Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende upadacitinib til behandling af psoriasisartrit (PsA)

Vers. 1.0

Bilagsoversigt

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Medicinrådet

Medicinrådets sundheds-økonomiske afrapportering

Upadacitinib

Til behandling af psoriasisartrit

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*.

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Indholdsfortegnelse

1. Begreber og forkortelser

AIP:	Apotekernes indkøbspris
DKK:	Danske kroner
DRG:	Diagnose Relaterede Grupper
DMARD:	Sygdomsmodificerende antireumatisk lægemiddel (*Disease Modifying Anti-Rheumatic Drug)*
PsA:	Psoriasisartrit
SAIP:	Sygehusapotekernes indkøbspris

2. Konklusion

Inkrementelle omkostninger og budgetkonsekvenser
I det scenarie, Medicinrådet mener er mest sandsynligt, er de inkrementelle omkostninger for upadacitinib ca. [redacted] DKK og ca. -3.807 DKK pr. patient for 18 måneders behandling, sammenlignet med hhv. adalimumab (behandlingsnaive patienter) og ixekizumab (behandlingserfarne patienter). Når analysen er udført med apotekernes indkøbspris (AIP), er de inkrementelle omkostninger til sammenligning ca. -14.000 DKK og -28.000 DKK pr. patient.

Medicinrådet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af upadacitinib som mulig standardbehandling vil være ca. [redacted] DKK og [redacted] DKK i det femte år efter en anbefaling.
[redacted] Når analysen er udført med AIP, er budgetkonsekvenserne ca. 95.000 DKK og -8.3 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 upadacitinib som mulig standardbehandling på danske hospitaler til behandling af psoriasisartrit (PsA).

Analysen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Abbvie. Medicinrådet modtog ansøgningen den 25. august 2021.

3.1 Patientpopulation

Psoriasisartrit (PsA) er en kronisk inflammatorisk ledsygdom, der ofte optræder sammen med den kroniske hudsygdom psoriasis [1,2]. Sygdommen er multifaktoriel og betinget af både genetiske og miljømæssige faktorer [3]. PsA-patienter rapporterer ofte om smerter, nedsat fysisk funktion, træthed og vanskeligheder med daglige aktiviteter [4,5].

Prævalensen er svær at estimere grundet manglen på klare diagnostiske kriterier. Baseret på estimater fra et studie fra 2008 og beregninger fra Gigtforeningen vurderer Medicinrådet, at prævalensen formentlig er mellem 6.000 og 25.000 personer [6,7]. Sygdommen debuterer oftest i alderen 40-50 år, og prævalensen er ens for mænd og kvinder

Yderligere information om sygdomsområdet kan findes i Medicinrådets vurderingsrapport.

3.1.1 Komparator

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

Klinisk spørgsmål 1:

Hvilken værdi har upadacitinib sammenlignet med adalimumab for behandlingsnaive patienter med PsA?

Klinisk spørgsmål 2:

Hvilken værdi har upadacitinib sammenlignet med ixekizumab for behandlingserfarne patienter med PsA?

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 upadacitinib sammenlignet med adalimumab og ixekizumab. Medicinrådet vurderer nedenfor den sundhedsøkonomiske analyse, som ansøger har indsendt.

4.1 Antagelser og forudsætninger for modellen

Sammenligningen med adalimumab er lavet på baggrund af data fra studiet SELECT-PsA 1 [8]. SELECT-PsA 1 var et dobbeltblindet, randomiseret fase III-studie i patienter med aktiv PsA, som ikke havde opnået tilstrækkeligt effekt ved behandling med minimum ét ikke-biologisk sygdomsmodificerende antireumatisk lægemiddel (*Disease Modifying Anti-Rheumatic Drug* (DMARD)). SELECT-PsA 1 undersøgte effekt og sikkerhed af upadacitinib (15 mg og 30 mg) sammenlignet med placebo og adalimumab.

Sammenligningen med ixekizumab er udarbejdet på baggrund af de kliniske studier SELECT-PsA 2 [9] og SPIRIT-P2 [10]. Begge var randomiseret, dobbeltblindet fase III-studier, hvor effekt og sikkerhed af hhv. upadacitinib og ixekizumab blev undersøgt i sammenligning med placebo. Yderligere information om studierne kan findes i Medicinrådets vurderingsrapport.

4.1.1 Modelbeskrivelse

Ansøger har indsendt en omkostningsminimeringsanalyse til at estimere omkostningerne forbundet med behandlingen med upadacitinib. Denne modeltype er valgt, da ansøger argumenterer for, at upadacitinib som minimum er klinisk ligeværdig med de valgte komparatorer til behandling af de to patientpopulationer beskrevet i klinisk spørgsmål 1 og 2. Modellen tager derfor kun højde for forskelle i omkostninger som følge af forskelle i lægemiddelomkostninger, administrations- og monitoreringsomkostninger, bivirkningsomkostninger og patientomkostninger.

Medicinrådets vurdering af ansøgers model
Medicinrådet accepterer ansøgers tilgang vedr. ansøgers model.

4.1.2 Analyseperspektiv

I overensstemmelse med Medicinrådets metoder har ansøger valgt et begrænset samfundsperspektiv til sin analyse. Analysen har en tidshorisont på 18 måneder. Denne tidshorisont er valgt, siden det også er den tidshorisont, der anvendes i Medicinrådets behandlingsvejledning for kronisk leddegigt, samt sammenligningsgrundlaget der lå til grund for RADS' vurdering af biologiske og syntetiske targeterede lægemidler til behandling af PsA [11].

Omkostninger, der ligger efter det første år, er diskonteret med en rate på 3,5 % pr. år.

Medicinrådets vurdering af ansøgers analyseperspektiv
Medicinrådet accepterer ansøgers valgte tidshorisont.

4.2 Omkostninger

I det følgende præsenteres ansøgers antagelser for omkostningerne i den sundhedsøkonomiske analyse af upadacitinib sammenlignet med adalimumab og ixekizumab. Ansøger har inkluderet lægemiddelomkostninger, hospitalsomkostninger og patientomkostninger.

4.2.1 Lægemiddelomkostninger

Ansøger har, jf. *Metodevejledning for omkostningsanalyser af nye lægemidler og indikationer i hospitalssektoren,* estimeret lægemiddelomkostninger på baggrund af apotekernes indkøbspris (AIP). Doser anvendt i ansøgers analyse er hentet i de respektive produkters produktresuméer (SPC'er). Der tages i modellen ikke højde for lægemiddelspild på de lægemidler, der gives intravenøst.

Medicinrådets vurdering af ansøgers antagelser vedr. lægemiddelomkostninger
Medicinrådet har udskiftet AIP med sygehusapotekernes indkøbspris (SAIP), se Tabel 1.

Tabel 1. Anvendte lægemiddelpriser, SAIP (April 2022)

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Upadacitinib	15 mg	28 stk.	5.573,36	Amgros
Adalimumab	40 mg	2 stk.	[redacted]	Amgros
Ixekizumab	80 mg	1 stk.	[redacted]	Amgros
Secukinumab*	300 mg	2 stk.	[redacted]	Amgros
Certolizumab*	200 mg	2 stk.	[redacted]	Amgros

* Disse lægemidler er inkulderet, da de anvendes i budgetkonsekvensanalysen.

Medicinrådet accepterer ansøgers valg vedr. lægemiddelomkostninger.

4.2.2 Hospitalsomkostninger

Ansøger inkluderer administrations- og monitoreringsomkostninger i sin analyse af hospitalsomkostninger.

Administrations- og monitoreringsomkostninger

Til at estimere administrations- og monitoreringsomkostninger for upadacitinib, adalimumab og ixekizumab har ansøger taget udgangspunkt i det udvidede sammenligningsgrundlag udarbejdet af Amgros i forbindelse med udarbejdelsen af lægemiddelrekommandationen til kronisk leddegigt, hvor omkostningerne for behandling af kronisk leddegigt med targeterede syntetiske DMARDs estimeres [12]. Rapporten estimerer omkostninger som følge af udgifter til arbejdstid, lokaler og diagnostiske test. Ansøger antager dermed, at administrations- og monitoreringsomkostningerne for patienter med kronisk leddegigt er sammenlignelige med patienter med PsA.

Da lægemidlerne upadacitinib og ixekizumab ikke bliver evalueret i det udvidede sammenligningsgrundlag, anvendes omkostningerne estimeret for lægemidlerne tofacitinib og certolizumab. Administrationsomkostningerne for upadacitinib baseres på omkostningerne for tofacitinib, da dette lægemiddel også gives oralt, mens administrationsomkostningerne for ixekizumab baseres på omkostningerne for certolizumab, da dette ligeledes gives subkutant.

Medicinrådets vurdering af ansøgers antagelser vedr. administrations- og monitoreringsomkostninger

Medicinrådet accepterer ansøgers tilgang til estimering af administrations- og monitoreringsomkostninger. Fagudvalget vurderer, at administration og monitorering af lægemidler til behandling af PsA vil svare til omkostningerne ved behandling af patienter med kronisk leddegigt, og at administrationsomkostningerne for upadacitinib og

ixekizumab kan baseres på de tilsvarende omkostninger for henholdsvis tofacitinib og certolizumab. Anvendte enhedsomkostninger kan ses i Tabel 2.

