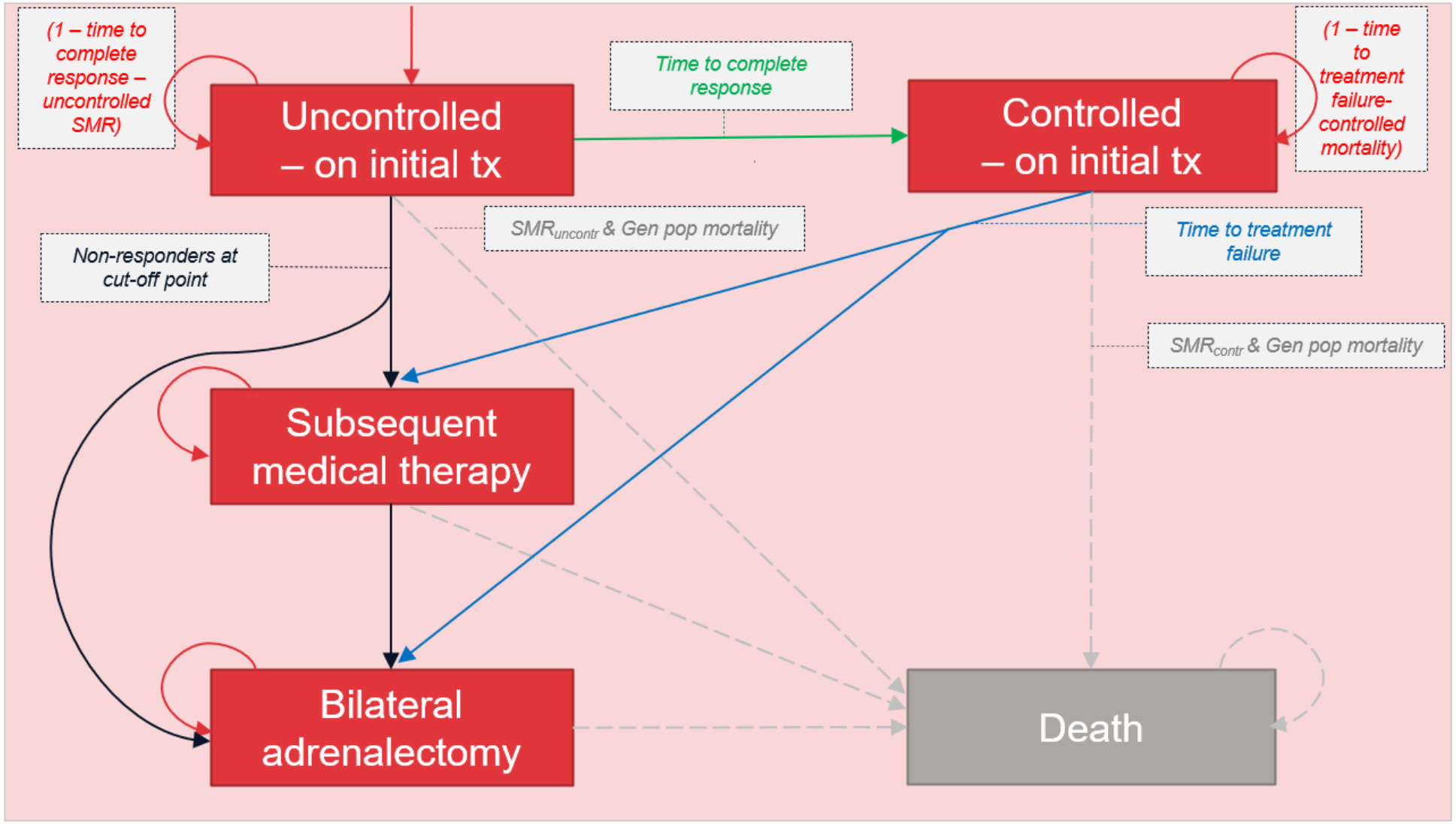
To assess the cost-effectiveness of osilodrostat, a cohort Markov state transition model has been developed in Microsoft Excel. For the purpose of this reimbursement submission the same approach has been used for the cost-analysis. The model splits the patient's health status into clearly defined, mutually exclusive health states, allowing the tracking of patients moving through the health states based on time to response data and time to treatment failure post-response. The health states defined in the model are:

- *Uncontrolled, on initial treatment*, defined by having mean urinary free cortisol (mUFC) > upper limit of normal (ULN)
- *Controlled, on initial treatment*, defined by patients having mean urinary free cortisol mUFC ≤ ULN
- *Subsequent medical therapy*, reflecting subsequent medical therapy provided in practice when no response occurs within the predetermined time cut-off point (6 months) or when controlled patients fail treatment
- *Bilateral adrenalectomy (BLA)*, as indicated by clinicians as the final treatment option for patients with CS
- *Death*, an absorbing health state

Time to response data and time to treatment failure post-response data are explicitly incorporated in the model structure to allow the model to capture rapid onset of response and prolonged duration in the controlled health state. In addition, it ensures that the health states align with the endpoints from the relevant clinical trials.

The health states and transitions between health states are described in more detail below. Figure 1 provides a visual representation of the model structure. Further details regarding the different health states can be found in the appendix 8.1.

Figure 1: Model structure



Key: SMR, standardized mortality ratio; tx, treatment.

3.1.1 Key features of the model

Table 5: Key features of the model

Elements	Rationale
All patients enter the model in the “uncontrolled – on initial tx” health state.	The patient population of interest consists of adult patients with uncontrolled CS because TSS or other first-line surgery did not achieve disease control or TSS or other first line surgery is contraindicated.
Patients who achieve response enter the “controlled - on initial tx” health state. Time to complete response data inform transitions from uncontrolled to controlled disease.	Long term comorbidities and quality of life are improved with complete response. Partial response is not taken into account as clinical experts have indicated that the decrease in mUFC with partial response is not enough to consider patients as normalized and does not yet provide health benefits. In addition, there is limited comparative evidence which reports the partial response rates for osilodrostat and comparators within the literature.
Patients in the “uncontrolled – on initial tx” health state who do not achieve response remain in the “uncontrolled – on initial tx” health state until the cut-off point.	Clinical experts have indicated that only after 6 months it is possible to evaluate whether a patient is controlled. Therefore, the model includes a cut-off point at 6 months, after which all remaining non-responders discontinue initial treatment. This approach means that discontinuation of initial treatment in the uncontrolled group is solely attributable to death or to lack of response at the cut-off point. We do not take patients discontinuing treatment before the cut-off point due to adverse events or lack of efficacy into account.
Patients in the “controlled – on initial tx” health state discontinue initial treatment due to treatment failure.	Time to treatment failure is a composite endpoint including discontinuation due to lack of efficacy, discontinuation due to adverse events, discontinuation due to physician's decision, treatment escape and death. Clinical experts have confirmed that patients discontinue medical therapy for these reasons. However, mortality in the trials was severely underestimated compared to general population mortality due to the low number of deaths observed in the trials. Therefore, time to treatment failure does not inform transitions to death. Instead, the economic model applies standardised mortality rates for patients in controlled disease versus the general population mortality.
Upon discontinuing initial treatment, patients either receive subsequent medical therapy or BLA.	There is no universal standard of care treatment pathway for CS patients for whom surgery did not achieve disease control or for whom surgery is contraindicated. Clinical experts have indicated that after initial medical therapy, the choice for a subsequent medical therapy is based on tailoring treatment to patient's and disease characteristics, and on balancing benefit and risk profiles of the different available treatments. BLA is the final treatment option and has a 100% response rate. The proportion of patients moving to subsequent medical therapy or BLA upon discontinuing initial treatment is based on clinician feedback. All patients receive subsequent medical therapy before moving to BLA.
The “subsequent medical therapy” health state consists of a mix of subsequent medical therapies and associated drug acquisition, drug administration and adverse events costs. HRQoL, comorbidity costs and resource use costs will depend on the weighted	Drug acquisition, drug administration and adverse event costs are related to the composition of the subsequent treatment basket. HRQoL, comorbidity costs and resource use costs are dependent on patients being uncontrolled or controlled, and therefore depend on the weighted response.

Elements	Rationale
% response of the subsequent treatment mix. Lack of evidence makes it infeasible and overly complex to model subsequent treatment lines explicitly and would add uncertainty.	
Patients stay in the subsequent medical therapy health state for an average duration of 12 months. After this treatment duration, all patients will move the BLA health state.	This average duration of 12 months is provided by clinical experts.
Radiotherapy and rTSS are not considered as subsequent treatments.	Clinicians have indicated that having rTSS after medical therapy is more of an exception than standard clinical practice. In addition, clinicians have indicated that radiotherapy should not be considered a competitor to medical therapy because it is generally combined with medical therapy given the uncertain and slow effect.
The “BLA” health state is considered a final health state with a 100% response rate until end of life.	Clinical experts have indicated that BLA is the final treatment option and has a 100% response rate (i.e. patients have controlled UFC levels until end of life). In addition, literature indicates increased risk of mortality during surgery, which supports the distinction between acute followed by chronic mortality risk.
Death is an absorbing state that can occur from all health states. Patients with uncontrolled disease have a higher mortality risk than controlled patients.	Patients with uncontrolled disease experience substantially higher comorbidity and mortality rates than controlled patients. Literature provides standardised mortality rates for patients in uncontrolled and controlled disease versus the general population mortality.
Key: AE, adverse event; BLA, bilateral adrenalectomy; CS, Cushing’s syndrome; HRQoL, health-related quality of life; mUFC, mean urinary free cortisol; rTSS, repeat transsphenoidal surgery; tx, treatment.	

3.2 Model settings

3.2.1 Time horizon

A time horizon of 2 years was adopted to ensure that all costs and health outcomes have been captured and is realistic to the actual duration of treatment in Denmark. This is aligned with the information described, based on the experience of a Danish clinician, in the clinical dossier of this application.

3.2.2 Cycle length

The model uses a cycle length of 1 week, which allows enough granularity to capture all relevant time to response and time to treatment failure events from patient-level data. As the model uses a cycle length of 1 week, a half-cycle correction is not required and, hence, is not applied within the model.

3.2.3 Discount rates

In line with the Danish guidelines, the costs are discounted at an annual rate of 4%.

4. Clinical data

Unfortunately, there were no head-to-head trials available to inform efficacy in the model as described in the clinical part of the submission. The data used to answer the questions as stated in the DMC protocol were not sufficient to develop a cost-effectiveness model. As previously mentioned, the global model was adapted to a cost-analysis in the Danish setting. Despite the lack of head-to-head data, there was patient-level data (PLD) available for the following studies:

- LINC-3 – osilodrostat;
- B2305B2305 trial (Colao et al., 2012) – pasireotide subcutaneous (SC);
- G2304 trial (Lacroix et al., 2018) – pasireotide long-acting release (LAR).

As a result, these data have been used as efficacy data for the model and a full description can be found in the appendix (section 8.2) of this economic report. The studies have been described in more details in the clinical dossier.

4.1 LINC-3

In LINC-3, patients who achieved a complete response without a dose increase entered the randomised withdrawal period at 26 weeks. As placebo is not a relevant comparator, patients who received placebo in this period are excluded from the efficacy analyses.

4.2 B2305 trial (Colao et al., 2012)

The pasireotide 900 mcg BID SC arm from the B2305 trial was excluded from the evidence base as the dose range does not align with the licensed dosage.

4.3 G2304 trial (Lacroix et al., 2018)

The pasireotide 30 mg LAR arm from the G2304 trial was excluded from the evidence base as it exceeds the initial licensed dose (10 mg).

5. Model inputs

5.1 Patient characteristics

The key baseline characteristics from the patient population that are used in the model are presented in **Table 6.** These are obtained from the osilodrostat LINC-3 trial.(3)

Table 6: Patient characteristics

Age (years)	41.2
Percentage female (%)	77%

5.2 Adverse events

5.2.1 Initial medical therapy

Relevant treatment-related Grade 3 or 4 AEs were identified by clinical experts. The number of patients experiencing these adverse events and the frequency of each adverse event for osilodrostat, pasireotide SC and pasireotide LAR are derived from the LINC-3 trial, the B2305 trial (Colao et al, 2012) and the G2304 trial (Lacroix et al, 2018), respectively. As no data are available on treatment-related Grade 3 or 4 adverse event inputs for ketoconazole and metyrapone, the model assumes that these treatments have the same safety profile as osilodrostat. However, functionality is included for the user to apply a ratio to account for any differences between the osilodrostat safety profile and the safety profile from ketoconazole and metyrapone.

Treatment-related Grade 3 or 4 adverse event inputs from the clinical trials are presented in Table 8. These inputs are calculated into adverse event rates per model cycle based on the mean time on treatment (weeks) from the trials, presented in Table 7.

Duration of adverse events is also included in the model and are presented in Table 9.

Table 7: Mean time on treatment (weeks)

	Osilodrostat (LINC 3 trial)	Pasireotide SC (B2305 trial)	Pasireotide LAR (G2304 trial)
Number of patients	137	82	74
Mean time on treatment (days)	639	508	593
Total time on treatment (weeks)	12467	5934	6244

Table 8: Adverse event medical therapies

Adverse event (grade 3+)	Patients who experienced the adverse event (n)			Number of times the adverse event is experienced per subject		
	Osilodrostat	Pasireotide SC	Pasireotide LAR	Osilodrostat	Pasireotide SC	Pasireotide LAR
Abdominal pain	1	1	1	1	1	1
Adrenal insufficiency	5	0	1	2	NA	1
Alanine aminotransferase increased	0	1	1	NA	1	1
Blood glucose increased	1	0	1	1	NA	1
Diabetes mellitus	0	8	9	NA	1	1
Diarrhoea	0	3	0	NA	2	NA
Glucocorticoid deficiency	5	0	0	2	NA	NA
Glycosylated haemoglobin increased	0	1	0	NA	1	NA
Hepatotoxicity	0	0	0	NA	NA	NA
Hirsutism	0	0	0	NA	NA	NA
Hyperglycaemia	0	7	7	NA	1	2
Hypertension	7	0	2	1	NA	1
Hypokalaemia	2	0	0	1	NA	NA
Hypotension	0	0	0	NA	NA	NA
Nausea	2	1	1	1	1	1
Oedema peripheral	0	0	0	NA	NA	NA
Vomiting	3	0	0	1	1	NA
Key: NA, not applicable.						

Table 9: Duration of adverse events (days)

Adverse event (grade 3+)	Osilodrostat			Pasireotide SC			Pasireotide LAR		
	Mean	SD	N	Mean	SD	N	Mean	SD	N
Abdominal pain	4	NR	1	2	NR	1	52	NR	1
Adrenal insufficiency	18.8	13.23	8	NA	NA	NA	18	NR	1
Alanine aminotransferase increased	NA	NA	NA	7	NR	1	54	NR	1
Blood glucose increased	1279	NR	1	NA	NA	NA	29	NR	1
Diabetes mellitus	NA	NA	NA	424.2	563.28	10	192.2	87.32	1
Diarrhoea	NA	NA	NA	23	23.86	6	NA	NA	NA
Glucocorticoid deficiency	17.2	8.27	11	NA	NA	NA	NA	NA	NA
Glycosylated haemoglobin increased	NA	NA	NA	33	NR	1	NA	NA	NA
Hepatotoxicity	NA	NA	NA	NA	NA	NA	NA	NA	NA
Hirsutism	NA	NA	NA	NA	NA	NA	NA	NA	NA
Hyperglycaemia	NA	NA	NA	92.4	82.89	7	96.5	102.49	11
Hypertension	295.8	488.86	8	NA	NA	NA	77	9.9	2
Hypokalaemia	17	4.24	2	NA	NA	NA	NA	NA	NA
Hypotension	NA	NA	NA	NA	NA	NA	NA	NA	NA
Nausea	19.5	16.26	2	50	NR	1	10	NR	1
Oedema peripheral	NA	NA	NA	NA	NA	NA	NA	NA	NA
Vomiting	3.7	3.79	3	50	NR	1	NA	NA	NA

Key: SD, standard deviation; N, number; NA, not applicable; NR, not reported.

5.2.2 Subsequent medical therapy basket

Adverse event rates per model cycle in the subsequent medical therapy basket are weighted based on the mix of subsequent medical therapies and the adverse events identified for the initial medical therapies.

5.2.3 BLA

Relevant complications associated with BLA were identified by clinical experts and presented in Table 10. The model includes the functionality to base the proportion of patients experiencing each complication on published estimates from literature or on user-defined inputs, which currently include inputs based on feedback from clinical experts. The model uses the user-defined inputs from clinical experts.

The duration of each complication is estimated by clinical experts. The average duration of a wound infection is set at 10 days, whereas Nelson syndrome and chronic pain have been identified by clinical experts as being chronic complications.

Table 10: Complications of BLA

Type of complication	Patients who experienced the complication (%)		Duration of the complication (days)*	Reference
	Published estimate	User-defined		
Nelson syndrome	43%	25%	Chronic	Reincke et al. (2021) (4); User-defined input based on clinical expert input
Wound infection	10%	10%	10	Pivonello et al. (2015) (5); User-defined input based on clinical expert input
Chronic pain	NR	5%	Chronic	User-defined input based on clinical expert input

Key: BLA, bilateral adrenalectomy.
Notes: *Estimates from clinical experts.

5.3 Costs

5.3.1 Treatment costs

The dosing schedule for each medical treatment considered in the model are presented in Table 11. The mean dose per administration for osilodrostat, pasireotide SC and pasireotide LAR is obtained from dose distribution tables from the relevant trials, presented in Appendix 8.6.

The mean dose per administration for ketoconazole and metyrapone is obtained from literature. The dose for metyrapone is based on the newest prospective data where at Wk36 metyrapone dose was higher in mUFC 2-fold ULN group than others (2357 vs 1618-1750 mg/d). The weighted

average could be calculated as mUFC was normal in 17 patients, < 2 × ULN in 11 and ≥ 2× ULN in 7 (6). Therefore the weighted average median dose is: (2357*7+1750*11+1618*17)/(7+11+17)= 1807.3 mg/day. Including waste results in a daily dose of 2000mg with metyrapone.

Table 11: Dosing schedule

Drug therapy	Dosing per admin as per indication (mg)	Mean dose per admin (mg)		Dosing frequency	Admin method	Reference
		Mean	Range			
Osilodrostat	2–30 mg	See Appendix 8.6		Twice daily	Oral (self)	EMA (2021) (1)
Pasireotide SC	0.3–0.9 mg	See Appendix 8.6		Twice daily	SC injection (self)	EMA (2021) (7)
Pasireotide LAR	10–40 mg	See Appendix 8.6		Every 4 weeks	Deep intramuscular injection (healthcare professional)	EMA (2021) (7)
Ketoconazole	400–1200 mg	800	200-1200	Daily	Oral (self)	EMA (2021)(8); Castinetti et al. 2014: mean final dose at last follow-up (779) including waste
Metyrapone	250–6000 mg	2000	500-4000	Daily	Oral (self)	Dutch Geneesmiddelen informatiebank (2021) (9); Nieman et al. 2021 PROMPT 36 week data shows a weighted average median dose of 1807.3mg/day thus including waste is is 2000mg

Key: EMA, European Medicines Agency; LAR, long-acting release; NA, not available; SC, subcutaneous.

The unit costs of each medical treatment considered in the model are presented in Table 12. The unit costs for each drug administration method are presented in Table 13. Table 14 presents the drug acquisition and drug administration costs per model cycle. Initial medical therapy drug acquisition and drug administration costs are applied per model cycle as long as patients are on initial medical therapy (either uncontrolled or controlled).

Drug acquisition and drug administration in the subsequent medical therapy basket are weighted based on the mix of subsequent medical therapies. These weighted costs are applied in the model per cycle for 12 months, which is the average treatment duration of the subsequent medical therapy basket, based on clinician feedback.

Table 12: Drug acquisition unit costs

Drug therapy	Dose per unit (mg, mg/ml or mg/vial)		Units per pack (number of tablets, capsules, ampules or vials)		Cost per pack (kr)	Reference
Osilodrostat	1	mg	60	tablets	11 890.00 DKK	www.medicinpriser.dk Accessed 28.11.2021. PPP excl. VAT
	5	mg	60	tablets	47 568.00 DKK	
	10	mg	60	tablets	49 948.00 DKK	
Pasireotide SC	0.3	mg	60	amps	NA	NA
	0.6	mg	60	amps	23 615.72 DKK	www.medicinpriser.dk Accessed 28.11.2021. PPP excl. VAT
	0.9	mg	60	amps	NA	NA
Pasireotide LAR	10	mg	1	vial	NA	NA
	20	mg	1	vial	22 102.22 DKK	www.medicinpriser.dk Accessed 28.11.2021. PPP excl. VAT
	30	mg	1	vial	NA	NA
	40	mg	1	vial	22 102.22 DKK	www.medicinpriser.dk Accessed 28.11.2021. PPP excl. VAT
	60	mg	1	vial	22 102.22 DKK	www.medicinpriser.dk Accessed 28.11.2021. PPP excl. VAT
Ketoconazole	200	mg	60	tablets	4 800.00 DKK	www.medicinpriser.dk Accessed 28.11.2021. PPP excl. VAT
Metyrapone	250	mg	50	caps	2 316.60 DKK	www.medicinpriser.dk Accessed 28.11.2021. PPP excl. VAT

Key: mg, milligram; ml, millilitre; NA, not available, PPP: pharmacy purchase price

Table 13: Drug administration unit costs

Administration method		Unit cost (kr)	Reference
Oral (self)		0.00 DKK	Assume no administration costs for oral (self) administration
Subcutaneous injection (self)	First admin	146.79 DKK	Assume first admin is equal to a GP visit in the outpatient clinic for training
	Subsequent admins	0.00 DKK	Assume no administration costs for subsequent subcutaneous self-injections
Deep intramuscular injection (healthcare professional)		146.79 DKK	Södra Regionvårdsnämnden (2021) (10). Sjukvårdande behandling (price incl medical service)

Key: GP, general practitioner.

Table 14: Drug costs per model cycle

Drug therapy		Drug acquisition costs - per model cycle	Drug administration costs - per model cycle
Osilodrostat		[redacted]	0 DKK
Pasireotide SC	First model cycle	[redacted]	147 DKK
	Subsequent model cycles		0 DKK
Pasireotide LAR*		[redacted]	147 DKK
Ketoconazole		[redacted]	0 DKK
Metyrapone		[redacted]	0 DKK
Mifepristone		NA	NA
Note: * The drug acquisition and drug administration costs presented here for pasireotide LAR are applied once per 4 weeks instead of each model cycle.			

BLA costs are applied in the model as one-off costs upon patients receiving BLA surgery. The costs of BLA are presented in Table 15.

Table 15: BLA unit cost

Medical procedure	Unit cost (kr)	Reference
BLA	67 544 DKK	Takstystem 2021. Surgery on the adrenal glands and pituitary gland, DRG code 10MP02. p52
Key: BLA, bilateral adrenalectomy		

5.3.2 Adverse event costs

Resource use related to AEs are presented in Section 5.2. The unit costs related to AEs are presented in Table 16. Initial medical therapy AE costs are applied per model cycle as long as patients are on initial medical therapy (either uncontrolled or controlled).

AE costs in the subsequent medical therapy basket are weighted based on the mix of subsequent medical therapies. These weighted costs are applied in the model per cycle for 12 months, which is the average treatment duration of the subsequent medical therapy basket, based on clinician feedback.

Table 16: Adverse events medical therapies unit costs

Adverse event (grade 3+)	Unit cost (DKK) - per event	Reference
Abdominal pain	146.79 DKK	Honorartabel, Apr-Sep 2021. https://www.laeger.dk/sites/default/files/honorartabel_01.04.2021.pdf. Primary care, general practitioner, 0101. Paragraph 50, p1.
Adrenal insufficiency	21 801.00 DKK	Takstystem 2021. Pituitary, adrenal, gonadal and other endocrine diseases, DRG code 10MA05. p52.

Adverse event (grade 3+)	Unit cost (DKK) - per event	Reference
Alanine aminotransferase increased	146.79 DKK	Honorartabel, Apr-Sep 2021. https://www.laeger.dk/sites/default/files/honorartabel_01.04.2021.pdf. Primary care, general practitioner, 0101. Paragraph 50, p1.
Blood glucose increased	146.79 DKK	
Diabetes mellitus	28 863.00 DKK	Takstystem 2021. Diabetes mellitus, DRG code 10MA03. p53.
Diarrhoea	146.79 DKK	Honorartabel, Apr-Sep 2021. https://www.laeger.dk/sites/default/files/honorartabel_01.04.2021.pdf. Primary care, general practitioner, 0101. Paragraph 50, p1.
Glycosylated haemoglobin increased	146.79 DKK	
Hypocortisolism	146.79 DKK	
Hepatotoxicity	33 590.00 DKK	Takstystem 2021. Acute infectious or toxic liver disease, DRG code 07MA06. p47.
Hirsutism	146.79 DKK	Honorartabel, Apr-Sep 2021. https://www.laeger.dk/sites/default/files/honorartabel_01.04.2021.pdf. Primary care, general practitioner, 0101. Paragraph 50, p1.
Hyperglycaemia	146.79 DKK	Honorartabel, Apr-Sep 2021. https://www.laeger.dk/sites/default/files/honorartabel_01.04.2021.pdf. Primary care, general practitioner, 0101. Paragraph 50, p1.
Hypertension	1 431,90 DKK	Takstystem 2021. Hypertension, DRG code 05MA11. p43.
Hypokalaemia	146.79 DKK	Honorartabel, Apr-Sep 2021. https://www.laeger.dk/sites/default/files/honorartabel_01.04.2021.pdf. Primary care, general practitioner, 0101. Paragraph 50, p1.
Hypotension	146.79 DKK	
Nausea	146.79 DKK	
Oedema peripheral	146.79 DKK	
Vomiting	146.79 DKK	

Resource use related to BLA complications are presented in section 5.2.3 (Table 10). The unit costs for these complications are presented in Table 17. These costs are applied in the model as one-off costs upon patients receiving BLA surgery.

Table 17 BLA complications unit costs

Type of complication	Unit cost (DKK) - per event	Reference
Nelson syndrome	19 645.00 DKK	Takstystem 2021. Surgery of cerebral nerves, peripheral nerves and nervous system in general, without complications, DRG code 01MP06. p39. CONFRIM - complicated 01MP05
Wound infection	27 594.00 DKK	Takstystem 2021. Postoperative and post-traumatic infections without complications, DRG code 18MA03. p59.
Chronic pain	0.00 DKK	Assume no costs as treated with painkillers

5.3.3 Comorbidity costs

Patients with CS often experience multiple comorbidities, with the risk of comorbidities being raised substantially if cortisol levels are not stabilized. The model therefore considers the incidence of acute and chronic comorbidities associated with uncontrolled and controlled disease. The relevant acute and chronic comorbidities for CS were identified by clinical experts. Acute comorbidities are assumed to be associated with one-time costs, whereas the chronic comorbidities are assumed to have recurring costs.

Resource use related to comorbidities are presented in Section 8.3. The unit costs related to acute and chronic comorbidities are presented in Table 18 and Table 19, respectively. Uncontrolled comorbidity costs are applied per model cycle as long as patients are uncontrolled on initial medical therapy. Controlled comorbidity costs are applied per model cycle as long as patients are controlled on initial medical therapy.

Comorbidity costs in the subsequent medical therapy basket are weighted depending on the percentage of patients responding to the subsequent treatment basket. These weighted costs are applied in the model per cycle for 12 months, which is the average treatment duration of the subsequent medical therapy basket, based on clinician feedback.

As patients in the BLA health state are controlled (i.e. 100% response rate), the comorbidity cost per model cycle in the BLA health state is equal to the comorbidity cost per model cycle in the controlled disease health state.

Table 18: Acute comorbidities unit costs

Acute comorbidities	Unit cost (DKK) - per event	Reference
Cardiovascular events	34 010.00 DKK	Takstystem 2021. Other heart diseases, procedure group B. DRG code 05MP53
Myocardial infarction	18 295.00 DKK	Takstystem 2021. Acute myocardial infarction with ST segment elevation, DRG code 05MA01. p43.
Stroke	32 320.00 DKK	Takstystem 2021. Thrombolysis treatment of acute stroke, DRG code 01MP11. p39.
Venous thromboembolism	20 692.00 DKK	Takstystem 2021. Peripheral vascular disease, DRG code 05MA12. p43.
Pneumonia	25 695.00 DKK	Takstystem 2021. Pneumonia pat. age 18-59, DRG code 04MA14. p43.
Skin infection	11 157.00 DKK	Takstystem 2021. Mild or moderate skin disease without complications, DRG code 09MA03. p.51
Muscle weakness	146.79 DKK	Honorartabel, Apr-Sep 2021. https://www.laeger.dk/sites/default/files/honorartabel_01.04.2021.pdf. Primary care, general practitioner, 0101. Paragraph 50, p1.
Hirsutism	146.79 DKK	
Sexual dysfunction	146.79 DKK	
Sleep disturbance	146.79 DKK	
Sepsis	42 770.00 DKK	Takstystem 2021. Sepsis, DRG code 18MA01. p59.

Table 19: Chronic comorbidities unit costs

Chronic comorbidities	Unit cost (DKK) - per year	Reference
Diabetes mellitus	28 863.00 DKK	Takstystem 2021. Diabetes mellitus, DRG code 10MA03. p53.
Metabolic syndrome	1 236.00 DKK	Assume equal to overweight or obese as the most important symptom of metabolic syndrome is weight gain
Overweight or obese	1 236.00 DKK	Medicinrådet, Værdisætning af enhedsomkostninger (https://medicinraadet.dk/media/weslftgk/vaerdisaetning-af-enhedsomkostninger-vers-13_adlegacy.pdf). Dietist / nutritionist. Table 2, p6. 412 DKK/hour. Assumption 3 visits/year. CONFIRM+UPDATE TO 2021. Litterature yearly?
Anxiety	58 972.00 DKK	Vestergaard Set al. (2020) (11)
Depression	77 832.00 DKK	Vestergaard et al. (2020) (11)
Osteoporosis	3 453.00 DKK	Svedbom et al (2013) (12)
Muscle weakness	146.79 DKK	Honorartabel, Apr-Sep 2021. https://www.laeger.dk/sites/default/files/honorartabel_01.04.2021.pdf. Primary care, general practitioner, 0101. Paragraph 50, p1.
Hirsutism	146.79 DKK	
Sexual dysfunction	146.79 DKK	
Sleep disturbance	146.79 DKK	
Sepsis	42 770.00 DKK	Takstystem 2021. Sepsis, DRG code 18MA01. p59.

5.3.4 Resource use costs

Resource use related to monitoring per health state is presented in Table 20. All these inputs are estimated by clinical experts. A distinction is made between resource use during BLA surgery and/or recovery and chronic resource use needs after BLA until end of life. The resource use needs during BLA represent additional resource use costs that are not captured in BLA unit costs.

The resource use unit costs are presented in Table 21.

Resource use costs in the subsequent medical therapy basket are weighted depending on the percentage of patients responding to the subsequent treatment basket. These weighted costs are applied in the model per cycle for 12 months, which is the average treatment duration of the subsequent medical therapy basket, based on clinician feedback.

Table 20: Resource use

Resource use	Uncontrolled disease (per year)	Controlled disease (per year)	After BLA surgery and/or recovery (chronic) (per year)	During BLA surgery and/or recovery (first 28 days)*
Endocrinologist	8	2	2	1
Other physician	5	2	2	0
Outpatient visit**	8	2	2	0
Emergency room	3	2	0.5	0.25
Hospital stay	18	4	1	4
Brain MRI	2	0.5	1	0
CT scan	0	0	0	0
ACTH test	8	4	2	1
24hr UFC test	6	0	0	0
Serum cortisol test	16	6	1	1
NA, K, creatinine	18	8	2	2
Testosterone test	1	2	1	0
Liver function test				
Glucose level test	4	2	2	10

Key: BLA, bilateral adrenalectomy; MRI, Magnetic resonance imaging; CT, computerised tomography; ACTH, Adrenocorticotropic hormone; UFC, urinary free cortisol; NA, sodium; K, potassium; TSH, Thyroid-stimulating hormone; IGF-1, Insulin-like growth factor 1.

* Additional resource use that is not captured in BLA unit costs

** Excluding endocrinologist or other physician

Table 21: Resource use unit costs

Resource use	Unit cost (DKK)- per visit	Reference
Endocrinologist	323.44 DKK	Medicinrådet, Værdisætning af enhedsomkostninger (https://medicinraadet.dk/media/weslftgk/vaerdisaetning-af-enhedsomkostninger-vers-13_adlegacy.pdf). Consultation with a specialist in internal medicine. 646,87 DKK/hour. P14. Assumption 30 minutes/visit.
Other physician	740.50 DKK	Medicinrådet, Værdisætning af enhedsomkostninger (https://medicinraadet.dk/media/weslftgk/vaerdisaetning-af-enhedsomkostninger-vers-13_adlegacy.pdf). Leading chief physician / professor. 1481 DKK/hour. p13. Assumption 30 minutes/visit.
Outpatient visit	146.79 DKK	Honorartabel, Apr-Sep 2021. https://www.laeger.dk/sites/default/files/honorartabel_01.04.2021.pdf. Primary care, general practitioner, 0101. Paragraph 50, p1.
Emergency room	2 155.00 DKK	Assume that is the same as hospital stay.
Hospital stay	2 155.00 DKK	Takstystem 2021. 3.1.1. DRG-rates p15.
Brain MRI	2 319.00 DKK	Takstystem 2021. MR scanning non complicated, DRG code 30PR03. p64.

Resource use	Unit cost (DKK)- per visit	Reference
CT scan	1 835.00 DKK	Takstystem 2021. CT scanning non complicated, DRG code 30PR07. p64.
ACTH test	130.00 DKK	Rigshospitalets Labportal (https://labportal.rh.dk/Metodeliste.asp). P-kortikotropin (CORTIC). External price.
24hr UFC test	336.00 DKK	Rigshospitalets Labportal (https://labportal.rh.dk/Metodeliste.asp). U-Kortisol frit (UCORTFRI). External price.
Serum cortisol test	109.00 DKK	Rigshospitalets Labportal (https://labportal.rh.dk/Metodeliste.asp). P-kortisol (CORT45). External price
NA, K, creatinine	63.00 DKK	Rigshospitalets Labportal (https://labportal.rh.dk/Metodeliste.asp). P-Kalium, P-Natrium, P-kreatinin. 17+17+29 DKK. External price.
Testosterone test	95.00 DKK	Rigshospitalets Labportal (https://labportal.rh.dk/Metodeliste.asp). P-Testosteron (TESTO). External price.
Liver function test	87.00 DKK	Rigshospitalets Labportal (https://labportal.rh.dk/Metodeliste.asp). P-Aspartattransaminas (ASAT), P-Alanintransaminas (ALAT), P-Bilirubiner (BILI). 29+29+29 DKK. External price.
Glucose level test	55.34 DKK	Takstkort 29A, April 2021. https://www.laeger.dk/sites/default/files/generellelaboratorieundersoegelser_takstkort_pr_040121.pdf. P-glucose (7113)
Key: Key: MRI, Magnetic resonance imaging; CT, computerised tomography; ACTH, Adrenocorticotropic hormone; UFC, urinary free cortisol; NA, sodium; K, potassium; TSH, Thyroid-stimulating hormone; IGF-1, Insulin-like growth factor 1.		

5.3.5 Societal Costs

Societal costs are included for the Danish cost analysis. The model has the functionality to include or exclude these costs. Patient productivity costs are taken into account by considering the weighted average proportion of patients working in the trial based on age distribution in the trial (Table 22), the proportion of working time lost due to the disease (Table 23), the average wage in Denmark and the average working hours per week in Denmark. An average working week is assumed to consist of 32.5 hours per week, based on data from Statista (13). According to Medicinrådet, the average wage is 179.00 DKK per hour.

The proportion of potential working time lost due to disease, are estimates based on clinical expert feedback. In the uncontrolled health state, patients cannot work so it is assumed that 100% of patients are on sick leave. In the controlled health state, approximately 20% of patients are not able to work. The same holds for controlled patients in the BLA health state. However, the model also takes into account that 100% of patients are not able to work for the first 9 months after BLA surgery. This is applied in the model as a one-off cost.

Table 22: Proportion of patients working

Age group	Patients in trial (%)	Percentage who work (in general population)	Reference
18-24	11%	53%	https://www.dst.dk/en/
25–34	20%	77%	
35–44	33%	84%	
45–54	18%	85%	
55–64	14%	71%	
65+	5%	0%	
Weighted proportion		73%	

Table 23: Proportion of potential working time lost due to disease (%)

Health state	Proportion of potential working time lost due to disease - per week (%)	Reference
Uncontrolled - on initial tx	100%	KOL inputs: Dutch clinical experts Professor Feelders and Professor Neggers (internist-endocrinologists from the Erasmus Medical Center in the Netherlands)
Controlled - on initial tx	20%	
During BLA surgery and/or recovery (one-off)	100%	
Controlled after BLA surgery and/or recovery (chronic)	20%	
Key: BLA, bilateral adrenalectomy; KOL, key opinion leader; tx, treatment.		

Carer costs are also taken into account. However, all inputs related to carer costs are based on assumptions as no evidence was available. It is assumed that 70% of carers are working. The proportion of patients who require a carer, and the number of care hours needed per health state, are presented in Table 24.

Table 24: Carer resource use

Health state	Proportion of patients who require a carer (%)	Hours of care required (per week)	Reference
Uncontrolled - on initial tx	25%	8	Assumptions
Controlled - on initial tx	25%	0	
During BLA surgery and/or recovery (one-off)	25%	8	
Controlled after BLA surgery and/or recovery (chronic)	0%	0	
Key: BLA, bilateral adrenalectomy; tx, treatment.			

Societal costs in the subsequent medical therapy basket are weighted depending on the percentage of patients responding to the subsequent treatment basket. These weighted costs are applied in the model per cycle for 12 months, which is the average treatment duration of the subsequent medical therapy basket, based on clinician feedback.

6. Results

6.1 Results generated by the cost-analysis

The cost analysis results are calculated using the inputs as described in the previous sections.