Tabel 2. Omkostninger til lægemiddeladministration

	Upadacitinib [DKK]	Adalimumab [DKK]	Ixekizumab [DKK]
Arbejdstid - læge	2753	2550	2550
Arbejdstid - sygeplejerske	1852	2114	2114
Blodprøver mm.	1437	1421	1421
Lokaler	65	72	72
Utensilier		78	78
Præmedicinering			
Inkrementelle administrationsomkostninger (18 måneder)	6107	6235	6235

Medicinrådet accepterer ansøgers tilgang vedr. administrationsomkostninger.

Bivirkningsomkostninger

Ansøger har ikke inkluderet omkostninger som følge af bivirkninger i sin analyse, da det vurderes, at sikkerhed ved behandling med upadacitinib som minimum er ligeværdigt med sikkerheden ved behandling med adalimumab eller ixekizumab.

Medicinrådets vurdering af ansøgers antagelser vedr. bivirkningsomkostninger

Medicinrådet accepterer, at bivirkningsomkostninger ikke inkluderes i omkostningsanalysen, da det i vurderingen af den kliniske merværdi også findes, at lægemidlerne er sammenlignelige, hvad angår bivirkningernes sværhedsgrad. Selvom lægemidlernes bivirkningsprofiler er forskellige, vurderes omkostningerne til håndtering af dem at være sammenlignelige. Yderligere information og lægemidlernes bivirkningsprofiler kan findes i Medicinrådets vurderingsrapport.

Fagudvalget har understreget, at der generelt er øget opmærksomhed blandt klinikere og patienter mht. sikkerheden ved behandling med JAK-hæmmere, da der er konstateret en øget risiko for VTE, alvorlige infektioner hos ældre, risiko for alvorlige kardiovaskulære hændelser og kræft ved behandling med tofacitinib. Det er endnu uklart, hvorvidt der er tale om, at disse bivirkninger er en klasseeffekt for JAK-hæmmere. Disse bivirkninger er grundet usikkerheden om prævalensen ikke inkluderet i omkostningsanalysen.

Medicinrådet accepterer ansøgers tilgang vedr. bivirkningsomkostninger.

4.2.3 Patientomkostninger

Til estimering af patientomkostninger har ansøger også taget udgangspunkt i det førnævnte udvidede sammenligningsgrundlag udarbejdet af Amgros. Patientomkostninger er estimeret på baggrund af administrations- og monitoreringsbesøg på hospitalet og inkluderer patientens effektive tid på hospitalet, ventetid og transporttid.

Medicinrådets vurdering af ansøgers antagelser vedr. patientomkostninger
Medicinrådet accepterer ansøgers estimerede patientomkostninger, som kan ses i Tabel 3.

Tabel 3. Estimerede patientomkostninger over 18 måneder

	Upadacitinib [DKK]	Adalimumab [DKK]	Ixekizumab [DKK]
Patienttid	1.284	2.256	1.813
Transport	1.651	1.642	1.642

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 nogen følsomhedsanalyser for omkostningsanalysen.

Medicinrådets vurdering af ansøgers valg af følsomhedsanalyser
Medicinrådet accepterer ansøgers valg om ikke at udarbejde følsomhedsanalyser for omkostningsanalysen.

Medicinrådet vælger ikke at udarbejde egne følsomhedsanalyser for analysen.

4.4 Opsummering af basisantagelser

I Tabel 9 opsummeres basisantagelserne i henholdsvis ansøgers og Medicinrådets hovedanalyse.

Tabel 4. Basisantagelser for ansøgers og Medicinrådets hovedanalyse

Basisantagelser	Ansøger	Medicinrådet
Tidshorisont	18 måneder	18 måneder
Diskonteringsrate	3,5 % p.a.	3,5 % p.a.

Basisantagelser	Ansøger	Medicinrådet
Inkluderede omkostninger	Lægemiddelomkostninger Administrationsomkostninger Patient- og transportomkostninger	Lægemiddelomkostninger Administrationsomkostninger Patient- og transportomkostninger
Dosering	Upadacitinib: 15 mg dagligt Adalimumab: 40 mg hver 2. uge Ixekizumab: 2 injektioner a 80 mg i uge 0 efterfulgt af 80 mg hver 4. uge efterfølgende	Upadacitinib: 15 mg dagligt Adalimumab: 40 mg hver 2. uge Ixekizumab: 2 injektioner a 80 mg i uge 0 efterfulgt af 80 mg hver 4. uge efterfølgende
Inkludering af spild	Nej	Nej

5. Resultater

5.1 Resultatet af Medicinrådets hovedanalyse

Medicinrådets hovedanalyse bygger på samme antagelser som ansøgers hovedanalyse.

Den gennemsnitlige inkrementelle omkostning pr. patient bliver ca. [redacted] og [redacted] for 18 måneders behandling i Medicinrådets hovedanalyse, når der sammenlignes med hhv. adalimumab og ixekizumab.

Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient ca. -14.000 DKK og -28.000 DKK.

Resultaterne fra Medicinrådets hovedanalyse er præsenteret i Tabel 5 og Tabel 6.

Tabel 5. Resultatet af Medicinrådets hovedanalyse ved sammenligning med adalimumab (klinisk spørgsmål 1), DKK, diskonterede tal

	Upadacitinib	Adalimumab	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	6.241	6.241	-
Patientomkostninger	3.458	3.902	-443
Totale omkostninger	[redacted]	[redacted]	[redacted]

Tabel 6. Resultatet af Medicinrådets hovedanalyse ved sammenligning med ixekizumab (klinisk spørgsmål 2), DKK, diskonterede tal

	Upadacitinib	Ixekizumab	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	6.241	6.113	128
Patientomkostninger	3.458	2.938	521
Totale omkostninger	[redacted]	[redacted]	[redacted]

6. Budgetkonsekvenser

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

- upadacitinib bliver anbefalet som mulig standardbehandling af Medicinrådet til indikationen, som denne analyse omhandler.
- upadacitinib 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 baseret patientantal på baggrund af Medicinrådets protokol, hvor prævalensen på baggrund af tal fra Dansk Reumatologisk Database vurderes at være ca. 2.560 patienter i biologisk behandling for PsA ved udgangen af 2019.
330 af disse patienter var behandlingsnaive og startede biologisk behandling, mens ca. 860 behandlingserfarne patienter skiftede over til et nyt biologisk lægemiddel i dette år.

Baseret på rangering af TNF-inhibitorerne adalimumab, infliximab og etanercept, antager ansøger, at disse anvendes til 90 % af de behandlingsnaive patienter defineret i klinisk spørgsmål 1. For de resterende 10 % forventes det, at behandling vil være med enten secukinumab, ixekizumab eller upadacitinib, såfremt denne anbefales. Andele for lægemidlerne i de to scenarier kan findes i Tabel 7.

Omkostninger for secukinumab er estimeret efter samme metode som de øvrige lægemidler, der indgår i analysen, hvor lægemiddelpriser er baseret på SAIP (se Tabel 1), og administrations- og monitoreringsomkostninger er estimeret på baggrund af det udvidede sammenligningsgrundlag, der er beskrevet i sektion 4.2.

For den behandlingserfarne patientpopulation defineret i klinisk spørgsmål 2, antages det, at 10 % behandles med adalimumab, og at 70 % behandles med ixekizumab, uafhængigt af om upadacitinib anbefales. Såfremt upadacitinib anbefales, vil en andel af

patienterne behandles med upadacitinib i stedet for certolizumab eller secukinumab. Andele for lægemidlerne i de to scenarier kan findes i Tabel 8. Omkostninger pr. patient ved behandling med certolizumab estimeres på samme vis som de øvrige lægemidler, der indgår i analysen.

Medicinrådets vurdering af ansøgers budgetkonsekvensanalyse

Medicinrådet accepterer ansøgers antagelser for budgetkonsekvensanalysen. Antal nye patienter pr. år for de behandlingsnaive patienter kan findes i Tabel 9. Antal nye patienter for de behandlingserfarne patienter kan findes i Tabel 10.