6.1.1 Discounted and undiscounted results

Table 25: Discounted deterministic base-case results

Treatment	Total costs (DKK)	Incremental costs (DKK)
Pasireotide SC	[redacted]	[redacted]
Osilodrostat	[redacted]	
Pasireotide LAR	[redacted]	[redacted]
Osilodrostat	[redacted]	
Ketoconazole	[redacted]	[redacted]
Osilodrostat	[redacted]	
Metyrapone	[redacted]	[redacted]
Osilodrostat	[redacted]	

Table 26: Undiscounted deterministic base-case results

Treatment	Total costs (DKK)	Incremental costs (DKK)
Pasireotide SC	[redacted]	[redacted]
Osilodrostat	[redacted]	
Pasireotide LAR	[redacted]	[redacted]
Osilodrostat	[redacted]	
Ketoconazole	[redacted]	[redacted]
Osilodrostat	[redacted]	
Metyrapone	[redacted]	[redacted]
Osilodrostat	[redacted]	

6.1.2 Disaggregated costs

Table 27: Discounted disaggregated costs per treatment

Category	Osilodrostat	Pasireotide SC	Pasireotide LAR	Ketoconazole	Metyrapone
Initial treatment					
Drug acquisition	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug administration	0 DKK	147 DKK	1404 DKK	0 DKK	0 DKK
Adverse events	715 DKK	1 360 DKK	1673 DKK	312 DKK	328 DKK
Comorbidity Uncontrolled	2 526 DKK	7 569 DKK	6 196 DKK	2 924 DKK	3 346 DKK
Comorbidity Controlled	10 233 DKK	1 984 DKK	5 092 DKK	3 265 DKK	3 246 DKK
Resource Use Uncontrolled	8 083 DKK	24 218 DKK	19 823 DKK	9 355 DKK	10 707 DKK
Resource Use Controlled	14 530 DKK	2 817 DKK	7 230 DKK	4 636 DKK	4 609 DKK
Societal Uncontrolled	29 970 DKK	89 794 DKK	73 500 DKK	34 685 DKK	39 699 DKK
Societal Controlled	44 915 DKK	8 707 DKK	22 350 DKK	14 332 DKK	14 246 DKK
Subsequent treatment					
Drug acquisition	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug administration	0 DKK	0 DKK	0 DKK	0 DKK	0 DKK
Adverse events	573 DKK	759 DKK	691 DKK	766 DKK	765 DKK
Comorbidity	12 200 DKK	15 524 DKK	14 120 DKK	15 668 DKK	15 467 DKK
Resource use	31 269 DKK	37 206 DKK	33 843 DKK	37 551 DKK	36 303 DKK
Societal	112 120 DKK	131 823 DKK	119 905 DKK	133 046 DKK	128 119 DKK
BLA					
Treatment	42 740 DKK	63 445 DKK	54 283 DKK	63 504 DKK	63 316 DKK
Adverse events	4 853 DKK	7 204 DKK	6 164 DKK	7 211 DKK	7 189 DKK
Comorbidity	4 952 DKK	6 761 DKK	5 709 DKK	8 441 DKK	8 199 DKK
Resource use	9 540 DKK	13 128 DKK	11 185 DKK	14 268 DKK	14 080 DKK

Category	Osilodrostat	Pasireotide SC	Pasireotide LAR	Ketoconazole	Metyrapone
Societal	107 391 DKK	157 413 DKK	134 424 DKK	163 242 DKK	162 021 DKK
Total costs	xxx XXX DKK	xxx XXX DKK	xxx XXX DKK	xxx XXX DKK	xxx XXX DKK

For the simplicity of this cost analysis, the disaggregated results for the undiscounted results are only included in the model and not presented here in the report.

6.2 Results generated by the budget impact analysis

For the calculation of the budget impact, we used the cost-analysis model and updated the settings to a 1-year time horizon and 0% discounting. This provided the costs per patient per year per treatment. Using these costs, together with the market shares as shown in section 2.2 we calculated the budget impact.

The results show the annual break down of the scenario when osilodrostat is not introduced is shown in Table 28, while the results of scenario when osilodrostat is introduced is shown in Table 29. The budget impact is shown in Table 30.

Table 28: Cost per treatment per year WITHOUT osilodrostat introduced

Treatment	Year 1	Year 2	Year 3	Year 4	Year 5
Osilodrostat	0 DKK	0 DKK	0 DKK	0 DKK	0 DKK
Metyrapone	4 300 325 DKK	9 030 683 DKK	9 245 699 DKK	9 460 715 DKK	9 675 731 DKK
Ketoconazole	3 766 875 DKK	6 672 750 DKK	6 242 250 DKK	5 811 750 DKK	5 381 250 DKK
Pasireotide sc + LAR	2 803 785 DKK	6 056 176 DKK	6 280 479 DKK	6 056 176 DKK	6 729 084 DKK

Table 29: Cost per treatment per year WITH osilodrostat introduced

Treatment	Year 1	Year 2	Year 3	Year 4	Year 5
Osilodrostat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metyrapone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ketoconazole	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pasireotide sc + LAR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 30: Budget impact of osilodrostat

Treatment	Year 1	Year 2	Year 3	Year 4	Year 5
Scenario when osilodrostat is NOT introduced	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario when osilodrostat is introduced	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact recommending osilodrostat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

7. References

1. European Medicines Agency. Isturisa 2021 [updated 16/06/2020. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/isturisa.

2. Björstad A, Schmid R, Roser B, cartographers. The Cost-Effectiveness of Ketoconazole Versus Metyrapone for the Treatment of Cushing's Syndrome in a Swedish Setting2016.

3. Novartis. A Phase III, multi-center, double-blind, randomized withdrawal study of LCI699 following a 24 week, single-arm, open-label dose titration and treatment period to evaluate the safety and efficacy of LCI699 for the treatment of patients with Cushing's disease. Clinical Study Report. Data on File2020.

4. Reincke M, Albani A, Assie G, Bancos I, Brue T, Buchfelder M, et al. Corticotroph tumor progression after bilateral adrenalectomy (Nelson's syndrome): systematic review and expert consensus recommendations. European journal of endocrinology. 2021;184(3):P1-p16.

5. Pivonello R, De Leo M, Cozzolino A, Colao A. The Treatment of Cushing's Disease. Endocrine reviews. 2015;36(4):385-486.

6. Nieman L, Boscaro M, Carla S, Deutschbein T, Mezosi E, Driessens N, et al., editors. Metyrapone treatment in endogenous Cushing's syndrome. Long term efficacy and safety results of the extension of the phase III/IV study PROMPT. Endocrine Abstracts; 2021: Bioscientifica.

7. European Medicines Agency. Signifor 2021 [updated 14/08/2020. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/signifor.

8. European Medicines Agency. Ketoconazole 2021 [Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/ketoconazole-hra.

9. Limited HPUaI. METOPIRONE 250 mg. Electronic Medicines Compendium (EMC)2021 (Lat updated 07/10/2020).

10. Regionvårdsnämnden S. Regionala priser och ersättningar för Södra sjukvårdsregionen 2021 [1-111]. Available from: https://sodrasjukvardsregionen.se/download/regionala-priser-och-ersattningar-for-sodra-sjukvardsregionen-2021/?wpdmdl=21717&refresh=60bf2649037751623139913.

11. Vestergaard SV, Rasmussen TB, Stallknecht S, Olsen J, Skipper N, Sørensen HT, et al. Occurrence, mortality and cost of brain disorders in Denmark: a population-based cohort study. BMJ open. 2020;10(11):e037564.

12. Hernlund E, Svedbom A, Ivergård M, Compston J, Cooper C, Stenmark J, et al. Osteoporosis in the European Union: medical management, epidemiology and economic burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Archives of osteoporosis. 2013;8(1):136.

13. Statista. Average usual weekly hours worked on the main job in Denmark 2020 2020 [Available from: https://www.statista.com/statistics/419551/main-job-average-weekly-working-hours-denmark-y-on-y/.

14. Colao A, Petersenn S, Newell-Price J, Findling JW, Gu F, Maldonado M, et al. A 12-month Phase III study of pasireotide in Cushing's disease. N Engl J Med. 2012;366(10):914-24.

15. Lacroix A, Gu F, Gallardo W, Pivonello R, Yu Y, Witek P, et al. Efficacy and safety of once-monthly pasireotide in Cushing's disease: a 12 month clinical trial. Lancet Diabetes Endocrinol. 2018;6(1):17-26.

16. Ceccato F, Zilio M, Barbot M, Albiger N, Antonelli G, Plebani M, et al. Metyrapone treatment in Cushing's syndrome: a real-life study. Endocrine. 2018;62(3):701-11.

17. Daniel E, Aylwin S, Mustafa O, Ball S, Munir A, Boelaert K, et al. Effectiveness of Metyrapone in Treating Cushing's Syndrome: A Retrospective Multicenter Study in 195 Patients. The Journal of clinical endocrinology and metabolism. 2015;100(11):4146-54.

18. Castinetti F, Guignat L, Giraud P, Muller M, Kamenicky P, Drui D, et al. Ketoconazole in Cushing's disease: is it worth a try? The Journal of clinical endocrinology and metabolism. 2014;99(5):1623-30.

19. Young J, Bertherat J, Vantyghem MC, Chabre O. Hepatic safety of ketoconazole in Cushing's syndrome: results of a Compassionate Use Programme in France. Eur J Endocrinol 2018;178(5):447-58.

20. Ragnarsson O, Olsson DS, Papakokkinou E, Chantzichristos D, Dahlqvist P, Segerstedt E, et al. Overall and Disease-Specific Mortality in Patients With Cushing Disease: A Swedish Nationwide Study. The Journal of clinical endocrinology and metabolism. 2019;104(6):2375-84.

21. Swearingen B, Wu N, Chen SY, Pulgar S, Biller BM. Health care resource use and costs among patients with cushing disease. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists. 2011;17(5):681-90.

22. Sharma ST, Nieman LK, Feelders RA. Cushing's syndrome: epidemiology and developments in disease management. Clinical epidemiology. 2015;7:281-93.

23. Kristo C, Jemtland R, Ueland T, Godang K, Bollerslev J. Restoration of the coupling process and normalization of bone mass following successful treatment of endogenous Cushing's syndrome: a prospective, long-term study. European journal of endocrinology. 2006;154(1):109-18.

24. Faggiano A, Pivonello R, Melis D, Filippella M, Di Somma C, Petretta M, et al. Nephrolithiasis in Cushing's disease: prevalence, etiopathogenesis, and modification after disease cure. The Journal of clinical endocrinology and metabolism. 2003;88(5):2076-80.

8. Appendices

8.1 Health states

8.1.1 Uncontrolled, on initial treatment

All patients are *uncontrolled* when starting initial treatment. Uncontrolled disease is defined by having mUFC > ULN. From this health state, patients either remain *uncontrolled* or move to:

- *Controlled, on initial treatment* health state. This movement is based on time to complete response data, indicated by the green arrow in Figure 1
- *Subsequent medical therapy* or *BLA* health state. The model includes a cut-off point after which all remaining non-responders in the *uncontrolled* health state discontinue initial treatment and move to *subsequent medical therapy* or *bilateral adrenalectomy* (black arrows in Figure 1). This cut-off point is set at 6 months, based on inputs from clinical experts who have indicated that after 6 months it is possible to evaluate whether a patient is controlled. Patients who fail initial treatment either receive subsequent medical therapy (*subsequent medical therapy* health state) or move to the *BLA* health state directly. The proportion of patients moving to subsequent medical therapy or BLA is based on clinician feedback. All patients receive subsequent medical therapy before moving to BLA
- *Death* health state. The probability of dying from the *uncontrolled* disease health is based on standardised mortality rates for patients in uncontrolled disease versus the general population mortality

8.1.2 Controlled, on initial treatment

Depending on time to complete response, patients can transition to the *controlled* health state. Controlled disease is defined by patients having mUFC ≤ ULN. From this health state, patients either remain controlled or move to:

- *Subsequent medical therapy* or *BLA* health state. This movement is based on time to treatment failure data (blue arrows in Figure 1). Patients who fail initial treatment either receive subsequent medical therapy (*subsequent medical therapy* health state) or move to the *BLA* health state directly. The proportion of patients moving to subsequent medical therapy or BLA is based on clinician feedback. All patients receive subsequent medical therapy before moving to BLA
- *Death* health state. The probability of dying from the *controlled* disease health state is based on standardised mortality rates for patients in controlled disease versus the general population mortality

8.1.3 Subsequent medical therapy

When no response occurs within the predetermined time cut-off point (6 months) or when controlled patients fail treatment (based on time to treatment failure data), patients receive subsequent medical therapy. As there is no universal standard of care treatment pathway after initial medical therapy, the *subsequent medical therapy* health state consists of a basket of treatment. The composition of the subsequent medical therapy basket can differ based on the initial treatment received. Table 31 presents the composition of the subsequent medical therapy. Please note that values could sum to more than 100% to capture the potential for patients to receive multiple lines of subsequent treatment. Repeated TSS and radiotherapy are not considered in the subsequent treatment line as clinicians have indicated that having rTSS after medical therapy is more of an exception than standard clinical practice. In addition, clinicians have indicated that radiotherapy should not be considered a competitor to medical therapy as it is generally combined with medical therapy given the uncertain and slow effect.

Table 31: Composition of subsequent medical therapy basket

To: Subsequent medical therapy	From: Initial treatment				
	Osilodrostat	**Pasireotide SC**	**Pasireotide LAR**	**Ketoconazole**	**Metyrapone**
Osilodrostat	0%	50%	50%	50%	50%
Pasireotide SC	0%	0%	0%	0%	0%
Pasireotide LAR	0%	0%	0%	0%	0%
Ketoconazole	50%	0%	0%	0%	50%
Metyrapone	50%	50%	50%	50%	0%
Total	**100%**	**100%**	**100%**	**100%**	**100%**

It is assumed that a certain proportion of patients in the subsequent medical therapy is controlled as they responded to the subsequent medical therapy, whereas the remaining proportion is unresponsive to subsequent medical therapy and therefore uncontrolled. Mean response probability with each subsequent treatment from literature is used to calculate a weighted average response rate in the subsequent medical therapy basket. This weighted average response rate impacts comorbidity costs and resource use costs in this health state. Drug acquisition, drug administration and adverse event costs are weighted based on the mix of subsequent medical therapies.

Lack of evidence makes it infeasible and overly complex to model the duration of subsequent treatment lines explicitly. Instead, the model uses an average duration of subsequent medical therapy, which is set at 12 months, based on clinician feedback. Patients who have had 12 months of subsequent medical therapy will move to the *BLA* health state.

The probability of dying from the *subsequent medical therapy* health state is a weighted probability based on the weighted average response rate in the subsequent medical therapy basket and the

standardised mortality rate for patients in uncontrolled and controlled disease versus the general population mortality.

8.1.4 BLA

After 12 months in the *subsequent medical treatment* health state, all patients transition to *BLA* where they will remain until *death*. Patients might also move directly to *BLA* immediately after initial treatment discontinuation, based on clinician feedback on proportion of patients receiving BLA immediately upon initial treatment discontinuation. Clinicians have indicated that BLA is the final treatment option for patients with CS and has a 100% response rate.

As patients in the *BLA* health state are controlled (i.e. 100% response rate, based on clinical experts), the probability of dying from the *BLA* health state is based on standardised mortality rates for patients in *controlled* disease versus the general population mortality. However, an additional hazard ratio is applied to account for the fact that there is a higher mortality risk for patients being controlled after BLA versus patients being controlled after medical therapy, informed by literature and clinician feedback. In addition, the model has the functionality to include a one-off acute mortality risk related to BLA surgery and/or recovery, however, this is not included as per clinician feedback.

8.1.5 Death

As described in the sections above, death can occur from every health based on general population mortality and standardised mortality ratios to account for additional mortality risk depending on disease status.

8.2 Efficacy

The following time-to-event endpoints were required to inform the cost-effectiveness model:

- Time to complete response (TTCR) – time from randomization to complete response, where complete response is defined as mUFC ≤ 1.0 x ULN. Patients who do not achieve complete response are considered non-responders
- Time to treatment failure post-response (TTFPR) – where treatment failure is defined as discontinuation due to adverse events (AEs), lack of efficacy, physician's decision, treatment escape and death

Data for both endpoints are available for osilodrostat, pasireotide and pasireotide LAR from the LINC-3 trial(3), the B2305 trial (Colao et al, 2012)(14) and the G2304 trial (Lacroix et al, 2018)(15), respectively. As PLD are available for these trials, a robust comparison for osilodrostat versus pasireotide SC and pasireotide LAR was formed using PLD population-adjustment methods.

No PLD are available for ketoconazole, mifepristone and metyrapone. Therefore, published data were used to form comparisons between osilodrostat and ketoconazole, mifepristone and metyrapone. However, in the absence of randomized controlled trials and given the small sample sizes and limited data available for patient characteristics (for comparators), it was unfeasible to use population-adjustment methods.

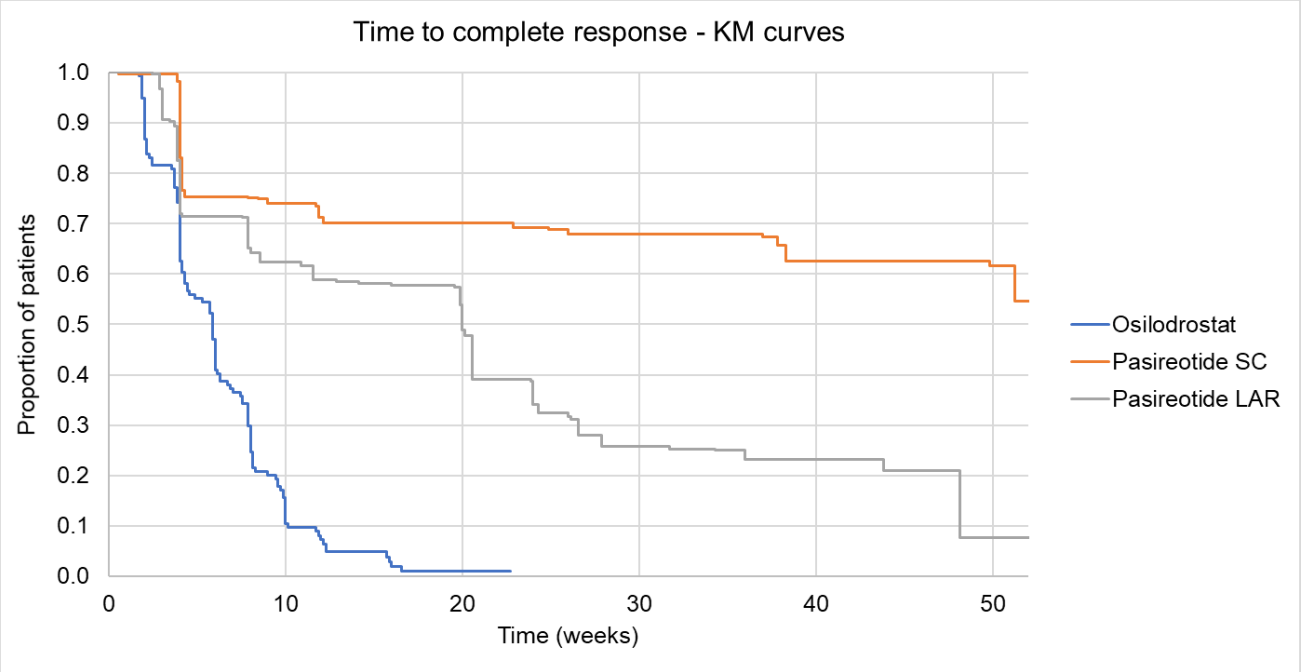
8.2.1 Time to complete response

8.2.1.1 Patient level data

TTCR Kaplan–Meier (KM) curves from the relevant clinical trials inform the transition from the uncontrolled health state to the controlled health state for osilodrostat, pasireotide SC and pasireotide LAR. Figure 2 presents the weighted TTCR KM curves for osilodrostat, pasireotide SC and pasireotide LAR, based on the outcomes of the population adjustment method. The pasireotide SC and pasireotide LAR populations were matched to the LINC-3 population. Appendix 8.4 presents the unadjusted KM curve for TTCR.

The weighted TTCR KM curves in Figure 3 are presented until the maximum cut-off point of 12 months. As described in Section 3.1, the model includes a cut-off point after which all remaining non-responders in the uncontrolled health state discontinue initial treatment. As the model uses a 6-month cut-off point, only the first 6 months of these KM curves are included in the model for time to complete response. After 6 months, all patients who have not yet responded discontinue initial treatment, based on clinician feedback.

Figure 2: Time to complete response – weighted KM curves



8.2.1.2 Naïve analyses

Given that the model was developed for global use, a broader SLR was used to identify outcomes of interest to support the analysis. Due to differences in the search string, the results of the naïve comparison vary slightly, to support the clinical evidence the data in the clinical dossier should be considered. The naïve comparisons based on published data were used to form comparisons between osilodrostat and ketoconazole and metyrapone. Table 32 presents the results of the naïve indirect treatment comparison (ITC) analyses for the complete response endpoint for osilodrostat relative to ketoconazole and metyrapone. Hazard ratios have been derived using the proportion of patients with complete response at a given time point. A HR greater than one provides evidence of improved outcomes for osilodrostat. Where no time point was reported, the average time on treatment in the comparator study was used, leading to uncertainty in the analyses.

Table 32: Summary of naïve comparisons – complete response

Endpoint	Time point (months)	Intervention		Comparator		HR (95% CI)
		Treatment (study)	Proportion of patients with CR	Treatment (study)	Proportion of patients with CR	
Complete response	3	Osilodrostat (LINC-3)	98/137	Metyrapone (Ceccato 2018)(16)	17/31	1.58 (0.99, 2.53)
	18.6[a]	Osilodrostat (LINC-3)	80/137	Metyrapone (Daniel 2015)(17)	9/38	3.24 (1.96, 5.37)

Endpoint	Time point (months)	Intervention		Comparator		HR (95% CI)
		Treatment (study)	Proportion of patients with CR	Treatment (study)	Proportion of patients with CR	
	24.8[a]	Osilodrostat (LINC-3)	64/137	Ketoconazole (Castinetti 2014)(18)	78/200	1.27 (0.91, 1.78)

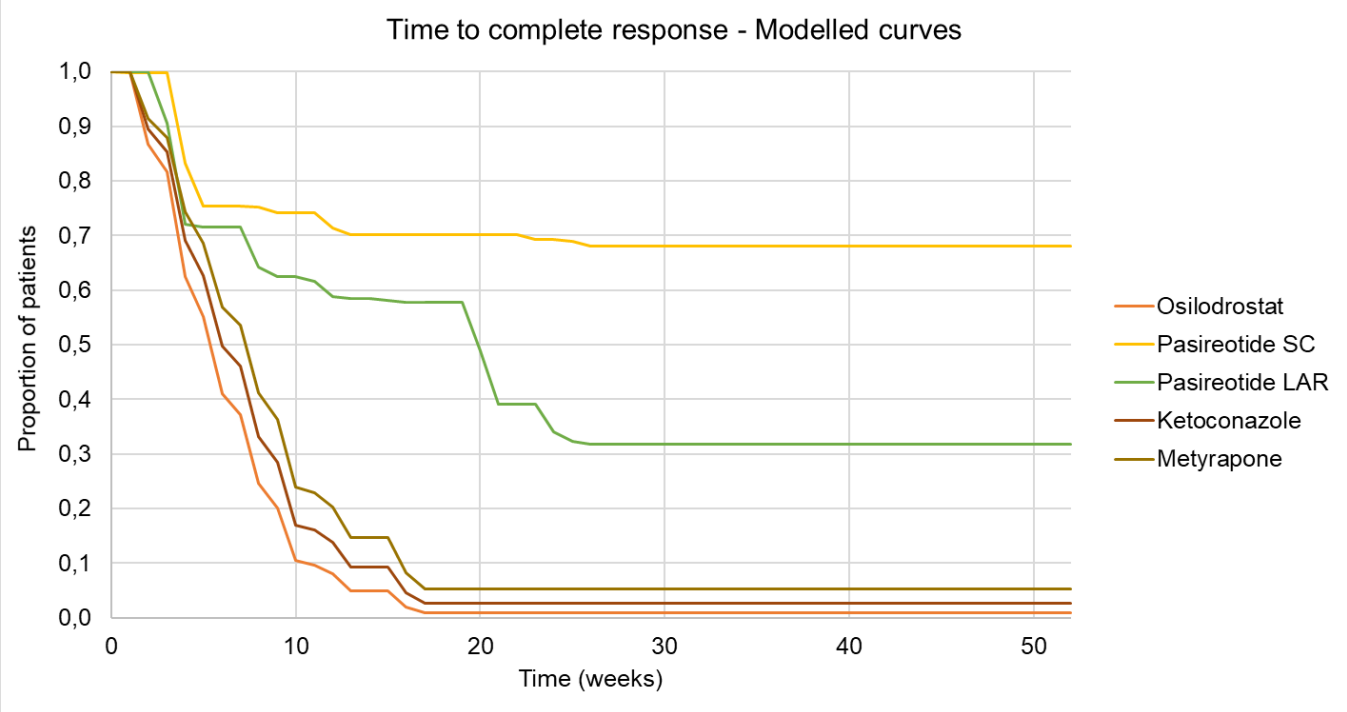
Key: CI, confidence interval; CR, complete response; HR, hazard ratio; OR, odds ratio.

Notes: HR > 1 favours osilodrostat. Significant results highlighted in bold. [a], time point not reported – average time on treatment in comparator study has been used.

8.2.1.3 Modelled time to complete response curves

Figure 3 presents the modelled TTCR curves for all treatments until the cut-off point at 6 months (approximately 26 weeks). Given that the model was developed for global use, mifepristone is shown in the figure, however given that this treatment was not included in the DMC protocol, this assumption has no impact on the results and is not considered in the cost calculations.

Figure 3: Time to complete response - Modelled curves



8.2.2 Time to treatment failure post-response

8.2.2.1 Patient level data

Time to treatment failure post-response (TTFPR) is a composite endpoint including discontinuation due to lack of efficacy, discontinuation due to adverse events, discontinuation due to physician's decision, treatment escape and death.

Because mortality in the trials was severely underestimated compared to general population mortality, the economic model applies standardised mortality rates for patients in controlled disease versus the general population mortality. Deaths were included as an event in the definition of treatment failure in the TTFPR analysis, hence any deaths in controlled patients as observed in the trials are double counted in the TTFPR analysis. As this is only applicable to one patient in the osilodrostat treatment arm, the limitation of double counting in the analysis is unlikely to affect the outcomes of the model.

Treatment escape is included as an event in the definition of treatment failure; however, the definition of treatment escape differs between studies. In the model, treatment escape in LINC-3 is re-defined to align with the B2305 trial and the G2304 trial.

The pasireotide SC and pasireotide LAR KM curves were weighted based on the outcomes of the population adjustment method. The pasireotide SC and pasireotide LAR populations were matched to the LINC-3 population. The weighted TTFPR KM curves were extrapolated to predict the time to treatment failure beyond the end of the observed study period. The following parametric distributions were calculated:

- Exponential
- Weibull
- Log-normal
- Log-logistic
- Gompertz
- Generalized gamma
- Gamma

The log-normal was considered the most appropriate model due to the goodness of fit of the curve (AIC/BIC values). Although the generalized gamma was the best fitting for osilodrostat and pasireotide LAR it did not converge for pasireotide SC (likely due to the low sample size as the generalized gamma is a more complex model). In addition, although the exponential was the best fitting for pasireotide SC, it provides the worst fit visually (AIC/BIC favours simpler models when sample size is low). The same distribution is usually used for all treatments, therefore, the log-normal was chosen as it was the best fitting model for osilodrostat, pasireotide LAR and pasireotide SC.

Figure 4, Figure 5 and Figure 6 present the extrapolated parametric distributions for osilodrostat, pasireotide SC and pasireotide LAR, respectively. The weighted KM curves have been overlaid to assess visual fit. Appendix 8.5 presents the unadjusted KM curves for TTFPR. The associated estimates are presented in Table 33, Table 34 and Table 35.

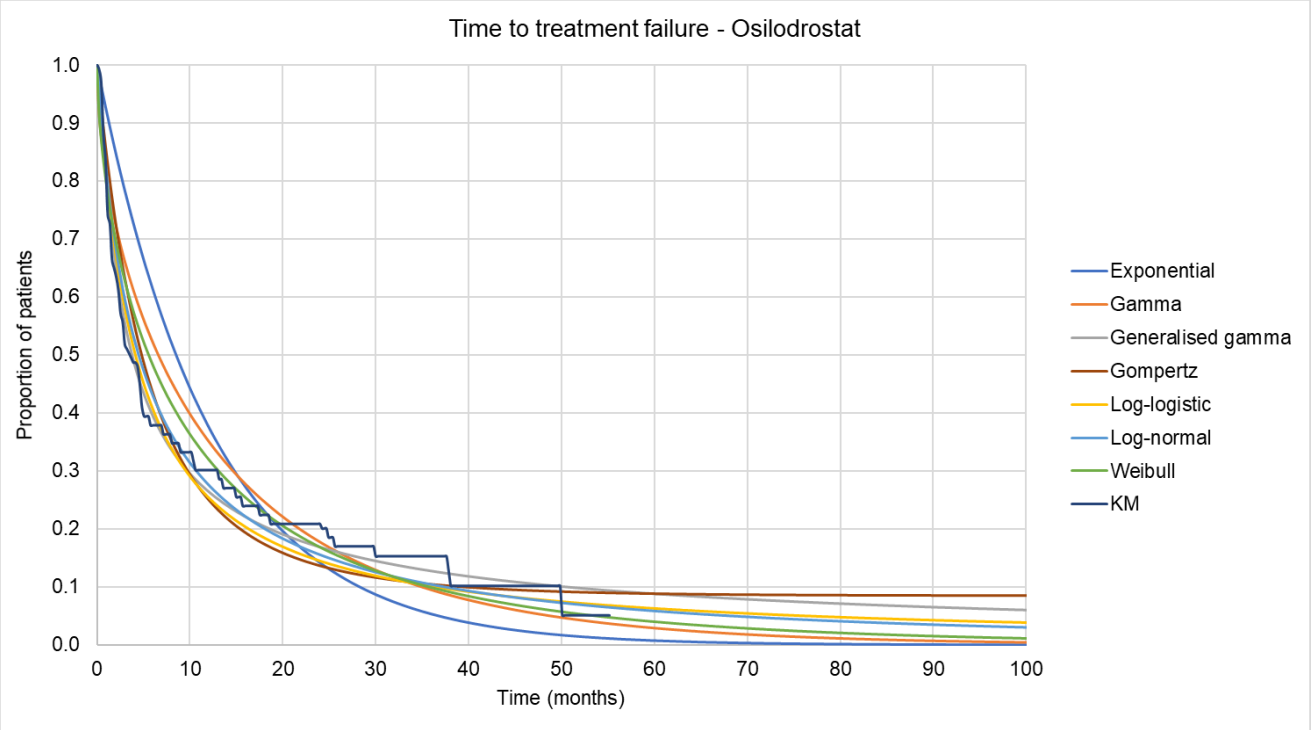
Akaike information criterion (AIC) and Bayesian information criterion (BIC) were used to assess goodness of fit. The lower the AIC or BIC, the better the model fit to the observed data. A nominal difference of approximately 5 or more in AIC and/or BIC is considered a meaningful difference in the fit of the parametric survival models to the observed data. The AIC and BIC values presented in Table 36 suggest the log-normal provides the best overall fit to the data, and was, therefore, selected as the curve for all three treatments.

The parametric models have difficulty fitting the data due to the strange shape of the Kaplan-Meier curves The sharp drop at the beginning of the pasireotide SC and pasireotide LAR curves may be due to the timing of assessments following complete response We have low sample sizes for the pasireotide SC and pasireotide LAR arms and the number at risk drops very quickly after the initial sharp drop giving very small patients at risk beyond 6 months (see Kaplan-Meier plots below). This also contributes to the strange shape

We believe the log-normal provides a reasonable fit to the data.

More complex/flexible models could be fitted but that may not be sensible due to the risk of overfitting and low sample size. The generalised gamma is the most complex model that we have fit to the data, and this model did not converge for the pasireotide SC data therefore it is likely even more complex models may have the same issue.

Figure 4: Fitted parametric survival curves for time to treatment failure post-response - osilodrostat



Key: KM, Kaplan–Meier.

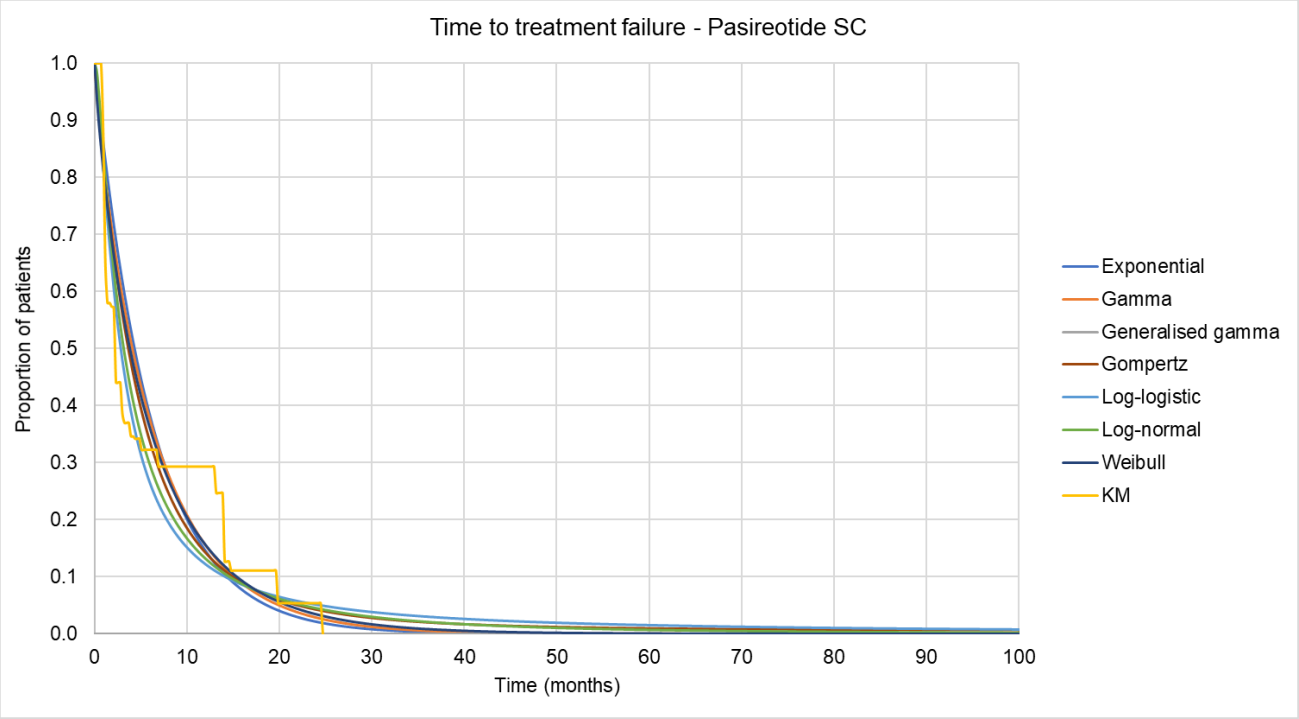
Table 33: Parametric survival curve estimates for treatment failure post-response – osilodrostat

Time, years (days)	Osilodrostat (% failed treatment)							
	KM data	Exponential	Gamma	Log-Logistic	Log-Normal	Weibull	Gen gamma	Gompertz
0.25 (91.31)	48.2%	21.7%	34.0%	42.1%	40.5%	37.3%	44.6%	36.9%
0.5 (182.63)	62.1%	38.7%	47.9%	59.4%	57.0%	51.8%	60.5%	56.6%
1 (365.25)	69.9%	62.5%	64.9%	74.6%	72.4%	68.0%	73.6%	75.0%
5 (1826.25)	94.8%*	99.3%	97.1%	93.7%	94.2%	96.0%	91.2%	91.2%
10 (3652.5)	94.9%*	100.0%	99.8%	96.8%	97.7%	99.4%	94.8%	91.5%

Key: KM, Kaplan–Meier.

Notes: *, Zero patients are at risk at this time, as such it has been assumed that the % of patients with treatment failure is the same as the last known time point.

Figure 5: Fitted parametric survival curves for time to treatment failure post-response – pasireotide SC



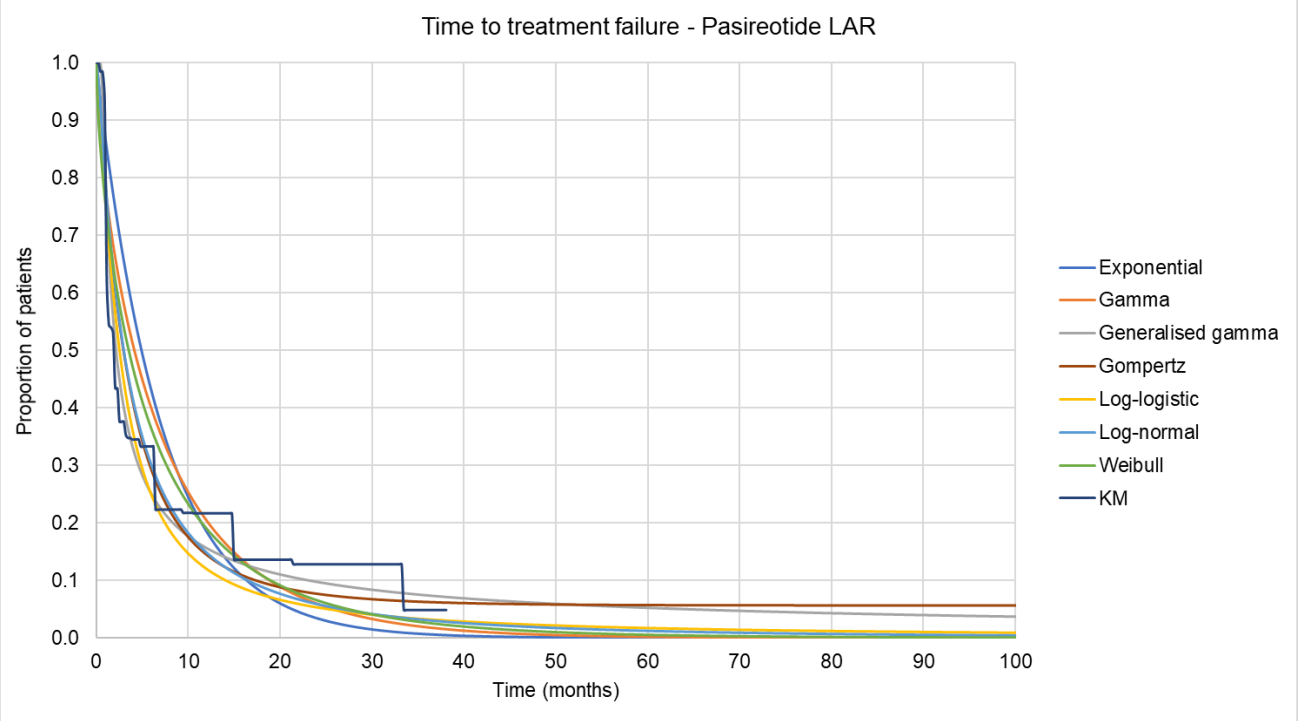
Key: KM, Kaplan–Meier.

Table 34: Parametric survival curve estimates for treatment failure post-response – pasireotide SC

Time, years (days)	Pasireotide SC (% failed treatment)						
	KM data	Exponential	Gamma	Log-Logistic	Log-Normal	Weibull	Gompertz
0.25 (91.31)	61.4%	38.3%	41.0%	52.1%	48.5%	43.2%	44.0%
0.5 (182.63)	67.7%	62.0%	62.7%	73.7%	70.6%	64.2%	66.5%
1 (365.25)	70.7%	85.6%	84.5%	87.9%	86.9%	84.5%	85.9%
5 (1826.25)	100.0%	100.0%	100.0%	98.5%	99.3%	99.9%	99.1%
10 (3652.5)	100.0%	100.0%	100.0%	99.4%	99.9%	100.0%	99.4%

Key: KM, Kaplan–Meier; SC, subcutaneous.
Notes: The generalized gamma model did not converge.

Figure 6: Fitted parametric survival curves for time to treatment failure post-response – pasireotide LAR



Key: KM, Kaplan–Meier.

Table 35: Parametric survival curve estimates for treatment failure post-response – pasireotide LAR

Time, years (days)	Pasireotide LAR (% failed treatment)							
	KM data	Exponential	Gamma	Log-Logistic	Log-Normal	Weibull	Gen gamma	Gompertz
0.25 (91.31)	62.4%	34.5%	42.0%	55.5%	50.1%	46.1%	60.0%	50.4%
0.5 (182.63)	66.7%	57.1%	60.2%	75.2%	70.0%	63.7%	75.0%	70.9%
1 (365.25)	78.4%	81.6%	79.7%	88.0%	85.2%	81.1%	84.4%	85.6%
5 (1826.25)	95.2%*	100.0%	99.8%	98.3%	98.8%	99.5%	94.8%	94.3%
10 (3652.5)	95.2%*	100.0%	100.0%	99.3%	99.7%	100.0%	96.8%	94.4%

Key: Gen, Generalized; KM, Kaplan–Meier; LAR, long-acting release.
Notes: *, Zero patients are at risk at this time, as such it has been assumed that the % of patients with treatment failure is the same as the last known time point.