Tabel 7. Fordeling af lægemidler der anvendes til behandlingsnaive patienter (klinisk spørgsmål 1)

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Adalimumab	90,0 %	90,0 %	90,0 %	90,0 %	90,0 %
Upadacitinib	2,0 %	3,0 %	4,0 %	4,0 %	4,0 %
Secukinumab	4,0 %	3,5 %	3,0 %	3,0 %	3,0 %
Ixekizumab	4,0 %	3,5 %	3,0 %	3,0 %	3,0 %
			Anbefales ikke		
Adalimumab	90,0 %	90,0 %	90,0 %	90,0 %	90,0 %
Upadacitinib	0,0 %	0,0 %	0,0 %	0,0 %	0,0 %
Secukinumab	5,0 %	5,0%	5,0 %	5,0 %	5,0 %
Ixekizumab	5,0 %	5,0 %	5,0 %	5,0 %	5,0 %

Tabel 8. Fordeling af lægemidler der anvendes til behandlingserfarne patienter (klinisk spørgsmål 2)

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Adalimumab	10,0 %	10,0 %	10,0 %	10,0 %	10,0 %
Upadacitinib	7,5 %	14,0 %	14,0 %	14,0 %	14,0 %
Secukinumab	10,0 %	5,0 %	5,0 %	5,0 %	5,0 %
Ixekizumab	70,0 %	70,0 %	70,0 %	70,0 %	70,0 %
Certolizumab	2,5 %	1,0 %	1,0 %	1,0 %	1,0 %
			Anbefales ikke		
Adalimumab	10,00 %	10 %	10 %	10 %	10 %
Upadacitinib	0,00 %	0 %	0 %	0 %	0 %
Secukinumab	15,00 %	15 %	15 %	15 %	15 %
Ixekizumab	70,00 %	70 %	70 %	70 %	70 %

Certolizumab	5,00 %	5 %	5 %	5 %	5 %

Tabel 9. Medicinrådets estimat af antal nye patienter pr. år for behandlingsnaive patienter (klinisk spørgsmål 1)

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Upadacitnib	7	10	13	13	13
Komparatorer	323	320	317	317	317
			Anbefales ikke		
Upadacitinib	0	0	0	0	0
Komparatorer	330	330	330	330	330

Tabel 10. Medicinrådets estimat af antal nye patienter pr. år for behandlingserfarne patienter (klinisk spørgsmål 2)

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Upadacitinib	65	120	120	120	120
Komparatorer	796	740	740	740	740
			Anbefales ikke		
Upadacitinib	0	0	0	0	0
Komparatorer	860	860	860	860	860

6.2 Medicinrådets budgetkonsekvensanalyse

Medicinrådet estimerer, at anvendelse af upadacitinib til behandlingsnaive patienter vil resultere i budgetkonsekvenser på ca. [redacted] i det femte år efter en anbefaling. Resultatet er præsenteret i Tabel 10. Anbefaling af upadacitinib til behandlingserfarne patienter estimeres at resultere i budgetkonsekvenser på ca. [redacted] DKK i det femte år efter en anbefaling. Resultatet er præsenteret i Tabel 11.

Er analysen udført med AIP, bliver budgetkonsekvenserne hhv. ca. 95.000 og -8.3 mio. DKK i år 5.

Tabel 11. Medicinrådets analyse af totale budgetkonsekvenser for behandlingsnaive patienter (klinisk spørgsmål 1), 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]

Tabel 12. Medicinrådets analyse af totale budgetkonsekvenser for behandlingserfarne patienter (klinisk spørgsmål 2), 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 upadacitinib er forbundet med inkrementelle omkostninger på ca. [redacted] DKK og [redacted] DKK sammenlignet med behandling med hhv. adalimumab og ixekizumab for behandling i 18 måneder. De inkrementelle omkostninger er næsten udelukkende drevet af omkostninger til lægemidler.

Den primære usikkerhed i modellen relaterer sig til behandlingsvarigheden, og hvorvidt patienter er længere eller kortere tid i behandling end 18 måneder. Her vurderes det dog, at valget af en tidshorisont på 18 måneder er rimeligt, da fagudvalget for andre gigtsygdomme har estimeret, at den typiske behandlingslængde før præparatskifte er 18 måneder. Denne behandlings anbefales også i Medicinrådets behandlingsvejledning for kronisk leddegigt, hvor der ikke er nogen umiddelbare holdepunkter for, at behandlingsvarigheden skulle være anderledes for patienter med PsA. En tilsvarende behandlingslængde blev også anvendt i RADS' udvidede sammenligningsgrundlag for biologiske og targeterede lægemidler til behandling af PsA [11]. Yderligere vurderes det,

at graden af usikkerhed omkring behandlingslængde er den samme for de forskellige lægemidler vurderet i analysen.

Medicinrådet understreger, at der generelt er øget opmærksomhed blandt klinikere og patienter mht. sikkerheden ved behandling med JAK-hæmmere jf. afsnit 4.2.2, hvilket ikke er muligt at inkludere i den sundhedsøkonomiske model. Såfremt der skulle være en øget forekomst af de beskrevne bivirkninger, vil de inkrementelle omkostninger være højere for behandling med upadacitinib, mens besparelsen på budgetkonsekvenser for behandlingserfarne patienter ville være af mindre størrelse.

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9. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	26.01.2022	Godkendt af Medicinrådet

10. Bilag

10.1 Resultatet af ansøgers hovedanalyse

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient ca. [redacted] DKK og [redacted] DKK, når der sammenlignes med hhv. adalimumab og ixekizumab over en tidshorisont på 5 år. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 13 og Tabel 14.

Tabel 13. Resultatet af ansøgers hovedanalyse ved sammenligning med adalimumab (klinisk spørgsmål 1), DKK, diskonterede tal

	Upadacitinib	Adalimumab	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	6.241	6.241	-
Patientomkostninger	3.458	3.902	-443
Totale omkostninger	[redacted]	[redacted]	[redacted]

Tabel 14. Resultatet af Medicinrådets hovedanalyse ved sammenligning med ixekizumab (klinisk spørgsmål 2), DKK, diskonterede tal

	Upadacitinib	Ixekizumab	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	6.241	6.113	128
Patientomkostninger	3.458	2.938	521
Totale omkostninger	[redacted]	[redacted]	[redacted]

10.2 Resultatet af ansøgers budgetkonsekvensanalyse

Ansøger har inkluderet de samme omkostninger i budgetkonsekvensanalysen, som er inkluderet i omkostningsanalysen, dog uden patientomkostninger.

Ansøger estimerer, at anvendelse af upadacitinib til behandlingsnaive patienter vil resultere i budgetkonsekvenser på ca. [redacted] DKK i det femte år efter en anbefaling. Resultatet er præsenteret i Tabel 15 . Anbefaling af upadacitinib til behandlingserfarne

patienter estimeres at resultere i budgetkonsekvenser på ca. [redacted] DKK i det femte år efter en anbefaling. Resultatet er præsenteret i Tabel 16.

Tabel 15. Medicinrådets analyse af totale budgetkonsekvenser for behandlingsnaive patienter (klinisk spørgsmål 1), 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]

Tabel 16. Medicinrådets analyse af totale budgetkonsekvenser for behandlingserfarne patienter (klinisk spørgsmål 2), 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]

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Forhandlingsnotat

Dato for behandling i Medicinrådet	23.02.2022
Leverandør	Abbvie
Lægemiddel	Upadacitinib (Rinvoq)
Ansøgt indikation	Upadacitinib er indikeret til aktiv psoriasisartrit hos voksne patienter, der har udvist utilstrækkeligt respons på eller er intolerante over for et eller flere sygdomsmodificerende anti-reumatiske Lægemidler (DMARD'er). Upadacitinib kan anvendes som monoterapi eller I kombination med methotrexat.

Forhandlingsresultat

Amgros har følgende pris på upadacitinib:

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke/dosis/form	Pakningsstørrelse	AIP (DKK)	Nuværende SAIP (DKK)	SAIP (DKK)*	Rabat ift. AIP
Upadacitinib	15 mg depot tablet	28 stk.	6.475,41	[redacted]	[redacted]	[redacted]

*Pris gældende fra d. 01.04.2022

I efteråret 2021 har Amgros udbudt alle lægemidler, der er en del af de biologiske behandlingsvejledninger indenfor reumatologi, dermatologi og gastroenterologi. Upadacitinib er en del af disse lægemidler. Aftalerne starter d. 01.04.2022.

Konkurrencesituationen

Medicinrådet besluttede den 20. november 2020 at udarbejde en behandlingsvejledning vedr. psoriasisartrit mhp. at erstatte nuværende RADS-behandlingsvejledning for anvendelse af biologisk behandling af psoriasisartrit.

[redacted]

Nedenstående tabel viser et udvalg af lægemidlerne godkendt til sammen indikation. Priserne gælder fra 01-04.2022 – 01.10.2022. Herefter er der mulighed for prisjustering til en lavere pris.

Tabel 2: Sammenligning af udvalgte nyere lægemidler og deres priser

Lægemiddel	Sammenligningsdosis	Vedligeholdelse sammenligningsdosis	Antal mg/18 måneder	Årlig lægemiddelpris SAIP pr. 18 md. (DKK)
Upadacitinib	15 mg depottablet daglig	15 mg daglig	8.218 mg	[redacted]
Ixekizumab*	160 mg (SC) i uge 0	80 mg hver 4. uge	1.700 mg	[redacted]
Secukinumab* (bioerfarne)	300 mg (SC) i uge 0, 1, 2, 3 og 4	300 mg 1 gang om mdr.	6.300 mg	[redacted]

*Data hentet fra lægemiddelrekommandationen som starter d.1/4-2022.

Status fra andre lande

Norge: Godkendt d. 21.06.2021[1]

Konklusion

Det er Amgros vurdering, at prisen for 18 måneder behandling er rimelig sammenlignet med andre nyere lægemidler til psoriasisartrit.

Amgros vurderer, at konkurrencen indenfor dette store område med lægemidler til mange indikationer, fungerer på bedste måde med et set-up med behandlingsvejledninger efterfulgt af udbud og rekommandation. Psoriasisartrit indgår endnu ikke som en af Medicinrådets nye behandlingsvejledninger, men der er en lægemiddelrekommandation, der er baseret på en RADS behandlingsvejledning.

Alle lægemidlerne med indikationen psoriasisartrit har også andre indikationer og er derfor med i det store fælles udbud og prisen pr. pakninger for lægemidlet er ens til alle indikationerne. Derfor er det også muligt at anvende de priser som firmaerne har indgivet i det store udbud til denne indikation.