Table 36: Parametric survival curves for time to treatment failure post-response – goodness of fit statistics

Model	Osilodrostat		Pasireotide SC adjusted		Pasireotide LAR adjusted		Overall	
	AIC (rank)	BIC (rank)	AIC (rank)	BIC (rank)	AIC (rank)	BIC (rank)	AIC (rank)	BIC (rank)
Exp	1173.0 (7)	1175.6 (7)	75.8 (1)	77.2 (1)	182.6 (6)	184.3 (5)	1431.3 (6)	1437.1 (6)
Gam	1150.0 (6)	1155.2 (6)	77.6 (6)	80.5 (6)	182.6 (7)	186.1 (7)	1410.3 (5)	1421.8 (5)
LL	1128.2 (3)	1133.3 (3)	76.7 (3)	79.6 (3)	176.6 (3)	180.1 (3)	1381.5 (2)	1393.0 (2)
LN	1124.5 (2)	1129.7 (2)	76.1 (2)	79.0 (2)	176.2 (2)	179.7 (2)	1376.9 (1)	1388.4 (1)
Wei	1142.3 (5)	1147.4 (5)	77.5 (5)	80.4 (5)	181.2 (5)	184.7 (6)	1400.9 (4)	1412.5 (4)
Gom	1138.8 (4)	1143.9 (4)	77.5 (4)	80.3 (4)	179.1 (4)	182.6 (4)	1395.3 (3)	1406.9 (3)
GG	1121.3 (1)	1129.0 (1)	Did not converge		171.1 (1)	176.4 (1)	Did not converge	

Key: AIC, Akaike information criterion; AFT, accelerated failure time; BIC, Bayesian information criterion; Exp, exponential; Gam, gamma; GG, generalized gamma; Gom, Gompertz; LAR, long-acting release; LL, log-logistic; LN, log-normal; PSM, parametric survival model; SC, subcutaneous; Wei, Weibull.
Notes: Green cells indicate models within five points of best fitting AIC/BIC.

8.2.2.2 Naïve analyses

Data for the composite treatment failure endpoint were not available from published data. Therefore, Table 37 presents the results of the naïve comparisons of osilodrostat relative to metyrapone for the following endpoints: treatment discontinuation, and discontinuation due to lack of efficacy or any adverse event (pooled).

Hazard ratios have been derived using the proportion of patients treatment discontinuation at a given time point. A HR less than one provides evidence of improved outcomes for osilodrostat. Where no time point was reported, the average time on treatment in the comparator study was used, leading to uncertainty in the analyses.

Treatment discontinuation is likely to be most aligned with the composite time to treatment failure endpoint used for osilodrostat, pasireotide SC and pasireotide LAR. Therefore, the model uses the HR for osilodrostat versus ketoconazole based on Young et al. (2018) (HR: 0.33 [95% confidence interval, CI: 0.20, 0.56), as this study did report a time point whereas Castinetti et al. (2014) did not.

The naïve analyses are subject to multiple limitations: small sample sizes, assumptions around time points when not reported, and limited data available for patient characteristics. Due to the lack of available, these analysis considered the most feasible approach for this cost calculations.

Table 37: Summary of naïve comparisons – time to treatment failure

Endpoint	Time point (months)	Intervention		Comparator		HR (95% CI)
		Treatment (study)	Proportion of patients	Treatment (study)	Proportion of patients	
Treatment discontinuation	6	Osilodrostat (LINC-3)	19/137	Ketoconazole (Young 2018)(19)	39/108	**0.33 (0.20, 0.56)**
	24.8[a]	Osilodrostat (LINC-3)	58/137	Ketoconazole (Castinetti 2014)(18)	118/160[b]	**0.41 (0.31, 0.55)**
Discontinuation due to lack of efficacy + any adverse event (pooled)	6	Osilodrostat (LINC-3)	14/137[b]	Ketoconazole (Young 2018)(19)	11/108	1.00 (0.46, 2.21)
	24.8[a]	Osilodrostat (LINC-3)	36/137[b]	Ketoconazole (Castinetti 2014)(18)	118/160[c]	**0.41 (0.29, 0.59)**

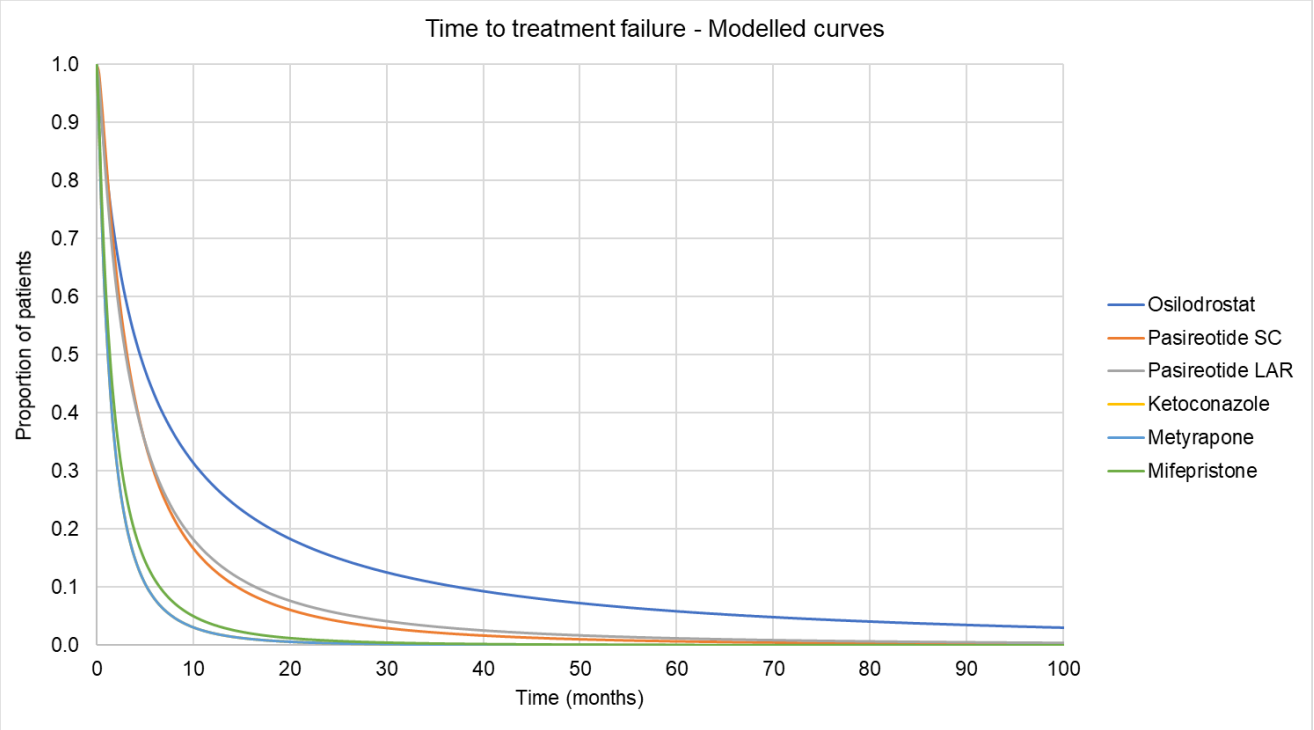
Key: CI, confidence interval; CR, complete response; HR, hazard ratio; ULN, upper limit of normal.

Notes: HR < 1 favours osilodrostat. Significant results highlighted in bold. [a], time point not reported – average time on treatment in comparator study has been used; [b], patients who discontinued treatment due to lack of efficacy, adverse events or physician's decision have been included; [c], 40/200 patients not assessed for withdrawal as ketoconazole was used as a pre-surgical treatment.

8.2.2.3 Modelled time to treatment failure post-response curves

Figure 7 presents the modelled TTFPR curves for all treatments. As there were no metyrapone studies reporting on the time to treatment failure endpoints, it has been assumed that metyrapone is equivalent to ketoconazole in terms of time to treatment failure.

Figure 7: Time to treatment failure post-response – Modelled curves



8.2.3 Subsequent medical therapy basket

Efficacy within the subsequent medical therapy basket is based on estimates on mean response probability with or after subsequent medical therapy from Table 38. These probabilities are used to calculate a weighted average response rate based on the composition of the subsequent medical therapy basket. Lack of evidence makes it infeasible and overly complex to model the duration of subsequent treatment lines explicitly based on an endpoint such as time to treatment failure. Instead, the model uses an average duration of subsequent medical therapy, which is set at 12 months, based on feedback from clinical experts. Patients who have had 12 months of subsequent medical therapy will move to the *BLA* health state.

Table 38: Response in subsequent medical therapies

Subsequent medical therapy	Mean response probability with/after treatment	Reference
Osilodrostat	67,9%	Osilodrostat LINC-3 CSR: At the end of the Core Period, 91/137 (66.4%) were complete responders.
Pasireotide SC	15%	Calao et al 2012: 12 out of 82 patients (14.6%, 95% CI: 7.0, 22.3) in the 600 µg bid group achieved response
Pasireotide LAR	41,9%	Lacroix et al. 2018: The primary efficacy response rates at Month 7 were 41.9% (31/74, 95% CI: 30.5%, 53.9%) in the pasireotide 10 mg arm.
Ketoconazole	48,5%	Castinetti et al. 2014: 48,5% were controlled at variable timing
Metyrapone	43%	Daniel et al 2015. 43% was controlled at variable timepoints; alternatively Nieman et al. 2021 where 41,5% (17/41) was controlled at week 36

8.2.4 BLA

Clinical experts have indicated that BLA has a 100% response rate. In addition, clinical experts have indicated that BLA is the final treatment option for patients with CS. Therefore, the model assumes that patients in the BLA health state have controlled UFC levels until end of life.

8.2.5 Mortality

The model includes standardized mortality ratios (SMRs) versus general population mortality for uncontrolled disease, controlled disease and a chronic SMR that is applied in the BLA health state to reflect SMR after BLA until end of life. General population mortality is obtained by using the deaths occured in 2020 and the size of overall population on the first day of Q1 2021 from Statistics Denmark.

From uncontrolled and controlled disease

SMR for uncontrolled and controlled disease versus general population mortality are obtained from Ragnarsson et al. (2019), presented in Table 39. Ragnarsson et al. is a recent study using data from a Swedish registry in CD and is assumed to be the most recent Nordic data and therefore applicable to Denmark.

Table 39: Health state SMR vs general population

Input	Mean	LB (95%CI)	UB (95%CI)	Reference
Uncontrolled disease SMR	6.90	4.30	10.00	Ragnarsson et al. (2019) (20)
Controlled disease SMR	1.90	1.50	2.30	
Key: SMR, standardised mortality ratio; LB, lower bound; UB, upper bound				

8.2.6 Subsequent medical therapy basket

The SMR in this health state is a weighted SMR depending on the percentage of patients responding to the subsequent treatment basket. Hence, no specific SMRs for the subsequent medical therapy health state are included.

8.2.7 BLA

As patients in the BLA health state are controlled (i.e. 100% response rate), the probability of dying in the BLA health state is based on standardized mortality rates for patients in controlled disease versus the general population mortality. However, an additional HR is applied to account for the fact that there is a higher mortality risk for patients being controlled after BLA versus patients being controlled after medical therapy. Ragnarsson et al. (2019) present a HR of 2.7 (95% CI 1.7, 4.3) for patients in remission after BLA versus patients in remission without BLA. However, clinical experts assumed that this HR is lower than 2.7. Therefore, a HR of 2.0 is assumed. In addition, while the

model has the functionality for the user to include a one-off acute mortality risk related to BLA surgery and/or recovery, this is not included, as per clinician feedback.

8.3 Comorbidities

Patients with CS often experience multiple comorbidities, with the risk of comorbidities being raised substantially if cortisol levels are not stabilized. The model therefore considers the incidence of acute and chronic comorbidities associated with uncontrolled and controlled disease. The relevant acute and chronic comorbidities for CS were identified by clinical experts. Acute comorbidities are assumed to be associated with one-time costs, whereas the chronic comorbidities are assumed to have recurring costs.

8.3.1 Uncontrolled disease comorbidities

Acute and chronic comorbidities for uncontrolled disease were estimated from the LINC-3 study. However, from the LINC-3 data it was difficult to summarize the number of patients experiencing an acute comorbidity during follow-up because it was impossible to separate acute comorbidities from the treatment-specific AEs during the trial. Therefore, the acute comorbidities, as identified by the clinical experts, have been obtained from the treatment-emergent AE analyses. The specific treatment-emergent AEs that matched the description of the acute comorbidities specified by the clinical experts were taken out of the summary of treatment-emergent AEs and instead, further analysed as acute comorbidities. Table 41 presents the number of patients experiencing each acute comorbidity and the number of times the acute comorbidity is experienced per patient while being uncontrolled. These frequencies were calculated to a comorbidity rate per week based on the mean time spent in the uncontrolled health state in LINC-3. Chronic comorbidities were estimated based on the number of patients with a chronic comorbidity at baseline in LINC-3 (Table 42).

Table 40: Mean time in health state in the LINC 3 trial

	Uncontrolled	Controlled
Number of patients	132	128
Mean time in health state (days)	42.6	32.2
Total time in health state (weeks)	801	587

Table 41: Uncontrolled disease comorbidities – Acute comorbidities

Acute comorbidities	Osilodrostat LINC 3 trial			Pasireotide LAR G2304 trial**		
	Number of patients who experienced the acute comorbidity (n)	Number of times the acute comorbidity is experienced per subject	Comorbidity rate (n/week)	Number of patients who experienced the acute comorbidity (n)	Number of times the acute comorbidity is experienced per subject	Comorbidity rate (n/year)
Cardiovascular events	7	1.1	0.010	NR	NR	NR
Myocardial infarction	0	0	0.000	NR	NR	0.000
Stroke	0	0	0.000	NR	NR	0.000
Venous thromboembolism	0	0	0.000	NR	NR	0.004
Pneumonia	0	0	0.000	NR	NR	0.010
Skin infection	0	0	0.000	NR	NR	0.011
Vertebrae fractures	0	0	0.000	NR	NR	0.002
Muscle weakness	0	0	0.000	NR	NR	NR
Hirsutism*	0	0	0.000	NR	NR	NR
Sexual dysfunction	0	0	0.000	NR	NR	NR
Sleep disturbance	0	0	0.000	NR	NR	NR
Sepsis	0	0	0.000	NR	NR	0.002

Key: NR, not reported; n, number, CD, Cushing's disease.
Notes: *Hirsutism only applies to women;

Table 42: Uncontrolled disease comorbidities - Chronic comorbidities

Chronic comorbidities	Osilodrostat LINC 3 trial	Pasireotide LAR G2304 trial**
	Comorbidity prevalence (% of patients)	Comorbidity prevalence (% of patients)
Diabetes mellitus	4%	21%
Metabolic syndrome	4%	Not reported
Overweight or obese	0%	16%
Anxiety	1%	14%
Cognitive deficit	1%	Not reported
Depression	1%	Not reported
Major depression/Major depressive disorder/Mixed anxiety-depressive disorder	4%	Not reported
Osteoporosis	4%	23%
Muscle weakness	0%	Not reported
Hirsutism*	0%	Not reported

Chronic comorbidities	Osilodrostat LINC 3 trial	Pasireotide LAR G2304 trial**
	Comorbidity prevalence (% of patients)	Comorbidity prevalence (% of patients)
Sexual dysfunction	0%	Not reported
Sleep disturbance	0%	Not reported
Sepsis	4%	Not reported
Notes: *Hirsutism only applies to women;		

8.3.2 Controlled disease comorbidities

No chronic comorbidity data for controlled disease was available from LINC-3. Instead, a relative risk for uncontrolled versus controlled disease from published literature is applied to uncontrolled disease comorbidity probabilities. All relative risks for acute and chronic comorbidities are presented in Table 43 and Table 44, respectively.

Table 43: Relative risk uncontrolled vs controlled disease from published literature - Acute comorbidities

Acute comorbidities	RR uncontrolled vs controlled disease	Reference
Cardiovascular events	1.5	Swearingen et al. (2011).(21) Cardiovascular events: 13.2% vs 8.7% (CD vs NFPA population as it has been reported by Sharma et al. (2015)(22) CS leads to an increased cardiovascular risk that may not return to baseline after successful treatment)
Myocardial infarction	2.8	Swearingen et al. (2011).(21) Myocardial infarction: 1.1% vs 0.4% (CD vs NFPA population as it has been reported by Sharma et al. (2015)(22) CS leads to an increased cardiovascular risk that may not return to baseline after successful treatment)
Stroke	1.3	Swearingen et al. (2011).(21) Stroke: 4.4% vs 3.3% (CD vs NFPA population as it has been reported by Sharma et al. (2015)(22) CS leads to an increased cardiovascular risk that may not return to baseline after successful treatment)
Venous thromboembolism	2.4	Swearingen et al. (2011).(21) Thrombosis: 3.3% vs 1.4% (CD vs NFPA population as it has been reported by Sharma et al. (2015)(22) CS leads to an increased cardiovascular risk that may not return to baseline after successful treatment)
Pneumonia	1.2	Swearingen et al. (2011).(21) Pneumonia: 2.6% vs 1.2% (CD vs control population as KOL confirmed this condition reverts to normal after full control of disease)
Skin infection	1.9	Swearingen et al. (2011).(21) Skin infection: 9.2% vs 3.4% (CD vs control population as KOL confirmed this condition reverts to normal after full control of disease)
Vertebrae fractures	8.0	Swearingen et al. (2011).(21) Compression fracture of vertebrae: 0.8% vs 0.1% (CD vs control population as it has been reported that bone mineral density revert to normal after full control of disease (Sharma et al. 2015(22); Kristo et al. 2006(23))

Acute comorbidities	RR uncontrolled vs controlled disease	Reference
Muscle weakness	1.5	KOL inputs: Dutch clinical experts Professor Feelders and Professor Neggers (internist-endocrinologists from the Erasmus Medical Center in the Netherlands)
Hirsutism*	2.3	KOL inputs: Dutch clinical experts Professor Feelders and Professor Neggers (internist-endocrinologists from the Erasmus Medical Center in the Netherlands)
Sexual dysfunction	1.3	KOL inputs: Dutch clinical experts Professor Feelders and Professor Neggers (internist-endocrinologists from the Erasmus Medical Center in the Netherlands)
Sleep disturbance	2.3	KOL inputs: Dutch clinical experts Professor Feelders and Professor Neggers (internist-endocrinologists from the Erasmus Medical Center in the Netherlands)
Sepsis	3.0	Swearingen et al. (2011).(21) Sepsis: 0.3% vs 0.1% (CD vs control population as KOL confirmed this condition reverts to normal after full control of disease)
Key: CD, Cushing's disease; KOL, key opinion leader; NFPA, non-functioning pituitary adenomas; RR, relative risk.		

Table 44: Relative risk uncontrolled vs controlled disease from published literature - Chronic comorbidities

Chronic comorbidities	RR uncontrolled vs controlled disease	Reference
Diabetes mellitus	1.8	Faggiano et al. (2003).(24) 16.60% vs 9.10% (Uncontrolled vs cured CD patients)
Metabolic syndrome	1.5	Swearingen et al. (2011). Metabolic syndrome: 66.9% vs 43.5% (CD vs NFPA population as it has been reported by Sharma et al. (2015)(22) that features of metabolic syndrome may not return to baseline after successful treatment
Overweight or obese	2.4	Faggiano et al. (2003).(24) 33.3% vs 13.6% (Uncontrolled vs cured CD patients)
Anxiety	1.4	Swearingen et al. (2011).(21) Anxiety: 10.4% vs 7.6% (CD vs NFPA population as Sharma et al. (2015)(22) indicate that although psychiatric and cognitive symptoms improve after remission, many symptoms may persist)
Depression	1.5	Swearingen et al. (2011).(21) Psychiatric disturbances: 15.6% vs 11.8% (CD vs NFPA population as Sharma et al. (2015)(22) indicate that although psychiatric and cognitive symptoms improve after remission, many symptoms may persist)
Major depression/Major depressive disorder/Mixed anxiety-depressive disorder	1.5	Swearingen et al. (2011).(21) Major depression: 7.8% vs 5.2% (CD vs NFPA as Sharma et al. (2015)(22) indicate that although psychiatric and cognitive symptoms improve after remission, many symptoms may persist)

Chronic comorbidities	RR uncontrolled vs controlled disease	Reference
Osteoporosis	3.7	Swearingen et al. (2011).(21) Osteoporosis: 6.7% vs 1.8% (CD vs control population as it has been reported that bone mineral density revert to normal after full control of disease (Sharma et al. 2015(22); Kristo et al. 2006(23))
Muscle weakness	1.5	KOL inputs: Dutch clinical experts Professor Feelders and Professor Neggers (internist-endocrinologists from the Erasmus Medical Center in the Netherlands)
Hirsutism*	2.3	KOL inputs: Dutch clinical experts Professor Feelders and Professor Neggers (internist-endocrinologists from the Erasmus Medical Center in the Netherlands)
Sexual dysfunction	1.3	KOL inputs: Dutch clinical experts Professor Feelders and Professor Neggers (internist-endocrinologists from the Erasmus Medical Center in the Netherlands)
Sleep disturbance	2.3	KOL inputs: Dutch clinical experts Professor Feelders and Professor Neggers (internist-endocrinologists from the Erasmus Medical Center in the Netherlands)
Sepsis	3.0	Swearingen et al. (2011).(21) Sepsis: 0.3% vs 0.1% (CD vs control population as KOL confirmed this condition revert to normal after full control of disease)
Key: CD, Cushing's disease; KOL, key opinion leader; NFPA, non-functioning pituitary adenomas; RR, relative risk.		

Table 45: Controlled disease – Acute comorbidities

Acute comorbidities	Osilodrostat LINC 3 trial	
	Number of patients who experienced the acute comorbidity (n)	Number of times the acute comorbidity is experienced per subject
Cardiovascular events	2	1.5
Myocardial infarction	0	0
Stroke	0	0
Venous thromboembolism	0	0
Pneumonia	0	0
Skin infection	0	0
Vertebrae fractures	0	0
Muscle weakness	0	0
Hirsutism*	0	0
Sexual dysfunction	0	0
Sleep disturbance	0	0
Sepsis	0	0
Notes: *Hirsutism only applies to women		

8.3.3 Subsequent medical therapy basket

Comorbidities in the subsequent medical therapy basked are weighted depending on the percentage of patients responding to the subsequent treatment basket.

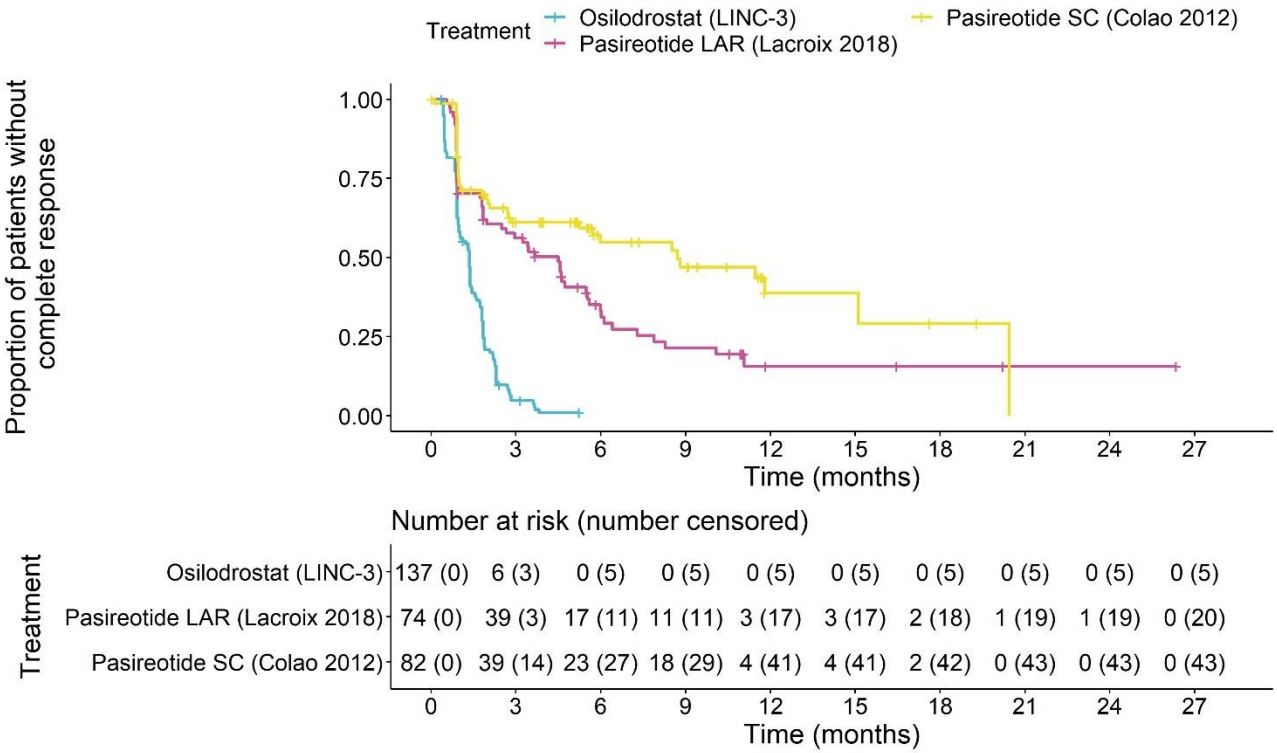
8.3.4 BLA

As patients in the BLA health state are controlled (i.e. 100% response rate), the comorbidity probability in the BLA health state is equal to the comorbidity probabilities in the controlled disease health state.

8.4 Unadjusted Kaplan–Meier curve for TTCR

Figure 8 presents the unadjusted Kaplan–Meier curve for TTCR. Note that no stopping rules have been applied to the data.

Figure 8: Kaplan–Meier for unadjusted time to complete response by treatment arm

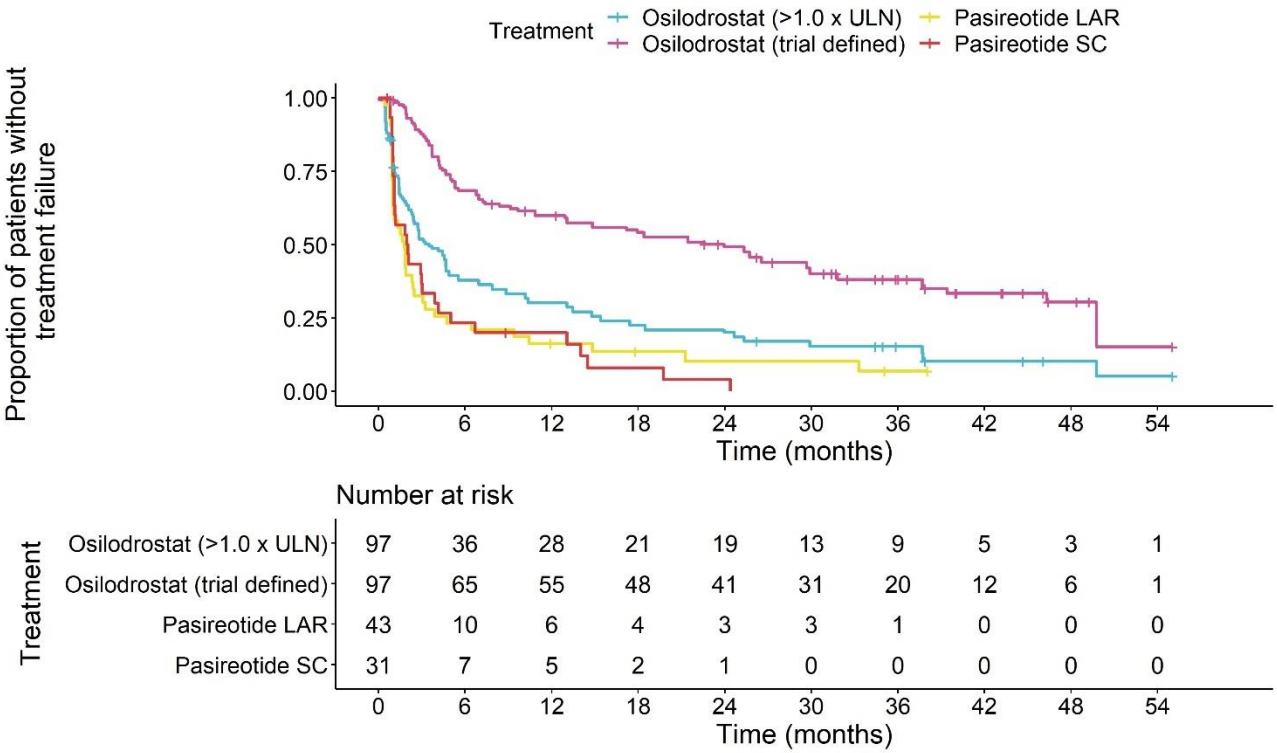


Key: LAR, long-acting release; SC, subcutaneous.

8.5 Unadjusted Kaplan–Meier curve for TTFPR

Figure 9 presents the unadjusted Kaplan–Meier curve for TTFPR. Note that no stopping rules were applied to the data for TTCR (which precedes TTFPR).

Figure 9: Kaplan–Meier for unadjusted time to treatment failure by treatment arm



Key: LAR, long-acting release; SC, subcutaneous; ULN, upper limit of normal.

8.6 Dose distribution tables

Table 46: Dose distribution table – Osilodrostat

Daily dose*	Number of tablets			Reference			
	1 mg tabs	5 mg tabs	10 mg tabs	LINC3 trial	LINC4 trial	LINC3/4	ATUc
1 mg	1			9%	11%	9%	7%
2 mg	2			14%	11%	13%	5%
3 mg	3			4%	4%	4%	14%
4 mg	4			16%	24%	18%	14%
5 mg	5			0%	0%	0%	2%
6 mg	6			9%	0%	10%	2%
7 mg	7			0%	13%	0%	7%
8 mg	8			1%	0%	1%	0%
9 mg	4	1		0%	0%	0%	0%
10 mg		2		16%	11%	15%	12%
11 mg	1	2		1%	0%	1%	0%
12 mg	2	2		1%	0%	1%	2%
13 mg	3	2		0%	0%	0%	2%
14 mg	4	2		6%	0%	5%	0%
15 mg	5	2		1%	3%	1%	2%
16 mg	6	2		0%	0%	0%	2%
17 mg	7	2		0%	0%	0%	0%
18 mg	8	2		0%	0%	0%	0%
19 mg	4	3		0%	0%	0%	0%
20 mg			2	14%	10%	13%	14%
21 mg	1		2	0%	0%	0%	0%
22 mg	2		2	0%	0%	0%	0%
23 mg	3		2	0%	0%	0%	0%
24 mg	4		2	0%	0%	0%	0%
25 mg	5		2	0%	0%	0%	0%
26 mg	6		2	0%	0%	0%	0%
27 mg	7		2	0%	0%	0%	0%
28 mg	8		2	0%	0%	0%	0%
29 mg	4	1	2	0%	0%	0%	0%
30 mg		2	2	2%	1%	2%	2%
31 mg	1	2	2	0%	0%	0%	0%
32 mg	2	2	2	0%	0%	0%	0%
33 mg	3	2	2	0%	0%	0%	0%
34 mg	4	2	2	0%	0%	0%	0%
35 mg	5	2	2	0%	0%	0%	0%

Daily dose*	Number of tablets			Reference			
	1 mg tabs	5 mg tabs	10 mg tabs	LINC3 trial	LINC4 trial	LINC3/4	ATUc
36 mg	6	2	2	0%	0%	0%	0%
37 mg	7	2	2	0%	0%	0%	0%
38 mg	8	2	2	0%	0%	0%	0%
39 mg	4	3	2	0%	0%	0%	0%
40 mg			4	4%	9%	5%	7%
41 mg	1		4	0%	0%	0%	0%
42 mg	2		4	0%	0%	0%	0%
43 mg	3		4	0%	0%	0%	0%
44 mg	4		4	0%	0%	0%	0%
45 mg	5		4	0%	0%	0%	0%
46 mg	6		4	0%	0%	0%	0%
47 mg	7		4	0%	0%	0%	0%
48 mg	8		4	0%	0%	0%	0%
49 mg	4	1	4	0%	0%	0%	0%
50 mg		2	4	0%	1%	0%	0%
51 mg	1	2	4	0%	0%	0%	0%
52 mg	2	2	4	0%	0%	0%	0%
53 mg	3	2	4	0%	0%	0%	0%
54 mg	4	2	4	0%	0%	0%	0%
55 mg	5	2	4	0%	0%	0%	0%
56 mg	6	2	4	0%	0%	0%	0%
57 mg	7	2	4	0%	0%	0%	0%
58 mg	8	2	4	0%	0%	0%	0%
59 mg	4		5	0%	0%	0%	0%
60 mg			6	1%	0%	1%	2%

Key: mg, milligram.

Notes: *Osilodrostat is given twice daily, which is already reflected in the daily dose in this table. For example, patients with a daily dose of 10 mg receive 5 mg twice daily, which is reflected in the number and size of the tabs needed.

Table 47: Dose distribution table – Pasireotide SC

Dose per admin	B2305 trial
0.3 mg	0%
0.6 mg	45%
0.9 mg	55%

Table 48: Dose distribution table – Pasireotide LAR

Dose per admin	G2304 trial
10 mg	68%
20 mg	0%
30 mg	20%
40 mg	12%
60 mg	0%
Notes: The distribution of the daily dose for Pasireotide LAR by formulation was calculated among patients randomized to a starting dose of 10 mg per day in the G2304 trial	

Medicinrådet

Medicinrådets protokol for vurdering vedrørende osilodrostat til behandling af Cushings syndrom

Version 1.0

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

Medicinrådet vurderer, om nye lægemidler og indikationsudvidelser skal anbefales som mulig standardbehandling. Medicinrådet udarbejder også behandlingsvejledninger og rekommandationer for anvendelse af medicin på sygehusene. Derudover kan Medicinrådet tage andre typer sager op, der handler om medicinanvendelse.

Om protokollen

Protokollen beskriver, hvordan Medicinrådet vil foretage vurderingen af lægemidlets værdi for patienterne. Den indeholder et eller flere kliniske spørgsmål, som den ansøgende virksomhed skal besvare i sin endelige ansøgning. Til hvert spørgsmål knytter sig en definition af patientgruppen, det lægemiddel, Medicinrådet undersøger, den behandling, Medicinrådet sammenligner med, og effektmålene. Udover de(t) kliniske spørgsmål indeholder protokollen også en beskrivelse af, hvordan litteratursøgning, -selektion og databehandling skal foregå.

Protokollen er udarbejdet med udgangspunkt i *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, som du kan finde på Medicinrådets hjemmeside under siden Metoder, og den ansøgende virksomheds foreløbige ansøgning, der fortæller, hvilke data der findes for lægemidlet.

Fremkommer der nye og væsentlige oplysninger i sagen af betydning for protokollens indhold, kan Medicinrådet tage protokollen op til fornyet behandling. Det samme gælder, hvis der er begået væsentlige fejl i forbindelse med sagsbehandlingen vedrørende protokollen. Hvis Medicinrådet foretager ændringer i protokollen, vil den ansøgende virksomhed få besked.

Dokumentoplysninger	
Godkendelsesdato	13. juli 2021
Dokumentnummer	116424
Versionsnummer	1.0

Indholdsfortegnelse

1. Begreber og forkortelser

ACTH:	Adrenokortikotropt hormon
EMA:	Det Europæiske Lægemiddelagentur (*European Medicines Agency*)
EPAR:	*European Public Assessment Report*
EUnetHTA:	*European Network for Health Technology Assessment*
FDA:	*The Food and Drug Administration*
FINOSE:	Finland, Norge og Sveriges samarbejde om medicinske teknologivurderinger
GRADE:	System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)
HTA:	Medicinsk teknologivurdering (*Health Technology Assessment)*
IQWIG:	*The Institute for Quality and Efficiency in Healthcare*
ITT:	*Intention-to-treat*
MKRF:	Mindste klinisk relevante forskel
NICE:	*The National Institute for Health and Care Excellence*
PICO:	Population, intervention, komparator og effektmål (*Population, Intervention, Comparison and Outcome)*
PP:	*Per Protocol*
RR:	Relativ risiko
SMD:	*Standardized Mean Difference*
mUFN	*Mean Urinary Free Cortisol*
ULN	*Upper Limit of Normal*

Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 13. juli 2021

2. Introduktion

Protokollen er udarbejdet, fordi Medicinrådet har modtaget en foreløbig ansøgning fra Recordati, som ønsker, at Medicinrådet vurderer osilodrostat (Isturisa) til endogent Cushings syndrom hos voksne. Medicinrådet modtog den foreløbige ansøgning den 22. december 2020. Isturisa fik markedsføringstilladelse i EU i januar 2020.

2.1 Cushings syndrom

Cushings syndrom er den kliniske tilstand, som fremkommer, når kroppen gennem længere tid udsættes for forhøjede mængder af binyrebarkhormon (kortisol). Kortisol dannes i binyrebarken, og syntesen stimuleres af kortikotropin (adrenokortikotropt hormon (ACTH)), som dannes i hypofysen [1].

Cushings syndrom kan skyldes en øget produktion af kortisol fra binyrerne (endogent Cushings syndrom) eller opstå som følge af langvarig behandling med lægemidler, som indeholder binyrebarkhormon (eksogent Cushings syndrom).
Denne protokol omhandler udelukkende endogent Cushings syndrom. Endogent Cushings syndrom kan yderligere opdeles i to grupper:

- ACTH-afhængigt Cushings syndrom, som skyldes:
    - en ACTH-producerende svulst i hypofysen (kaldet Cushings sygdom) – ca. 75 % af patienterne
      eller
    - en ACTH-producerende svulst uden for hypofysen (ektopisk Cushings syndrom) – ca. 5 % af patienterne
- ACTH-uafhængigt Cushings syndrom, som skyldes:
    - en autonom kortisolproduktion fra binyrebarken, som skyldes en godartet eller ondartet kortisolproducerende svulst i en eller begge binyrer – ca. 20 % af patienterne.

Kortisolreceptorer findes i det meste af kroppens væv, hvorfor symptombilledet hos patienterne er meget bredt, se tabel 1.

Tabel 1. Symptomer og kliniske fund ved Cushings syndrom [1]

Udseende	Vægtøgning med især abdominal fedme, måneansigt, tyrenakke (*buffalo hump*), pletorisk udseende (tomatansigt), tynde ekstremiteter
Hjerte/kar	Hypertension, forhøjet niveau af lipider og triglycerider, øget forekomst af type 2 diabetes, tromboemboliske episoder
Kønsorganer	Akne og hirsutisme (unormal hårvækst hos kvinder), blødningsforstyrrelser, impotens
Muskler	Nedsat muskelstyrke, muskelsvaghed og muskelsmerter
Mentale	Psykiske forstyrrelser fra let irritabilitet til depression, mani eller psykoser, generel utilpashed og kognitive problemer, træthed
Hud	Tynd og skrøbelig hud med blødningstendens og dårlig sårheling, tendens til perifere ødemer
Skelet	Smerter, knogleskørhed
Andet	Øget infektionstendens

De forskellige symptomer ved Cushings syndrom og medfølgende multiorgansygdomme skyldes det kronisk forhøjede kortisolniveau og i enkelte tilfælde co-produktion af androgener (mandlige kønshormoner) i binyrerne [2–6]. Insulinsekretion og -sensitivitet påvirkes i negativ retning med risiko for udvikling af type 2 diabetes [2], som sammen med dyslipidæmi og hypertension øger risikoen for alvorlig hjertekarsygdom og øget mortalitet [6]. Øget kortisolniveau er også en stærk prædiktor for udvikling af knogleskørhed. Det skyldes, at det høje kortisolniveau både direkte og indirekte påvirker knogledensiteten ved blandt andet at hæmme genopbygning af knoglemasse [3]. Risikoen for infektioner øges også, idet kortisol har brede og potente immunsupprimerende effekter [5]. Symptomerne præsenterer sig gennem måneder til år, og der er stor variation både i udbredelse og alvorlighed hos de enkelte patienter.