[1] Upadacitinib (Rinvoq) - Indikasjon II (nyemetoder.no)

AbbVie response to The Danish Medicines Council evaluation report of upadacitinib for the treatment of psoriatic arthritis

First of all, AbbVie would like to thank The Danish Medicines Council for the evaluation report and for the opportunity to comment on the contents of the report.

AbbVie would like to use this opportunity address a few things mentioned in the report:

1. **FDA and EMA safety warnings of tofacitinib regarding VTE and MACE**

The Medicines Council mentions the FDA and EMA safety warnings of tofacitinib in the report and AbbVie would like to provide additional context regarding the safety warnings.

First of all, all JAK-inhibitors are not the same. For example, there are quite significant differences when it comes to the pharmacokinetics of the different JAK inhibitors available on the market. The metabolism of the drugs differs from primarily hepatic clearance (tofacitinib) to mainly renal excretion (baricitinib) and the half-life of the substances also differs from 3h (tofacitinib) to 23h (filgotinib) (1–3). The chemical compositions have a large variation which for example might lead to differences in selectivity over one JAK isoform vs another, which in turn might affect different signaling pathways in the immunomodulatory cascade (4–10). Hence, leading to differences in efficacy and safety profiles of the different JAK inhibitors. Efficacy and safety data of randomized clinical trials in the JAK inhibitor class have shown to differ as well, though a final conclusion cannot be drawn since randomized head-to-head studies have not been made.

The safety warnings from FDA and EMA are based on the ORAL surveillance study, a randomized clinical study specifically designed to assess the safety of the JAK-inhibitor tofacitinib vs. the TNF-inhibitors adalimumab and etanerecept in patients with rheumatoid arthritis (RA). ORAL surveillance was mandated by the US FDA after seeing signs of possible VTE and MACE safety concerns early in the development program for tofacitinib. The FDA considered that a traditional post-marketing phase 4 observational study would not be sufficient to identify these risks and demanded a randomized clinical trial with a selected patient group to be undertaken. Results from this trial indicates an increased risk of VTE and MACE for patients treated with tofacitinib compared to adalimumab and etanerecept (11–15).

Upadacitinib has an extensive clinical trial program for several indications across many different therapeutical areas, such as rheumatology, dermatology and gastroenterology. No increased safety concerns regarding VTE and MACE has been identified in the earlier phases of the development program of upadacitinib **and long term follow-up data and integrated safety analyses also indicate no increased risk of VTE and MACE compared to adalimumab** (16–19). AbbVie refers to data shared under chapter 6.3 in the submission dossier (p. 55-57), data which is also mentioned in the assessment report by The Medicines Council. Existing data demonstrates that upadacitinib has a well-defined safety profile and that there is no increased risk of VTE and MACE compared to adalimumab.

The Medicines Council mentions on p. 21 in the assessment report that no post marketing study has been performed on upadacitinib. AbbVie would like to clarify that we have initiated a post-marketing surveillance study programme of upadacitinib, which is standard procedure when a new substance is approved. In the US, data will be collected via the Corrona-registry while in the EU data will be collected from 5 European registers, amongst them ARTIS in Sweden and DANBIO in Denmark

(20). These studies will specifically gather data on adverse events of interest such as e.g VTE, MACE, malignancies and serious infections. However, there has been no demands put forth by the FDA or EMA regarding a specific patient population for these studies, as was the case with tofacitinib.

Furthermore, AbbVie will continuously collect and gather data on Rinvoqs safety and efficacy across the rheumatological indications in the long term, which will give use head-to-head data vs adalimumab for up to 10 years.

AbbVie fully supports that caution and consideration of possible adverse events, such as VTE and MACE, should always be taken when administering new treatments. However, no JAK-inhibitor is the same and available safety data on upadacitinib does not point to any increased risk of VTE and MACE, as has been the case with tofacitinib.

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Medicinrådet

Medicinrådets vurdering vedrørende upadacitinib til behandling af psoriasisartrit

Version 1.2

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 (gældende for lægemidler, hvor en foreløbig ansøgning er indsendt inden 31. dec. 2020).

Dokumentoplysninger	
Godkendelsesdato	26. januar 2022
Dokumentnummer	133394
Versionsnummer	1.2

Indholdsfortegnelse

1. Medicinrådets konklusion

Medicinrådet har vurderet upadacitinib til patienter med psoriasisartrit uden moderat til svær plaque psoriasis, som har haft et utilstrækkeligt respons på, eller som har været intolerante over for en forudgående behandling med et konventionelt sygdomsmodificerende antireumatisk lægemiddel.

Til patienter uden forudgående behandling med biologiske/targeterede syntetiske antireumatiske lægemidler vurderer Medicinrådet, at upadacitinib ingen dokumenteret merværdi har sammenlignet med adalimumab.

Til patienter, som tidligere har modtaget behandling med biologiske/targeterede syntetiske antireumatiske lægemidler, vurderer Medicinrådet, at den samlede værdi af upadacitinib sammenlignet med ixekizumab ikke kan kategoriseres efter Medicinrådets metoder. Den indirekte sammenligning tyder på, at der ikke er forskel mellem upadacitinib og ixekizumab, hvad angår sygdomsaktivitet, livskvalitet eller alvorlige uønskede hændelser. Resultaterne skal dog tages med forbehold, da patienter med psoriasisartrit er en heterogen patientpopulation, hvilket betyder, at sammenligninger på tværs af studier generelt er behæftet med usikkerhed. Derfor finder Medicinrådet, at det indirekte sammenligningsgrundlag er utilstrækkelig til at drage konklusioner i forhold til effekt og bivirkninger.

Medicinrådet understreger, at der er øget opmærksomhed på sikkerheden ved behandling med JAK-hæmmere. Før dette er afklaret nærmere, vil Medicinrådet ikke tage stilling til, om upadacitinib kan ligestilles med de øvrige biologiske og targeterede syntetiske lægemidler til disse patientgrupper.

Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 27. januar 2022

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

ACR50: *American College of Rheumatology 50 % response*

bDMARD: Biologisk *Disease Modifying Anti-Rheumatic Drug*

CI: Konfidensinterval

CRP: C-reaktivt protein

csDMARD: Konventionel *Disease Modifying Anti-Rheumatic Drug*

DANBIO: Dansk Reumatologisk Database

DMARD: Sygdomsmodificerende antireumatisk lægemiddel (*Disease Modifying Anti-Rheumatic Drug)*

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

EPAR: *European Public Assessment Report*

FDA: *The Food and Drug Administration*

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

HR: *Hazard ratio*

IL-17: Interleukin 17

IL-23: Interleukin 23

ITT: *Intention-to-treat*

MKRF: Mindste klinisk relevante forskel

mTSS: *Modified Total Sharp Score*

MTX Methotrexat

PASI: *Psoriasis Area Severity Index*

PsA: Psoriasisartrit

RCT: Randomiseret kontrolleret studie *(Randomised Controlled Trial)*

RR: Relativ risiko

SF-36: Short Form 36

SMD: *Standardized Mean Difference*

tsDMARD: Targeteret syntetisk *Disease Modifying Anti-Rheumatic Drug*

VAS: *Visual Assessment Scale*

VTE: Venøs tromboemboli

3. Introduktion

Formålet med Medicinrådets vurdering af upadacitinib (Rinvoq®) til psoriasisartrit er at vurdere den værdi, lægemidlet har sammenlignet med dansk standardbehandling.

Vurderingen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Abbvie. Medicinrådet modtog ansøgningen den 25. august 2021.

De kliniske spørgsmål er:

1. Hvilken værdi har upadacitinib sammenlignet med adalimumab for behandlingsnaive patienter med PsA?
2. Hvilken værdi har upadacitinib sammenlignet med ixekizumab for behandlingserfarne patienter med PsA?

3.1 Psoriasisartrit

Psoriasisartrit (PsA) er en kronisk inflammatorisk ledsygdom, der ofte (men ikke nødvendigvis) optræder sammen med den kroniske hudsygdom psoriasis [1,2]. Patogenesen er en T-celle-medieret inflammation og involverer en kompleks række interaktioner mellem immunceller og proinflammatoriske cytokiner, hvor T-celler og makrofager rekrutteres til led- og hudvæv [3]. Disse immunceller fremmer derefter inflammatoriske processer involveret i sygdommen, hvoraf inflammation medieret af det ekstracellulære interleukin 17 og 23 (IL-17 og IL-23) ser ud til at spille en nøglerolle [3–6]. Sygdommen er multifaktoriel og betinget af både genetiske og miljømæssige faktorer [7].

PsA kan både manifestere sig ved inflammation i perifere led og i rygsøjlen, og der kan desuden optræde ekstraartikulære symptomer som inflammation i senetilhæftninger (entesit), hævede fingre eller tæer (daktylit) og negledystrofi [8]. Patienterne kan også have betændelse i øjets regnbue- og årehinde (uveitis) eller have kronisk inflammatorisk tarmsygdom. Det kan være vanskeligt at skelne diagnostisk mellem PsA med aksial involvering og rygsøjlegigt (spondylartrit) af anden art. De kliniske manifestationer varierer betydeligt mellem patienter [9–11] og har stor betydning for patienternes liv. PsA-patienter rapporterer ofte om smerter, nedsat fysisk funktion, træthed og vanskeligheder med daglige aktiviteter [12,13].

I den nationale behandlingsvejledning for PsA fra Dansk Reumatologisk Selskab fremgår det, at der mangler validerede kliniske diagnosekriterier for PsA, men at der er udviklet klassifikationskriterier, som kan benyttes som støtte. Diagnosen stilles på baggrund af en objektiv undersøgelse af bevægeapparat og hud sammen med serologi og biokemi [8].

Prævalensen er svær at estimere grundet manglen på klare diagnostiske kriterier. Baseret på estimater fra et studie fra 2008 og beregninger fra Gigtforeningen finder Medicinrådet, at prævalensen formentlig er mellem 6.000 og 25.000 personer [14,15]. Det skønnes desuden, at op til ca. 15 % af patienter med psoriasis udvikler PsA [8]. Sygdommen debuterer oftest i alderen 40-50 år, og prævalensen er ens for mænd og kvinder.

3.2 Upadacitinib

Upadacitinib er en selektiv Janus kinase (JAK) inhibitor, der primært hæmmer JAK1 og JAK1/3. JAK spiller en vigtig rolle i betændelsesprocessen og i den beskadigelse af leddene, som finder sted ved PsA.

Der er tale om en indikationsudvidelse til PsA med følgende EMA-indikation:

Upadacitinib er indiceret til aktiv psoriasisartrit hos voksne patienter, der har udvist utilstrækkeligt respons på eller er intolerante over for et eller flere sygdomsmodificerende anti-reumatiske lægemidler (DMARD'er). Upadacitinib kan anvendes som monoterapi eller i kombination med methotrexat.

Den anbefalede daglige dosis af upadacitinib er 15 mg oralt. Lægemidlet er formuleret som en depottablet.

Upadacitinib er i forvejen indiceret til behandling af kronisk leddegigt, og Medicinrådet anbefalede det som mulig standardbehandling i september 2020 [16]. Sideløbende med denne vurdering er Medicinrådet ved at vurdere upadacitinib til patienter med ankyloserende spondylitis (AS).

3.3 Nuværende behandling

Der findes ingen behandling, som kan kurere PsA. Den nuværende behandling er i stedet målrettet patienternes smerter og symptomer som beskrevet i afsnit 3.1. Behandlingsmålet er, at patienterne opnår så lav sygdomsaktivitet som muligt og helst remission, så symptomer og inflammation er kontrollerede. Dette er bl.a. for at optimere patientens livskvalitet og sociale liv, forhindre progredierende strukturelle ledskader og bevare så højt funktionsniveau som muligt.

Sygdomsmodificerende behandling (*disease modifying antirheumatic drugs* (DMARDs)) gives ved betydelig affektion af led. Til patienter med lav sygdomsaktivitet og lav risiko for progressiv ledsygdom (ledaffektion i mindre end fem led) anvendes monoterapi med lægemidler af typen konventionelle DMARDs (csDMARDs), hvor methotrexat sædvanligvis er førstevalg i dansk klinisk praksis [8].

Hos patienter med betydelig ledaffektion (mere end fire led) eller ved utilstrækkelig effekt af csDMARDs, eventuelt i kombination med lokale steroidinjektioner [17], kan biologisk behandling med antistoffer (bDMARDs) eller targeteret syntetisk behandling med små molekyler (tsDMARDs) indledes. Kriterierne for at indlede b/tsDMARD-behandling omfatter moderat til svær sygdomsaktivitet, fravær af kontraindikationer og at beslutningen træffes på konference med speciallæger i reumatologi [8]. Af b/tsDMARDs-behandling benyttes på nuværende tidspunkt forskellige TNF-alfa-hæmmere, monoklonale antistoffer rettet mod IL-12, -17 og -23 samt en JAK-hæmmer.

Medicinrådets nuværende lægemiddelrekommandation for biologisk behandling af PsA [18] er delt op i behandling til flere forskellige patientgrupper, afhængigt af om patienten samtidig har moderat til svær plaque psoriasis, uveitis eller inflammatorisk tarmsygdom (Crohns sygdom eller colitis ulcerosa). Flere af lægemidlerne er godkendt til både PsA og en eller flere af de nævnte indikationer, hvilket har betydning for, hvilke lægemidler der anvendes til de relevante patientgrupper.

TNF-hæmmeren adalimumab er p.t. billigst og dermed førstevalg for behandling af alle patientpopulationerne inden for PsA [18]. Jf. RADS' baggrundsnotat for biologiske og syntetiske targeterede lægemidler til behandling af PsA udelukker behandlingssvigt ved anvendelse af en TNF-hæmmer ikke muligheden for effekt af en ny TNF-hæmmer eller lægemidler med anden virkningsprofil. Efter svigt af to effektfulde TNF-hæmmere (sekundært svigt) eller ved manglende respons fra start (primært svigt) kan et lægemiddel med anden virkningsprofil overvejes [19]. Ixekizumab, som er en IL-17A-hæmmer, er p.t. det lægemiddel der anvendes efter forudgående behandling med TNF-hæmmer [18].

I DANBIO (Dansk Reumatologisk Database) var der ved udgangen af 2019 registreret ca. 2.560 patienter i biologisk behandling for PsA, hvoraf ca. 330 patienter startede på biologisk behandling (behandlingsnaive), og ca. 860 patienter skiftede behandling (behandlingserfarne). Tallene dækker over alle PsA-patienter inkl. dem, der har følgesygdommene uveitis og inflammatorisk tarmsygdom.

4. Metode

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

5. Resultater

De kliniske spørgsmål afspejler populationerne i lægemiddelrekommandationen. Da upadacitinib imidlertid ikke er godkendt til behandling af uveitis, Crohns sygdom, colitis ulcerosa eller moderat til svær plaque psoriasis, vil Medicinrådets vurdering af upadacitinib ikke omhandle patienter med PsA, der også har en af disse sygdomme. Derudover afspejler de kliniske spørgsmål, at der i dansk klinisk praksis skelnes mellem såkaldt behandlingsnaive patienter (der ikke tidligere har været behandlet med b/tsDMARDs og skal begynde behandling med en af disse) og behandlingserfarne patienter (der tidligere har været behandlet med b/tsDMARDs og skal skifte til en anden).

5.1 Klinisk spørgsmål 1

Det kliniske spørgsmål er:

Hvilken værdi har upadacitinib sammenlignet med adalimumab for behandlingsnaive patienter med PsA?

5.1.1 Litteratur

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

Ansøgningen baserer sig på publikationen af McInnes et al. 2021 [20], der er angivet i protokollen. Derudover har Medicinrådet suppleret med data med længere opfølgningstid (McInnes et al. 2021, konference abstrakt [21]) samt EMAs EPAR og produktresuméerne for upadacitinib [22,23] og adalimumab [24].

Tabel 1. Oversigt over studier

Publikationer	Klinisk forsøg	NCT-nummer	Population	Intervention vs. komparator
McInnes et al. 2021 [20] McInnes et al. 2021, konference abstrakt [21]	SELECT-PsA 1	NCT03104400	Behandlings-naive patienter med aktiv psoriasis-artrit	Upadacitinib 15 mg (p.o.) dagligt vs. adalimumab 40 mg (s.c.) hver anden uge
				Upadacitinib 15 mg (p.o.) dagligt vs. placebo
				Upadacitinib 30 mg (p.o.) dagligt vs. adalimumab 40 mg (s.c.) hver anden uge
				Upadacitinib 30 mg (p.o.) dagligt vs. placebo

SELECT-PsA 1

SELECT-PsA 1 var et dobbeltblindet, randomiseret fase III-studie i patienter med aktiv PsA, som ikke havde opnået tilstrækkeligt effekt ved behandling med minimum ét csDMARD. SELECT-PsA 1 undersøgte effekt og sikkerhed af upadacitinib (15 mg og 30 mg) sammenlignet med placebo og adalimumab. Studiet inkluderede voksne patienter, som var diagnosticeret med PsA og nuværende eller tidligere plaque psoriasis. Patienter skulle have mindst tre hævede led (af 66 undersøgte) og mindst 3 ømme led (af 68 undersøgte), tilstedeværelse af en eller flere erosioner i hænder eller fødder (bestemt radiologisk) eller et forhøjet niveau af C-reaktivt protein (CRP). Patienter skulle desuden have utilstrækkelig effekt eller uacceptable bivirkninger af csDMARD. Patienter kunne modtage behandling med NSAID (*nonsteroidal antiinflammatory drugs*), glukokortikoider

og op til to csDMARDs. Patienter blev ekskluderet, hvis de tidligere havde modtaget biologisk behandling eller behandling med JAK-inhibitorer [20].