Tilstanden er sjælden, og i Danmark er der ca. 20-30 nye tilfælde af endogent Cushings syndrom om året, men der er usikkerhed ved dette estimat. Tilstanden er hyppigst i 20-50 års-alderen og hyppigere hos kvinder end hos mænd. Der er stor forskel på, hvornår i sygdomsforløbet patienterne diagnosticeres, da sygdommen præsenterer sig individuelt, og de enkelte symptomer kan forveksles med andre sygdomme. Mistanke om Cushings syndrom opstår typisk på baggrund af mønstergenkendelse af symptomerne og hos personer med en atypisk klinisk præsentation (fx debut i ung alder) af flere af de kendte følgesygdomme [1].

Ubehandlet forværres sygdommen, og patienterne har høj dødelighed på grund af hjertekarsygdomme og den øgede risiko for infektioner. Prognosen hos patienterne er dog god, forudsat at behandlingen startes tidligt. Cushings syndrom har betydelig negativ effekt på patienternes livskvalitet, som skyldes både ændret udseende såvel som kortisols indvirkning på psyken, og patienterne oplever ofte vedvarende psykiske senfølger, selv efter behandling er iværksat [1,7].

2.2 Osilodrostat

Osilodrostat er en kortisolsyntesehæmmer (adrenal steroidsyntesehæmmer). Det er en potent hæmmer af 11β-hydroxylase (CYP11B1), som er det enzym, der er ansvarlig for det sidste trin i syntesen af kortisol i binyrerne. CYP11B1-hæmning er forbundet med ophobning af forstadier til kortisol (11-deoxycortisol) og dermed en acceleration af adrenal syntese, herunder androgener (mandlige kønshormoner) [8]. Osilodrostat hæmmer også CYP11B2, som er ansvarlig for syntesen af aldosteron [9].

Osilodrostat findes som tabletter i styrkerne 1 mg, 5 mg og 10 mg. Den anbefalede startdosis er 2 mg osilodrostat to gange dagligt. Dosis kan titreres gradvist på baggrund af den enkelte patients respons og tolerance, med det mål at opnå normale kortisolniveauer. Den sædvanlige vedligeholdelsesdosis i kliniske studier varierede mellem 2 og 7 mg to gange dagligt. Den anbefalede maksimumdosis af osilodrostat er 30 mg to gange dagligt.

Osilodrostat har indikation til behandling af endogent Cushings syndrom hos voksne.

Isturisa (osilodrostat) modtog *orphan drug status* af EMA i 2014 og fik markedsføringstilladelse i EU i januar 2020.

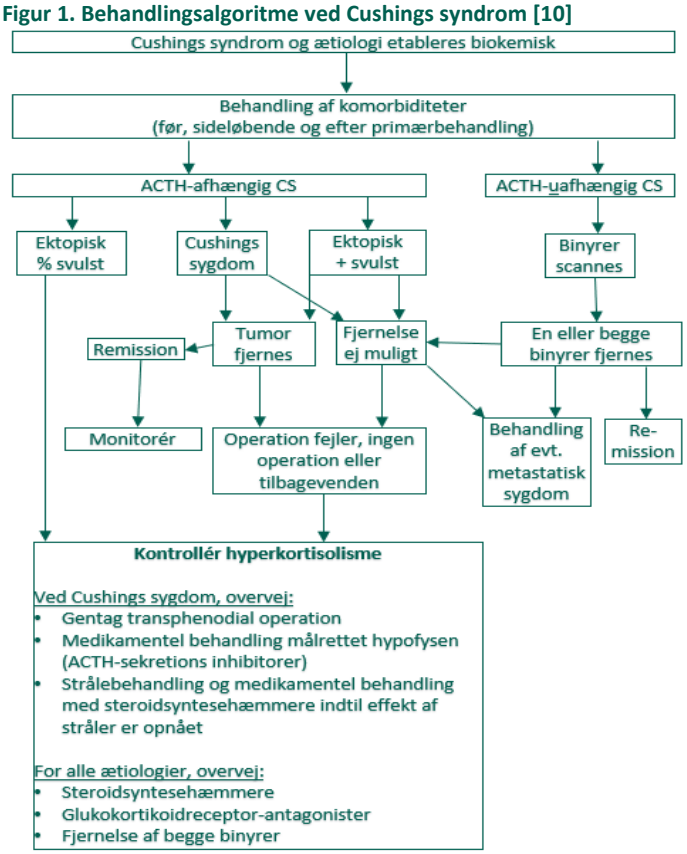
Evidensen bygger primært på data fra et randomiseret fase 3-studie, som kun inkluderer patienter med Cushings sygdom (hypofysær). Det er dog EMAs vurdering – på baggrund af osilodrostats virkningsmekanisme – at behandlingen forventes at være effektiv hos alle former for Cushings syndrom. Ekstrapolation af effekten til patienter med de øvrige former af endogent Cushings syndrom antages derfor af EMA som værende ukontroversiel [9].

2.3 Nuværende behandling

Den primære behandling af både ACTH-afhængigt og ACTH-uafhængigt Cushings syndrom er kirurgi, hvor den hormonproducerende svulst fjernes. Ved succesfuld operation vil patienterne få fjernet deres kortisoloverskud, og med tiden normaliseres kroppens udseende og funktion. Det tager dog typisk lang tid – også efter en vellykket operation – før patienterne genvinder deres normale funktionsniveau såvel fysisk som psykisk. På grund af risiko for tilbagefald (specielt for Cushings sygdom) er der behov for livslang endokrinologisk kontrol.

Udover primær kirurgi består de yderligere behandlingsmodaliteter af re-operation, medicinsk behandling, strålebehandling mod hypofyselejet og/eller fjernelse af begge binyrer, se figur 1.

Figur 1. Behandlingsalgoritme ved Cushings syndrom [10]



Medicinsk behandling
Medicinsk behandling anvendes i Danmark til at kontrollere kortisolniveauet i disse situationer:

- Når en kirurgisk fjernelse af svulsten ikke lykkes eller ikke er mulig (ca. 25 % af patienterne med Cushings sygdom). Behandlingen er typisk midlertidig, indtil definitiv behandling er mulig (strålebehandling, fjernelse af begge binyrer eller gentaget hypofyseoperation).
- Før operation for at kontrollere et betydende forhøjet kortisolniveau og dermed opnå klinisk bedring hos patienter med svære komplikationer (ca. 10 % af patienter med Cushings syndrom).
- Metastatisk Cushings syndrom.

Den medicinske behandling er ofte kun midlertidig, typisk 2-6 måneder, og kun i sjældne tilfælde (10 %) vil patienterne fortsætte i livslang behandling. Fagudvalget vurderer, at ca. 5-8 patienter om året er kandidater til medicinsk behandling.

Valg af medicinsk behandling
Der er flere tilgængelige lægemidler, som kan anvendes i den kortisolhæmmende behandling af Cushings syndrom [1]. Behandlingerne gives enten alene eller i kombination efter behov:

- Hæmmere af binyrebarkens hormonproduktion (adrenale steroidsyntese-hæmmere): Ketoconazol, metyrapon, mitotane og etomidat.
  Kan anvendes til behandling af alle former af Cushings syndrom.
  Mitotane anvendes i Danmark kun til patienter med metastatisk sygdom.
  Etomidat anvendes udelukkende i intensivt regi (ikke markedsført i Danmark).

- Hæmmere af ACTH-sekretionen: Cabergolin og pasireotid.
  Kan anvendes til behandling af Cushings sygdom, hvorimod effekten er uafklaret ved ektopisk CS. I Danmark anvendes udelukkende pasireotid (cabergolin er ikke markedsført til indikationen i Danmark).

- Glukokortikoid receptor antagonist: Mifepristone.
  Kan anvendes til behandling af alle typer Cushings syndrom (ikke markedsført til indikationen i Danmark). Anvendes sjældent på grund af risiko for overdosering.

På grund af patientgruppens heterogene præsentation af symptomer og kliniske fund samt komorbiditeter er der ikke en klart defineret medicinsk standardbehandling i Danmark. Fagudvalget vurderer, at den medicinske behandling i klinisk praksis består af ketoconazol, metyrapon og pasireotid. Valg af præparat afhænger af klinisk erfaring og en individuel helhedsvurdering af patienten samt præparaternes bivirkningsprofil. Den kliniske erfaring med ketoconazol og metyrapon er lang (> 30 år), men evidensen består af retrospektive opgørelser og *case-reports*, der primært inkluderer patienter med Cushings sygdom [11,12]. Den kliniske erfaring med pasireotid er kortere, men evidensen består af randomiserede fase 3-studier [13].

Behandlingsstrategien er enten *block-replacement*-terapi ved behov for en hurtig effekt eller en normaliseringsstrategi. Ved *block-replacement*-terapi tilstræbes det at reducere det endogene kortisolniveau til et lavt niveau og supplere med hydrokortison i substitutionsdoser for at undgå binyrebarkinsufficiens. Ved normaliseringsstrategi tilstræbes eukortisolisme (fysiologisk kortisolniveau med normal døgnvariation).

Doseringen af lægemidlerne justeres individuelt efter patientens kortisolniveau og afhængigt af tolerabilitet. Ved behandling med en steroidsyntesehæmmer skal kortisolniveauerne monitoreres med få ugers mellemrum i starten. Ved behandling med pasireotid anbefales klinisk evaluering efter to måneders behandling.
Lægemidlerne har en høj grad af interaktioner med andre lægemidler. Blandt andet er ketoconazol en kraftig hæmmer af enzymet CYP3A4. CYP3A4 er med til at omsætte en lang række lægemidler i kroppen, hvorfor det er vigtigt at have opmærksomhed på dette ved opstart og under behandling [11].

Kirurgi antages dog fortsat at være den primære behandling af Cushings syndrom. Fagudvalget forventer derfor, at behandling med osilodrostat som udgangspunkt også skal anvendes midlertidigt som de øvrige tilgængelige lægemidler.

Øvrig behandling
Udover en normalisering af kortisolniveauet er behandlingsmålet ved Cushings syndrom også at behandle komorbiditeter og den mangel på binyrebarkhormon (binyrebarkinsufficiens), som typisk opstår efter fjernelse af en hormonproducerende svulst.

Behandling af komorbiditet
Cushings syndrom er som anført associeret med en lang række komorbiditeter (kardiovaskulær sygdom, knogleskørhed, diabetes og psykiske symptomer), som behandles før, sideløbende og efter behandling af primær sygdom [1]. Behandlingen sker som udgangspunkt i endokrinologisk regi parallelt med kontrolbesøg for den primære sygdom.

Behandling af binyrebarkinsufficiens
Efter en vellykket primær operation og ved *block-replacement*-terapi vil patienterne næsten altid få binyrebarkinsufficiens. Der er ligeledes risiko for binyrebarkinsufficiens ved medicinsk normaliseringsstrategi specielt i stresssituationer. Der kan dog opleves symptomer trods substitution med fysiologiske doser hydrokortison.
Symptomer omfatter kvalme, anoreksi, vægttab og mere uspecifikke symptomer såsom træthed, udmattelse og influenzalignende muskel- og ledsmerter. Nogle patienter udvikler depression, angst og panik. Symptomlindring opnås ved at øge substitutionsdosis, men det er omvendt vigtigt at reducere dosis igen, når det er muligt, for at undgå påført Cushings syndrom [1]. Patienterne skal derfor informeres om og uddannes i at genkende tegn og symptomer på binyrebarkinsufficiens.

3. Kliniske spørgsmål

Medicinrådet bruger kliniske spørgsmål til vurderinger af lægemidlers værdi for patienterne. Til hvert spørgsmål knytter sig en definition af patientgruppen (population), af det lægemiddel, Medicinrådet undersøger (interventionen), af den behandling, Medicinrådet sammenligner med (komparator(er)), og af effektmålene.

Jf. afsnit 2.3 afhænger valg af behandling i klinikken af erfaring og en helhedsvurdering af den enkelte patient. Derfor er der ikke én behandling, som i klinikken er foretrukket frem for en anden, og fagudvalget ønsker derfor en sammenligning med alle tre komparatorer.

3.1 Klinisk spørgsmål 1

Hvilken værdi har osilodrostat sammenlignet med ketoconazol til voksne patienter med endogent Cushings syndrom?

Population
Voksne patienter med endogent Cushings syndrom, jf. situationer afsnit 2.3.

Intervention
Osilodrostat (startdosis 2 mg to gange dagligt, derefter individuel dosering på baggrund af respons og tolerabilitet).

Komparator
Ketoconazol startdosis 200 mg x 2-3 dagligt, max dosis 1.600 mg.

Effektmål
De valgte effektmål fremgår af tabel 2.

3.2 Klinisk spørgsmål 2

Hvilken værdi har osilodrostat sammenlignet med metyrapon til voksne patienter med endogent Cushings syndrom?

Population
Voksne patienter med endogent Cushings syndrom, jf. situationer afsnit 2.3.

Intervention
Osilodrostat (startdosis 2 mg to gange dagligt, derefter individuel dosering på baggrund af respons og tolerabilitet).

Komparator
Metyrapon startdosis 250 mg x 3-4 dagligt, max dosis 6.000 mg.

Effektmål
De valgte effektmål fremgår af tabel 2.

3.3 Klinisk spørgsmål 3

Hvilken værdi har osilodrostat sammenlignet med pasireotid til voksne patienter med endogent Cushings syndrom?

Population
Voksne patienter med endogent Cushings syndrom, jf. situationerne i afsnit 2.3.

Intervention
Osilodrostat (startdosis 2 mg to gange dagligt, derefter individuel dosering på baggrund af respons og tolerabilitet).

Komparator
Pasireotid[1] 600-900 mikrogram s.c. x 2 dagligt eller 10-40 mg i.m. hver 4. uge.

Effektmål
De valgte effektmål fremgår af tabel 2.

3.4 Effektmål

Medicinrådet mener, at vurderingen af lægemidlets værdi bliver bedst understøttet af de effektmål, der er nævnt i tabel 2. For hvert effektmål har Medicinrådet fastsat en mindste klinisk relevant forskel (MKRF). I det følgende afsnit argumenterer Medicinrådet for valget af effektmål og MKRF.

Tabel 2. Oversigt over valgte effektmål

Effektmål*	Vigtighed	Effektmålsgruppe**	Måleenhed	Mindste klinisk relevante forskel
Normalisering af kortisolniveau	Vigtigt	Livskvalitet, alvorlige symptomer og bivirkninger	Andel patienter, der opnår et komplet respons på koncentration af gennemsnitlig kortisol i døgnurin (mUFC[a] < ULN[b])	20 %-point
Livskvalitet	Vigtigt	Livskvalitet, alvorlige symptomer og bivirkninger	*CushingQoL Questionnaire*	10,1 point
Bivirkninger	Vigtigt	Livskvalitet, alvorlige symptomer og bivirkninger	Andel patienter, der oplever behandlingskrævende bivirkninger	10 %-point
			Kvalitativ gennemgang	

[1] Kun indikation til patienter med Cushings sygdom (hypofysær).

* For alle effektmål ønsker Medicinrådet data med længst mulig opfølgningstid, medmindre andet er angivet.
** Effektmålsgruppe refererer til de væsentlighedskriterier, som Medicinrådet lægger til grund for kategoriseringen af de relative forskelle i effekt, bivirkninger eller livskvalitet. [a)] Mean Urinary Free Cortisol (mUFC), [b)] Upper Limit of Normal (ULN).

3.4.1 Vigtige effektmål

Normalisering af kortisolniveau

Som beskrevet i afsnit 2.1 er patienter med Cushings syndrom i risiko for at udvikle mange alvorlige symptomer og følgesygdomme på grund af deres kronisk forhøjede kortisolniveau i blodet. Ved at normalisere kortisolniveauet vil symptomer og følgesygdomme over tid normaliseres [7,10]. På den baggrund vurderer fagudvalget, at effektmålet normalisering af kortisolniveau er et vigtigt effektmål, da det er et surrogat endepunkt, som giver mulighed for at vurdere behandlingen og dens afledte effekt på symptomer og følgesygdomme.
Det kan ikke udelukkes, at patienter med Cushings sygdom, trods normalisering af ovennævnte, har en overdødelighed [4,6]. Fagudvalget vurderer dog ikke, at det påvirker valg af effektmål.

Kortisol omsættes i leveren og udskilles som vandopløselige metabolitter og frit kortisol i urinen. Ved meget højt kortisol i blodbanen vil mængden af frit kortisol derfor stige, og udskillelsen i urinen af frit kortisol vil stige tilsvarende. Der er en normal fysiologisk døgnvariation af kortisolniveauet i blodet (højest om morgenen og lavest ved midnat), hvorfor måling af gennemsnitlig døgnurin-kortisol er et godt estimat for den biologisk aktive fraktion af kortisol i blodet. Kortisolniveauet kan også måles som serum-/plasma-kortisol eller i spyt, men døgnurin-kortisol anses som det bedste mål for døgnets samlede kortisolproduktion.
Patienternes respons på behandlingen kan defineres som følger:

- Komplet respons er defineret som døgnurin-kortisol ≤ øverste normal niveau (ULN).
- Partielt respons er defineret som døgnurin-kortisol > ULN, men med mindst 50 %'s reduktion fra baseline.
- "Overall" respons er defineret som et af de to ovennævnte.

Fagudvalget finder, at komplet respons er det bedste mål til at vurdere, hvor effektiv en ny behandling er. Fagudvalget ønsker effektmålet opgjort som andel patienter, der opnår et komplet respons ved henholdsvis 4 uger, 12 uger og med længst mulig opfølgningstid. På den måde vurderes behandlingen både i titreringsperioden og ved vedligeholdelsesdosis.
Der er foreligger ingen veldefineret grænse for, hvor stor en andel der skal opnå et komplet respons, før en forskel er klinisk relevant, men fagudvalget vurderer, at den mindste klinisk relevante forskel er 20 %-point.

Fagudvalget er opmærksom på, at behandling med lægemidlerne foregår ved, at dosis titreres i henhold til patientens respons. Fagudvalget ønsker derfor, at ansøger bidrager med information vedrørende regler for titrering i de inkluderede studier.

Livskvalitet
Patienter med Cushings syndrom har ofte en stærkt forringet livskvalitet som følge af symptomer og følgesygdomme [7]. Fagudvalget betragter derfor effektmålet som vigtigt for vurderingen.

Fagudvalget vurderer, at det sygdomsspecifikke livskvalitetsværktøj *CushingQoL Questionnaire,* som er valideret til patienter med Cushings syndrom, er et relevant værktøj at anvende i denne vurdering [14]. Værktøjet består af 12 punkter, som fanger patientens respons inden for syv områder: daglige aktiviteter, heling og smerte, humør og selvtillid, sociale bekymringer, fysisk optræden, hukommelse og bekymringer for fremtiden. Scoren beregnes ved at sammenlægge de individuelle scorer, som herefter standardiseres, så den totale score går fra 0-100. En stigning i score i forhold til scoren ved baseline indikerer en forbedring af livskvalitet hos patienten.

I værktøjet er den mindste relevante forskel fastsat på baggrund af 0,5 standardafvigelse forskel fra baseline, hvilket svarer til en ændring på 10,1 point fra baseline. Fagudvalget ønsker at se resultater for livskvalitet opgjort samlet og betragter en forskel i gennemsnitlig ændring fra baseline på 10,1 point som den mindste klinisk relevante forskel.

Hvis der ikke foreligger data fra *CushingQoL Questionnaire*, foretrækker fagudvalget data fra et andet valideret instrument, som er relevant for patienter med Cushings syndrom, fx det generiske EQ-5D.