Patienter blev randomiseret 2:2:2:1:1 til upadacitinib 15 mg (n=429), upadacitinib 30 mg (n=423), adalimumab 40 mg (n=429), placebo efterfulgt af upadacitinib 15 mg (n=211) eller placebo efterfulgt af upadacitinib 30 mg (n=212). Randomiseringen var stratificeret efter graden af psoriasis (≥ 3 % vs. < 3 % involveret kropsareal), nuværende brug/ikke brug af mindst et csDMARD samt tilstedeværelse af dactylitis (diffus hævelse af fingre eller tæer) og tilstedeværelse af enthesitis (inflammation ved senetilhæftningen på knoglevæv) [20]. Studiet var inddelt i to perioder. Første periode varede 56 uger, hvor de første 24 uger var en dobbeltblindet, placebo- og aktiv komparatorkontrolleret periode, mens de efterfølgende 32 uger var en blindet aktiv komparatorkontrolleret periode, hvor patienter, der havde modtaget placebo de første 24 uger, skiftede til upadacitinib 15 mg eller 30 mg. Periode 2 var en ublindet opfølgningsperiode på op til tre års samlet behandling [20]. Studiets primære effektmål var andelen af patienter, der opnåede ARC20-respons for upadacitinib vs. placebo ved uge 12. Øvrige effektmål, der var relevante i forhold til Medicinrådets protokol for vurdering af upadacitinib til PsA var sygdomsaktivitet opgjort som ACR50, defineret som en 50 % forbedring i både ømme og hævede led samt 50 % forbedring inden for mindst tre ud af fem sygdomsrelevante domæner og modified Total Sharp Score (mTSS), et radiografisk effektmål, der kan tolkes som udtryk for leddestruktion og dermed sygdomsprogression, uønskede hændelser og livskvalitet opgjort ved det generiske spørgeskema SF-36.

Analyser for effekt blev foretaget på en modificeret intention-to-treat population, som inkluderede alle patienter, der var blevet randomiseret, og havde modtaget mindst én dosis af upadacitinib, placebo eller adalimumab. Uønskede hændelser blev rapporteret af blindede investigatorer og blev rapporteret til og med uge 24.

Tabel 2. Baselinekarakteristika for SELECT-PsA 1[#] [20]

SELECT-PsA 1	Upadacitinib 15 mg (n=429)	Adalimumab 40 mg (n=429)
Kvinder, antal (%)	238 (55,5)	222 (51,7)
Alder, år	51,6±12,2	51,4±12,0
Etnicitet, antal kaukasiske (%)	386 (90,0)	375 (87,4)
Body-mass index ≥ 25 kg/m^2, antal (%)	342 (79,7)	334 (77,9)
PsA sygdomsvarighed, år	6,2±7,4	5,9±7,1

SELECT-PsA 1	Upadacitinib 15 mg (n=429)	Adalimumab 40 mg (n=429)
csDMARD behandling ved baseline, antal (%) §	353 (82,3)	347 (80,9)
Methotrexate monoterapi	279 (65,0)	270 (62,9)
Methotrexate + anden ikke-biologisk DMARD	20 (4,7)	16 (3,7)
Ikke-biologisk DMARD, som ikke er methotrexate	54 (12,6)	61 (14,2)
Brug af glukokortikoider ved baseline, antal (%)	73 (17,0)	72 (16,8)
Antal ømme led, 0-68	20,4±14,7	20,1±13,8
Antal hævede led, 0-66	11,6±9,3	11,6±8,8
Baseline CRP >ULN*, antal (%)	324 (75,5)	308 (71,8)
HAQ-DI score (fra 0-3)	1,2±0,7	1,1±0,6
Patientens vurdering af smerte ¤	6,2±2,1	6,0±2,1
Kropsareal berørt af psoriasis (BSA) ≥ 3 %, antal (%)	214 (49,9)	211 (49,2)
PASI-score, 0-72	9,8±10,0	9,4±8,5
IGA-score, antal (%)		
0	34 (7,9)	34 (7,9)
1	73 (17,0)	65 (15,2)
2	170 (39,6)	181 (42,2)
3	133 (31,0)	132 (30,8)
4	19 (4,4)	17 (4,0)
Tilstedeværelse af enthesitis, antal (%)§§	270 (62,9)	265 (61,8)
Tilstedeværelse af dactylitis, antal (%)**	136 (31,7)	127 (29,6)

Alle værdier er opgjort som gennemsnit (SD), medmindre andet er specificeret.
§ Tilladte ikke-biologiske DMARDs var methotrexate, sulfasalazine, leflunomide, apremilast, hydroxychloroquine, bucillamine og iguratimod.
*ULN = *Upper limit of the normal range* (øvre grænse for normal niveau) = 2,87 mg/L på baggrund af high-sensitivity C-reactive protein.
¤ Patientens vurdering af smerte på en nomerisk skala fra 0 til 10, hvor højere score indikerer større smerte.
§§ Tilstedeværelse af enthesitis var defineret som en score > 0 på Leeds Enthesitis Index (på en skala 0-6, hvor en højere score indikerer flere påvirkede områder).
** Tilstedeværelse af dactylitis var defineret som en score > 0 på Leeds Dactylitis Index (hvor en højere score indikerer flere påvirkede områder).

Fagudvalget finder, at der ikke er nogen betydende forskelle i baselinekarakteristika mellem de to studiearme, og at patientkarakteristika i studierne ikke afviger væsentligt fra den danske patientpopulation eller patientpopulationen defineret i det kliniske spørgsmål. Fagudvalget bemærker, at der er flere patienter, der modtager behandling med glukokortikoider i forhold til dansk klinisk praksis [25], hvilket vil være forbundet med flere bivirkninger. Da forbruget er ens mellem de to arme, er dette af mindre betydning for vurdering af behandlingseffekten.

Fagudvalget påpeger, at patienter med psoriasisartrit er en heterogen population, hvad angår deres symptomer og sygdomsbillede. Dette kan være svært at tage fuldt hensyn til i randomiseringen i de kliniske studier.

5.1.2 Databehandling og analyse

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

For samtlige effektmål har ansøger foretaget en direkte sammenligning af upadacitinib og adalimumab med data fra SELECT PsA-1 studiet. Ansøger har indsendt data for alle effektmål efter 24 ugers opfølgningstid. Der er derudover publiceret data for 56 ugers opfølgningstid i et abstract af McInnes et al. 2021 for effektmålet ACR50 [21].

Den direkte sammenligning er foretaget i henhold til Medicinrådets metoder. Medicinrådet har ikke fundet anledning til at foretage ændringer af beregninger foretaget af ansøger eller supplere med yderligere beregninger.

Ansøgningen indeholder data for alle effektmål, som er defineret i Medicinrådets protokol, dog har ansøger indsendt data på alvorlige uønskede hændelser (*serious adverse events* (SAE)) fremfor alvorlige bivirkninger (*serious adverse reactions* (SAR)) som specificeret i protokollen, da der ikke foreligger data på SAR fra SELECT PsA-1. Fagudvalget accepterer dette, og tager højde for afvigelsen i vurderingen af evidensens kvalitet.

5.1.3 Evidensens kvalitet

Medicinrådet har anvendt GRADE til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen. Nedenfor følger en beskrivelse af vurderingen af de væsentligste domæner for hvert klinisk spørgsmål. Vurdering af risikoen for bias ved

Cochrane risk of bias tool 2.0 for de enkelte studier fremgår af bilag 1. Den fuldstændige GRADE-vurdering og begrundelserne er samlet i en GRADE-profil (bilag 2).

Overordnet var SELECT-PsA 1-studiet af upadacitinib sammenlignet med adalimumab af meget lav kvalitet, hvilket betyder, at nye studier med høj sandsynlighed kan ændre konklusionen. Evidensen er nedgraderet på baggrund af inkonsistens (kun ét studie), indirekthed (data opgjort som alvorlige uønskede hændelser (SAE) fremfor alvorlige bivirkninger (SAR)) samt unøjagtighed (konfidensintervallet for SAE rummer muligheden for at upadacitinib har ingen merværdi eller negativ værdi).

5.1.4 Effektestimater og kategorier

I tabellen herunder fremgår de absolutte og relative effektforskelle, de foreløbige og aggregerede kategorier, den samlede kategori og den samlede kvalitet af evidensen for klinisk spørgsmål 1.

Tabel 3. Resultater for klinisk spørgsmål 1 – upadacitinib sammenlignet med adalimumab til behandlingsnaive patienter med PsA uden moderat til svær plaque psoriasis ved uge 24

Effektmål	Målenhed (MKRF)	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi for effektmålet
			Forskel (95 % CI)	Foreløbig værdi	Forskel (95 % CI)	Foreløbig værdi	
Sygdomsaktivitet - ledaffektion	Andel patienter, der oplever respons på ACR50 (MKRF: 15 %-point)	Kritisk	8,2 %-point (1,5; 14,8)	Ingen dokumenteret merværdi	RR: 1,2 (1,03; 1,36)	Merværdi af ukendt størrelse	Ingen dokumenteret merværdi
	Andel patienter uden progression, jf. mTSS (MKRF: 10 %-point)		1,0 %-point (-2; 3,9)	Ingen dokumenteret merværdi	RR: 1,01 (0,98; 1,04)	Ingen dokumenteret merværdi	
Bivirkninger	Andel patienter, der oplever alvorlige bivirkninger (MKRF: 5 %-point)	Kritisk	-0,47 %-point (-2,12; 2,87)	Kan ikke kategoriseres	RR: 0,88 (0,43; 1,77))	Kan ikke kategoriseres	Kan ikke kategoriseres
	Gennemgang af bivirkningsprofil		Se nedenfor				
Livskvalitet	Gennemsnitlig ændring fra baseline på SF-36, energi-subdomæne (MKRF: 7,8 point)	Kritisk	1,93 point (0,76; 3,09)	Ingen dokumenteret merværdi	Kan ikke estimeres*	Kan ikke kategoriseres*	Ingen dokumenteret merværdi
	Gennemsnitlig ændring fra baseline på SF-36, den fysiske komponent summary (MKRF: 7,2 point)		1,83 point (0,75; 2,91)	Ingen dokumenteret merværdi	Kan ikke estimeres*	Kan ikke kategoriseres*	

Effektmål	Målenhed (MKRF)	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi for effektmålet
			Forskel (95 % CI)	Foreløbig værdi	Forskel (95 % CI)	Foreløbig værdi	
	Gennemsnitlig ændring fra baseline på SF-36, den mentale komponent summary (MKRF: 3,1 point)		0,55 point (-0,62; 1,71)	Ingen dokumenteret merværdi	Kan ikke estimeres*	Kan ikke kategoriseres*	

Konklusion	
Samlet kategori for lægemidlets værdi	Ingen dokumenteret merværdi
Kvalitet af den samlede evidens	Meget lav

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

*Det er ikke muligt at regne relativ risiko for effektmål opgjort på en kontinuerlig skala. Derfor kan den foreløbige værdi ikke kategoriseres.

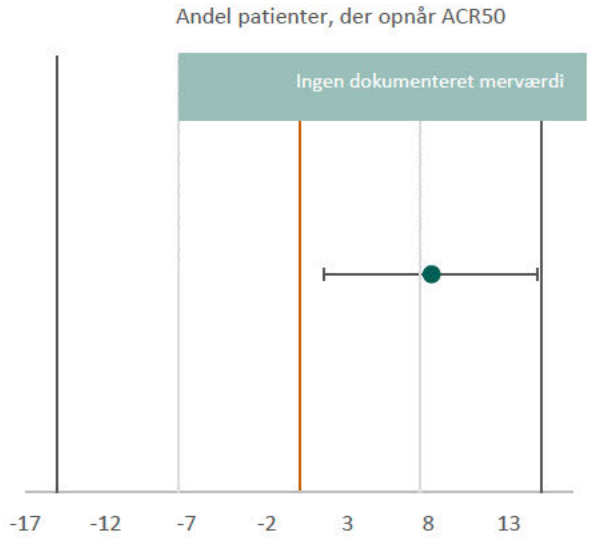
Sygdomsaktivitet - ledaffektion

Som beskrevet i protokollen er effektmålet *Sygdomsaktivitet – ledaffektion* kritisk for vurderingen af lægemidlets værdi for patienterne, fordi patienter, der oplever nedsat sygdomsaktivitet, opnår forbedret funktionsniveau, livskvalitet og tilknytning til arbejdsmarkedet [7,8]. Fagudvalget ønsker effektmålet belyst ved data på andel patienter, der oplever respons på ACR50 og andel patienter uden progression, jf. mTSS.

ACR50

Det primære mål for effekt på sygdomsaktivitet er respons på ACR50. Dette er defineret som en 50 % forbedring i både ømme og hævede led samt 50 % forbedring inden for mindst tre ud af følgende fem domæner: patientens overordnede vurdering af, hvor meget gigten som helhed påvirker hverdagen (Visual Assessment Scale (VAS) global), patientens vurdering af smerte, lægens overordnede vurdering af patientens samlede sygdomsaktivitet (VAS doctor), HAQ-DI score, som måler patientens funktionsniveau, og C-reaktivt protein (CRP). Medicinrådet vurderer, at en 50 % forbedring er et patientrelevant effektmål og betragtes her som tilstrækkeligt for at definere respons.

Efter 24 ugers behandling havde 225 ud af 429 patienter (52,4 %) i upadacitinib 15 mg-armen opnået ACR50, mens 190 ud af 429 patienter (44,3 %) havde opnået ACR50 i adalimumab-armen. For placeboarmen var andelen af patienter, der opnåede ACR50 18,9 % [20]. Den absolutte forskel er vist i Figur 1 nedenfor.



Figur 1. Punktestimat og 95 % konfidensinterval for den absolutte forskel for andel patienter, der oplever respons på ACR50. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Fagudvalget har i protokollen defineret MKRF til 15 %-point. Punktestimatet for den absolutte effektforskel er på 8,2 %-point (1,5; 14,8). Punktestimatet for den absolutte effektforskel afspejler dermed ikke en klinisk relevant effektforskel, da det ligger under den mindste klinisk relevante forskel på 15 %-point. Den nedre grænse for

konfidensintervallet er tættere på 0 (ingen effektforskel) end på den mindste klinisk relevante forskel. Omvendt inkluderer konfidensintervallet ikke effektstørrelser med en negativ værdi. Derfor er den foreløbige værdi af upadacitinib, baseret på den absolutte effektforskel, ingen dokumenteret merværdi vedr. ACR50.

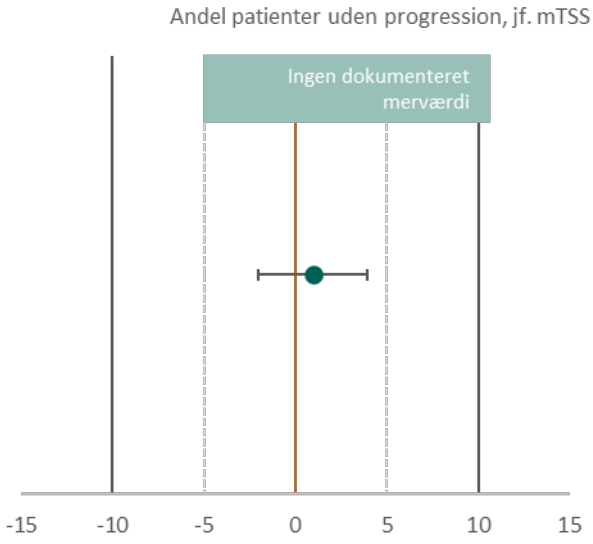
Baseret på den relative effektforskel, opgjort som en relativ risiko på 1,2 (1,03; 1,36) som fremgår af Tabel 3, har upadacitinib foreløbigt en merværdi af ukendt størrelse vedr. ACR50.

Efter 56 ugers opfølgningstid havde 59,7 % af patienterne i upadacitinib 15 mg-armen og 51,3 % af patienterne i adalimumab-armen opnået ACR50. I begge grupper havde lidt flere patienter dermed opnået ACR50 ved 56 uger end ved 24 uger (hhv. 52,4 % og 44,3 % for upadacitinib og adalimumab) [21]. Fagudvalget vurderer derfor, at effekten er vedvarende i mindst et år.

mTSS

Medicinrådet ønsker at benytte et radiografisk effektmål, der kan tolkes som udtryk for leddestruktion og dermed sygdomsprogression. Medicinrådet ønsker at benytte en modificeret udgave af Total Sharp Score (mTSS), som er udviklet til scoring af patienter med PsA [9].

Efter 24 ugers opfølgning havde 371 ud af 387 patienter (95,9 %) uændret mTSS i forhold til baseline, målt som en ændring fra baseline ≤ 0,5 i Sharp/van der Heidje score i upadacitinib-armen. Dette var tilfældet for 371 ud af 391 patienter (94,9 %) i adalimumab-armen [20]. For placeboarmen var tallet 91,9 %. Den absolutte forskel er vist i Figur 2 nedenfor.



Figur 2. Punktestimat og 95 % konfidensinterval for den absolutte forskel for *Andel patienter uden progression, jf. mTSS*. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Fagudvalget har i protokollen defineret MKRF til 10 %-point. Punktestimatet på 1,0 %-point (-2; 3,9) for den absolutte effektforskel afspejler ikke en klinisk relevant effektforskel. Den nedre grænse for konfidensintervallet er tættere på 0 (ingen effekt) end på en negativ klinisk relevant forskel. Derfor har upadacitinib, baseret på den absolutte effektforskel, foreløbigt ingen dokumenteret merværdi vedr. mTSS.

Baseret på den relative effektforskel 1,01 (0,98; 1,04), som fremgår af Tabel 3, har upadacitinib foreløbigt ingen merværdi vedr. mTSS.

Samlet for effektmålet *Sygdomsaktivitet - ledaffektion*

Baseret på ovenstående gennemgang af effektmålet *Sygdomsaktivitet – ledaffektion*, målt med ACR50 og radiologisk progression, vurderer fagudvalget, at upadacitinib for dette effektmål har **ingen dokumenteret merværdi** sammenlignet med adalimumab.

Fagudvalget har lagt vægt på, at der ikke er klinisk betydende effektforskel på sygdomsaktivitet eller radiologisk progression ved sammenligning af upadacitinib og adalimumab.