Bivirkninger
Fagudvalget vurderer, at bivirkninger er et vigtigt effektmål, da det har betydning for den enkelte patients livskvalitet og for compliance. Fagudvalget vurderer dog, at villigheden til at acceptere bivirkninger er høj, da behandlingen ofte kun er midlertidig, og patienternes sygdomsbyrde ved opstart af behandling er høj.

Forekomst af behandlingskrævende bivirkninger kan være et udtryk for alvorlig toksicitet af lægemidlet, og disse kan have væsentlig indvirkning på patienternes helbred og velbefindende. Hos patienter med Cushings syndrom, som i forvejen er i forhøjet risiko for kardiovaskulære, metaboliske og infektiøse komplikationer, vil bivirkninger svarende til disse systemer forværre sygdommen yderligere. Fagudvalget ønsker effektmålet opgjort som andelen af patienter, der oplever behandlingskrævende bivirkninger med længst mulig opfølgningstid. Fagudvalget vurderer, at en forskel på 10 %-point er klinisk relevant. Fagudvalget ønsker som supplement en oversigt over, hvilke bivirkninger der kræver behandling.

Fagudvalget ønsker som supplement til effektmålet behandlingskrævende bivirkninger, at ansøger opgør bivirkningsprofilerne for både intervention og komparatorer med henblik på en kvalitativ gennemgang. Opgørelsen skal indeholde alle bivirkninger af enhver grad rapporteret i de kliniske studier. Bivirkninger af grad 3-4 bedes opgjort separat. Fagudvalget vil ud fra denne opgørelse vurdere håndterbarhed og tyngde af bivirkningsprofilen. Fagudvalget er særligt opmærksom på risiko for QT-forlængelse,

hypokortisolisme, levertoksicitet, diabetes (HbA1C), hypertension og påvirkning af kaliumbalancen samt testosteronniveau hos kvinder.

Hvis der ikke findes opgørelser over bivirkninger, kan Medicinrådet acceptere opgørelser over uønskede hændelser.

4. Litteratursøgning

Medicinrådets vurdering af lægemidlets værdi vil i udgangspunktet være baseret på data fra fuldtekstartikler publiceret i videnskabelige, fagfællebedømte (peer-reviewed) tidsskrifter og data fra Det Europæiske Lægemiddelagenturs (EMA) European Public Assessment Reports (EPAR). Herudover kan data fra Food and Drug Administration (FDA) og internationalt anerkendte HTA-agenturer (fx NICE, EUnetHTA, FINOSE og IQWiG) indgå i vurderingen. Medicinrådet kan også inddrage upublicerede og eventuelt fortrolige data – se Medicinrådets principper for anvendelse af upublicerede data.

Medicinrådet er i den foreløbige ansøgning blevet orienteret om, at der ikke findes studier, hvor osilodrostat er sammenlignet direkte med komparatorerne. Derfor skal ansøger søge efter studier til en indirekte sammenligning.

Søgestrengene fremgår af bilag 1. Derudover skal ansøger konsultere EMAs EPAR for både det aktuelle lægemiddel og dets komparator(er).

Ansøger skal ekskludere artikler med andre populationer end de, der er specificeret i protokollen, og artikler, der ikke rapporterer mindst ét af de kritiske eller vigtige effektmål.

Kriterier for litteratursøgning
Ansøger skal søge relevant litteratur i databaserne PubMed og CENTRAL (via Cochrane Library). Ansøger skal dokumentere søgningen for hver af de to databaser, fx i form af et skærmklip eller en downloadet søgestrategi. Eventuelle ændringer/tilføjelser til søgestrategien skal fremgå af dokumentationen.

Kriterier for udvælgelse af litteratur
Ansøger skal screene de artikler, der identificeres ved databasesøgningerne, for overensstemmelse med det/de i protokollen definerede kliniske spørgsmål samt kriterier for studie- og publikationstype(r). Det vil sige, at ansøger skal ekskludere artikler med andre populationer end de i protokollen specificerede. Dette gælder ligeledes for artikler, som ikke rapporterer mindst ét af de kritiske eller vigtige effektmål.

Den ansøgende virksomhed skal ved screening af artikler først ekskludere på titel- og abstractniveau, dernæst ved gennemlæsning af fuldtekstartikler. Artikler, der ekskluderes ved fuldtekstlæsning, skal fremgå af en eksklusionsliste, hvor eksklusionen begrundes kort. Den samlede udvælgelsesproces skal afrapporteres ved brug af et flowdiagram som beskrevet i PRISMA-Statement.

Ved usikkerheder om, hvorvidt en artikel på titel- og abstractniveau lever op til inklusions- og eksklusionskriterierne, skal virksomheden anvende et forsigtighedsprincip til fordel for artiklen, hvorved fuldtekstartiklen skal vurderes.

5. Den endelige ansøgning

Ansøger skal bruge Medicinrådets ansøgningsskema til sin endelige ansøgning. Vær opmærksom på følgende:

Studier og resultater

- Beskriv de inkluderede studier og baselinekarakteristikken af studiepopulationerne.
- Angiv, hvilke studier/referencer der er benyttet til at besvare hvilke kliniske spørgsmål.
- Brug som udgangspunkt ansøgningsskemaet til ekstraktion af al relevant data.
- Krydstjek de ekstraherede data med de resultater, der fremgår af de relevante EPARs.
- Angiv årsager, hvis der er uoverensstemmelser mellem resultaterne fra artikler og EPARs.
- Angiv årsager, hvis der er uoverensstemmelser i forhold til PICO (population, intervention, komparator og effektmål) mellem protokollen og studierne.
- Vurdér, hvordan uoverensstemmelserne påvirker estimaterne.

Statistiske analyser

- Begrund valget af syntesemetode (metaanalyse eller narrativ beskrivelse), og lad specifikke analysevalg fremgå tydeligt.
- Udfør en komparativ analyse for hvert enkelt effektmål på baggrund af de ekstraherede data.
- Hvis data for et effektmål ikke er baseret på alle deltagere i et studie, skal ansøger ikke gøre forsøg på at erstatte manglende data med en meningsfuld værdi.
- Angiv for hvert effektmål og studie, hvilken analysepopulation (fx intention-to-treat (ITT), per-protocol) der er anvendt.
- Angiv en sensitivitetsanalyse baseret på ITT-populationen, hvis den komparative analyse ikke er baseret herpå.
- Angiv for hvert effektmål og studie, hvilken statistisk analysemetode der er anvendt.
- Basér de statistiske analyser for dikotome effektmål på den relative forskel.
- Beregn den absolutte forskel med udgangspunkt i den estimerede relative forskel for et antaget niveau på hændelsesraten i komparatorgruppen (jf. appendiks 5 i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser).

- Foretag eventuelt en indirekte analyse, hvis der ikke foreligger direkte sammenlignende studier, og hvis intervention og komparator er sammenlignet med samme alternative komparator i separate studier. Anvend eventuelt Buchers metode for indirekte justeret sammenligning.

Metaanalyser

- Foretag en metaanalyse for de effektmål, hvor det er metodemæssigt forsvarligt, hvis der er mere end ét sammenlignende studie.
- Basér metaanalyser vedr. effektmål, hvor forskellige måleinstrumenter er brugt på tværs af de inkluderede studier, på standardized mean difference (SMD). Omregn den estimerede SMD til den foretrukne skala for effektmålet (jf. appendiks 7 i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser).
- Udfør alene netværksmetaanalyse i de undtagelsesvise situationer, hvor Medicinrådet specifikt beder om det i protokollen. Redegør i disse tilfælde for, i hvilken grad antagelserne om transitivitet og konsistens er opfyldt (gerne ved hjælp af passende statistiske metoder).
- Begrund for alle statistiske analyser valget mellem 'fixed effects'-modeller og 'random effects'-modeller.
- Beskriv den anvendte metode detaljeret.

Narrative analyser

- Begrund valget af syntesemetode (metaanalyse eller narrativ beskrivelse), og lad specifikke analysevalg fremgå tydeligt.
- Syntetisér data narrativt, hvis det ikke er en mulighed at udarbejde komparative analyser baseret på statistiske metoder.
- Beskriv studie- og patientkarakteristika samt resultater fra de inkluderede studier narrativt og i tabelform med angivelse af resultater pr. effektmål for både intervention og komparator(er).
- Beskriv forskelle mellem studier, og vurdér, hvorvidt resultaterne er sammenlignelige.

Vær opmærksom på, at Medicinrådets sekretariat forbeholder sig retten til at foretage sensitivitets- og subgruppeanalyser på baggrund af studiernes validitet og relevans, uanset valg af analysemetode.

Sundhedsøkonomiske analyser

En sundhedsøkonomisk ansøgning består af en sammenhængende, dynamisk sundhedsøkonomisk model og et teknisk dokument, hvor modellen og de antagelser, der er bygget ind i modellen, beskrives, og hvor ansøgers sundhedsøkonomiske analyse fremgår. Ved dynamisk forstås, at en variabel kun skal ændres ét sted for at være gennemgående for hele modellen. Anvend eventuelt Medicinrådets metodevejledning og tjekliste til sundhedsøkonomiske modeller til at teste modellens dynamik, og at modellen overholder formelle krav.

En sundhedsøkonomisk analyse er ikke et resultat, men er en bred analyse af modellens dynamik, hvilke parametre der har indflydelse på resultaterne, samt hvorfor og hvordan disse parametre indgår. Derfor skal det tekniske dokument som minimum indeholde følgende:

- Beskriv den valgte modelstruktur grundigt.
- Beskriv, hvis der er anvendt en indirekte analyse, hvordan den vil blive håndteret i den sundhedsøkonomiske analyse.
- Begrund og beskriv samtlige antagelser i modellen, og lad specifikke analysevalg fremgå tydeligt.
- Beskriv alle de inkluderede studier, argumentér for deres relevans, og beskriv, hvor og hvordan data anvendes i modellen.
- Begrund både de inkluderede og ekskluderede omkostninger.
- Beskriv, hvad der driver modellen, fx behandlingslængde eller lægemiddelomkostninger.
- Ekstrapoleret data skal beskrives.
- Udfør følsomhedsanalyser, som belyser, hvilke parametre i modellen der har størst indflydelse på resultatet.
- Argumentér for eventuelle afvigelser fra protokollen og den kliniske ansøgning.
- Budgetkonsekvensanalysen skal være dynamisk med omkostningsanalysen, uden diskontering og patientomkostninger.

6. Evidensens kvalitet

Medicinrådet anvender GRADE (Grading of Recommendations, Assessments, Development and Evaluation) til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen. Evidensens kvalitet fortæller, i hvor høj grad man kan have tiltro til den evidens, Medicinrådet baserer vurderingen af lægemidlets værdi på.

7. Andre overvejelser

7.1 Hypokortisolisme

Fagudvalget ønsker, at ansøger redegør for, hvordan hypokortisolisme er målt (blodprøve, patientvurdering e.l.) og vurderet i de inkluderede studier som bivirkning. Herunder også hvilke assays (immunoassay eller massespektometri-assay) der anvendt til at måle kortisolniveauerne specielt i plasma i de inkluderede studier, i forhold til at

vurdere risikoen for krydsaktivitet og dermed medbestemmelse af kortisol-forstadier, fx 11-deoxycortisol.

7.2 Compliance

Fagudvalget ønsker, at ansøger bidrager med en oversigt over håndtering og opbevaring af lægemidlerne (intervention og komparatorer) samt forhold vedrørende indtagelse m.v., i forhold til at vurdere compliance.

7.3 Behandlingsvarighed

Fagudvalget ønsker, at ansøger redegør for, hvor længe patienterne kan forventes at være i behandling med intervention og komparatorer. Den forventede behandlingsvarighed bedes afspejlet i tidshorisonten i den sundhedsøkonomiske model.

7.4 Efterfølgende behandlingslinjer

Fagudvalget ønsker informationer, der kan belyse en vurdering af, hvorvidt og hvordan indførelsen af den ansøgte intervention i dansk klinisk praksis vil påvirke behandlinger i efterfølgende behandlingslinjer, hvad angår type, varighed og forventet effekt.

8. Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning.

9. Referencer

1. Dansk endokrinologisk selskab. National behandlingsvejledning: Cushings syndrom [internet]. 2018. Tilgængelig fra: https://endocrinology.dk/nbv/hypofyse-og-binyresygdomme/cushings-syndrom/

2. Scaroni C, Zilio M, Foti M, Boscaro M. Glucose Metabolism Abnormalities in Cushing Syndrome: From Molecular Basis to Clinical Management. Endocr Rev. 2017;38(3):189–219.

3. Canalis E, Mazziotti G, Giustina A, Bilezikian JP. Glucocorticoid-induced osteoporosis: pathophysiology and therapy. Osteoporos Int. 2007;18(10):1319–28.

4. Clayton RN, Jones PW, Reulen RC, Stewart PM, Hassan-Smith ZK, Ntali G, et al. Mortality in patients with Cushing's disease more than 10 years after remission: a multicentre, multinational, retrospective cohort study. lancet Diabetes Endocrinol. 2016;4(7):569–76.

5. Cain DW, Cidlowski JA. Immune regulation by glucocorticoids. Nat Rev Immunol. 2017;17(4):233–47.

6. Ragnarsson O, Olsson DS, Papakokkinou E, Chantzichristos D, Dahlqvist P, Segerstedt E, et al. Overall and disease-specific mortality in patients with cushing disease: A Swedish nationwide study. J Clin Endocrinol Metab. 2019;104(6):2375–84.

7. Lindsay JR, Nansel T, Baid S, Gumowski J, Nieman LK. Long-Term Impaired Quality of Life in Cushing ' s Surgical Remission. 2006;91(2):447–53.

8. European Medicines Agency (EMA). Bilag I Produktresumé - Isturisa. 2020;1–22. Tilgængelig fra: https://ec.europa.eu/health/documents/community-register/2017/20171003139003/anx_139003_da.pdf

9. European Medicines Agency (EMA). Isturisa - EPAR. 2020;31(November 2019).

10. Nieman LK, Biller BMK, Findling JW, Murad MH, Newell-Price J, Savage MO, et al. Treatment of cushing's syndrome: An endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2015;100(8):2807–31.

11. European Medicines Agency (EMA). Ketoconazole - EPAR. 2014;44(September). Tilgængelig fra: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003906/WC500181493.pdf

12. Daniel E, Aylwin S, Mustafa O, Ball S, Munir A, Boelaert K, et al. Effectiveness of metyrapone in treating cushing's syndrome: A retrospective multicenter study in 195 patients. J Clin Endocrinol Metab. 2015;100(11):4146–54.

13. European Medicines Agency (EMA). Bilag I produktresumé Signifor. 2014;44(0).

14. Webb SM, Badia X, Baarahona MJ, Colao A, Strasburger CJ, Tabarin A, et al. Evaluation of health-related quality of life in patients with Cushing's syndrome with a new questionnaire. Eur J Endocrinol. 2008;158(5):623–30.

10. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende Cushings syndrom

Sammensætning af fagudvalg	
Formand	**Indstillet af**
Claus Larsen Feltoft *Overlæge*	Lægevidenskabelige Selskaber og Dansk Endokrinologisk Selskab
Medlemmer	**Udpeget af**
Eigil Husted Nielsen *Overlæge*	Region Nordjylland
Marie Juul Ørnstrup *Afdelingslæge*	Region Midtjylland
Meena Asmar *Overlæge*	Region Syddanmark
Har ikke specialet	Region Sjælland
Mikkel Andreassen *Overlæge*	Region Hovedstaden
Torben Laursen, *Overlæge, klinisk lektor*	Dansk Selskab for Klinisk Farmakologi
Gitte Stampe Møller *Klinisk farmaceut*	Dansk Selskab for Sygehusapoteksledelse
Lone Muxoll Storkfelt *Sygeplejerske*	Dansk Sygepleje Selskab
Kan ikke udpege	Danske Patienter
Gry Bispelund Knudsen	Inviteret af formanden

Medicinrådets sekretariat

Medicinrådet

Dampfærgevej 27-29, 3.th.

2100 København Ø

+45 70 10 36 00

medicinraadet@medicinraadet.dk

11. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	13. juli 2021	Godkendt af Medicinrådet.

12. Bilag

Bilag 1: Søgestrenge

Søgestreng til PubMed:

#	Søgestreng	Kommentar
#1	Cushing Syndrome[mh]	Population
#2	Cushings syndrome[tiab] OR Cushing's syndrome[tiab] OR cushing syndrome[tiab]	
#3	hypercortisolism[tiab]	
#4	Pituitary ACTH Hypersecretion[mh]	
#5	cortisol hypersecretion[tiab] OR ACTH hypersecretion[tiab] OR adrenocorticotropic hormone secreti*[tiab] OR adrenocorticotrophic hormone secreti*[tiab] OR ACTH secreti*[tiab]	
#6	Cushings disease[tiab] OR Cushing's disease[tiab] OR cushing disease[tiab]	
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	
#8	Osilodrostat[nm] OR osilodrostat[tiab] OR Isturisa*[tiab]	Intervention & komparator
#9	Ketoconazole[mh] OR ketoconazole[tiab] OR Nizoral*[tiab]	
#10	Metyrapone[mh] OR metyrapone[tiab] OR Metopiron*[tiab]	
#11	pasireotide[nm] OR pasireotide[tiab] OR Signifor*[tiab]	
#12	#8 OR #9 OR #10 OR #11	
#13	#7 AND #12	
#14	english[la] AND hasabstract	Afgrænsning til artikler på engelsk, med abstracts
#15	Animals[mh] NOT Humans[mh]	Eksklusion af dyrestudier og irrelevante publikationstyper
#16	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Guideline[pt] OR Letter[pt] OR News[pt] OR Review[pt] OR case report[ti] OR Systematic Review[pt] OR review[ti]	
#17	(#13 AND #14) NOT (#15 OR #16)	

#18	Clinical Trial[pt] OR Comparative Study[pt] OR Multicenter Study[pt]	Filter til identifikation af kliniske studier (rct, observationelle m.fl.)
#19	(clinical[tiab] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR controlled[tiab] OR case-control[tiab] OR prospective[tiab] OR multicenter[tiab] OR multicentre[tiab] OR comparative[tiab] OR open-label[tiab] OR phase II[tiab] OR phase III[tiab]) AND (trial[tiab] OR study[tiab])	
#20	Observational Study[pt] OR Cohort Studies[mh]	
#21	(observational[tiab] OR cohort[tiab] OR retrospective*[tiab]) AND (study[tiab] OR analy*[tiab])	
#22	Registries[mh] OR registry[tiab] OR nation-wide[tiab] OR nationwide[tiab] OR population-based[tiab] OR real-world[tiab]	
#23	#18 OR #19 OR #20 OR #21 OR #22	
#24	#17 AND #23	Endelig søgning

Søgestreng til CENTRAL:

#	Søgestreng	Kommentar
#1	(cushing* next (disease or syndrome)):ti,ab,kw	Population
#2	hypercortisolism:ti,ab	
#3	[mh "Pituitary ACTH Hypersecretion"]	
#4	((cortisol or ACTH or adrenocorticotropic or adrenocorticotrophic) next (secreti* or hypersecretion)):ti,ab	
#5	#1 OR #2 OR #3 OR #4	
#6	(osilodrostat or Isturisa*):ti,ab,kw	Intervention & komparator
#7	(ketoconazole or Nizoral*):ti,ab,kw	
#8	(metyrapone or Metopiron*):ti,ab,kw	
#9	(pasireotide or Signifor*):ti,ab,kw	
#10	#7 OR #8 OR #9	
#11	#5 AND #10	
#12	(clinicaltrials.gov or trialsearch):so	

#13	("conference abstract" or review):pt,ti	Eksklusion af irrelevante publikationstyper
#14	(abstract or conference or meeting or proceeding*):so	
#15	NCT*:au	
#16	#12 or #13 or #14 or #15	
#17	#11 not #16	
#18	#17 not pubmed:an	Endelig søgning, fratrukket referencer fra Pubmed. Afgræns til Trials