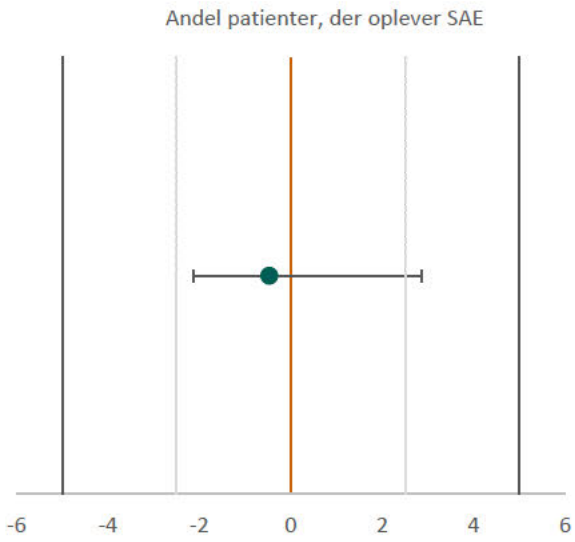
Bivirkninger

Som beskrevet i protokollen er effektmålet *Bivirkninger* kritisk for vurderingen af lægemidlets værdi for patienterne. Effektmålet er delt op på to delmål: alvorlige bivirkninger og en kvalitativ gennemgang af de to lægemidlers bivirkningsprofiler.

Andel patienter, der oplever alvorlige bivirkninger

Medicinrådet ønsker data på alvorlige bivirkninger (*serious adverse reactions* (SAR)), da disse særligt frygtes af patienter og klinikere, siden de kan forårsage pauser i behandlingen med risiko for forværring af symptomer og sygdomsprogression. Ansøger har indsendt data på alvorlige uønskede hændelser (*serious adverse events* (SAE)) fremfor alvorlige bivirkninger (SAR) som specificeret i protokollen, da der ikke foreligger data på SAR fra SELECT PsA-1. Fagudvalget accepterer, at data på alvorlige uønskede hændelser anvendes i stedet.

14 ud af 429 patienter (3,3 %) oplevede alvorlige uønskede hændelser i upadacitinib-armen, mens 16 ud af 429 patienter (3,7 %) i adalimumab-armen oplevede alvorlige uønskede hændelser. For placeboarmen var tallet 3,1 % [20]. Den absolutte forskel er vist i Figur 3 nedenfor.



Figur 3. Punktestimat og 95 % konfidensinterval for den absolutte forskel for *andel patienter, der oplever SAE*. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Fagudvalget har i protokollen defineret MKRF til 5 %-point, og punktestimatet på -0,47 %-point (-2,12; 2,87) afspejler derfor ikke en klinisk relevant forskel. Konfidensintervallet rummer muligheden for, at upadacitinib har ingen merværdi eller negativ værdi. Derfor kan den foreløbige værdi af upadacitinib, baseret på den absolutte effektforskel vedr. alvorlige uønskede hændelser, ikke kategoriseres efter Medicinrådets metoder.

Baseret på den relative effektforskel på 0,88 (0,43; 1,77), som fremgår af Tabel 3, har upadacitinib foreløbig en værdi vedr. alvorlige uønskede hændelser, der ikke kan kategoriseres.

Gennemgang af bivirkningsprofilen

Gennemgangen af bivirkningsprofilen tager udgangspunkt i lægemidlernes produktresuméer, hvor bivirkningerne er sammenlagt fra de underliggende kliniske studier [22,24]. Gennemgangen af bivirkningsprofilen i produktresuméet for upadacitinib tager udgangspunkt i kronisk leddegigt. Samlet set svarer sikkerhedsprofilen for patienter med psoriasisartrit til den sikkerhedsprofil, der blev set hos patienter med kronisk leddegigt.

Upadacitinib

I de kliniske studier af upadacitinib var den hyppigste bivirkning infektioner. På tværs af de kliniske studier fik 19,5-27,4 % af patienterne infektioner svarende til 93,7 hændelser pr. 100 patientår. De hyppigst indberettede infektioner var infektioner i de øvre luftveje (19,5 % - 25,4 %), bronkitis, herpes zoster, herpes simplex (8,4 %), follikulitis (betændelse i hårsækkene) og influenza. Hyppigheden af alvorlige infektioner var 0,6-1,2 % svarende til 3,8 hændelser pr. 100 patientår. Den hyppigste alvorlige infektion var

lungebetændelse. Der blev set en højere hyppighed af alvorlige infektioner for patienter med psoriasisartrit, hvor hyppigheden af alvorlige infektioner var 2,6 hændelser pr. 100 patientår for patienter, der modtog behandling med upadacitinib i kombination med methotrexat (MTX) mod 1,3 hændelser pr. 100 patientår for patienter, der modtog monobehandling.

Forekomsten af opportunistiske infektioner (herunder tuberkulose, herpes zoster (helvedes ild), svampeinfektion i mund eller spiserør og cryptokokkose (svampeinfektion startende i lungerne)) i de kliniske studier var 0,0-0,5 % for patienter, der modtog behandling med upadacitinib, svarende til 0,6 hændelser pr. 100 patientår. For patienter behandlet med placebo eller MTX var forekomsten 0,2-0,3 %.

I de kliniske studier havde patienter, der modtog upadacitinib 15 mg hyppigere forhøjede lipider sammenlignet med patienter, der modtog placebo (hyppigheden af patienter med total kolesterol ≥ 5,17 mmol/L var hhv. 62 % og 31 %). 0,4-2,1 % af patienter, der modtog upadacitinib 15 mg, havde forhøjede leverenzymer, mens 1,1 % havde nedsatte neutrofiltal (< 1 x 10^9 celler/L).

Adalimumab
De hyppigst rapporterede bivirkninger er øvre luftvejsinfektioner, reaktioner på injektionsstedet (udslæt (erytem), kløe, blødning, smerter eller hævelse), hovedpine og muskuloskeletal smerte. Ved brug af adalimumab er der rapporteret om dødelige og livstruende infektioner (inkl. blodforgiftning, opportunistiske infektioner og tuberkulose), hepatitis B-reaktivering og leverenzymforhøjelse. Dertil kan en øget risiko for malignt melanom og non-melanom hudkræft ikke udelukkes. Der er også rapporteret om alvorlige hæmatologiske (blodmangel, leukopeni, pancytopeni), neurologiske (Guillain-Barré syndrom) og autoimmune reaktioner. Sjældne bivirkninger er bl.a. tarmperforation, lungefibrose, Stevens-Johnsons syndrom og dissemineret sklerose.

Øvrige overvejelser vedr. risiko for bivirkninger
Medicinrådet har tidligere udtrykt en bekymring for den øgede risiko for lungeemboli og venøs tromboemboli (VTE) hos patienter med risikofaktorer for VTE samt øget risiko for alvorlige infektioner hos patienter over 65 år ved behandling med JAK-hæmmeren tofacitinib [26]. Den bekymring er baseret på EMAs og FDAs udtalelser omkring JAK-hæmmere [27–29]. I den forbindelse er det relevant at undersøge, om behandling med upadacitinib, ligesom tofacitinib, er forbundet med samme risiko for patienterne. Derudover ønskede fagudvalget i protokollen en redegørelse for lægemidlernes toksicitet ift. hhv. reproduktion og malignitet.

Der er rapporteret om tilfælde af dyb venetrombose og lungeemboli hos patienter i behandling med JAK-hæmmere, herunder upadacitinib. En integreret sikkerhedsanalyse fra SELECT fase III-programmet for PsA har vist, at der ikke var forskel mellem upadacitinib og adalimumab hvad angår VTE-rater (E/100PY [95 % CI]: 0,3 [0,0; 0,6] for upadacitinib 15 mg og 0,4 [-0,1; 0,9] for adalimumab) [30]. Dette er sammenligneligt med de rater, der er rapporteret i SELECT fase III-programmet for kronisk leddegigt (E/100PY [95 %]: 0,5 [0,3; 0,7] for upadacitinib 15 mg og 0,5 [0,3; 0,7] for adalimumab) [31]. Alle patienter der oplevede en VTE-hændelse havde underliggende risikofaktorer så

som tidligere VTE, alder over 65 år og behandling med NSAIDs eller statiner. Der er ikke evidens for en dosisafhængig risiko for VTE ved behandling med upadacitinib [32].

Risikoen for alvorlige infektioner var sammenlignelig mellem upadacitinib og adalimumab i SELECT-PsA 1-studiet (hhv. 1,2 % og 0,7 %) [20] og for begge lægemidler gælder det generelt, at ældre patienter er i øget risiko for at udvikle alvorlige infektioner.

Der er observeret cancertilfælde i kliniske studier med upadacitinib, ligesom der er rapporteret om non-melanom hudkræft (NMSC) hos patienter i behandling med upadacitinib. Den integrerede sikkerhedsanalyse fra SELECT fase III-programmet for PsA har vist, at der ikke var forskel mellem upadacitinib og adalimumab, hvad angår malignitet (E/100PY [95% CI]: 0,7 [0,3; 1,2] for upadacitinib 15 mg og 0,7 [0,0; 1,4] for adalimumab) [30].

Der er begrænset evidens fra mennesker, hvad angår upadacitinibs toksicitet mht. reproduktion, især hos gravide. Dyrestudier har vist, at upadacitinib kan forårsage fosterskader, hvorfor behandling med lægemidlet er kontraindiceret under graviditet. Dyrestudier har ikke påvist en effekt på fertilitet ved behandling med upadacitinib [22].

Samlet for effektmålet bivirkninger

Baseret på ovenstående gennemgang af effektmålet *Bivirkninger* vurderer fagudvalget, at upadacitinib for dette effektmål har en værdi, som **ikke kan kategoriseres** efter Medicinrådets metoder sammenlignet med adalimumab.

Der er ikke fundet en klinisk betydende forskel mellem adalimumab og upadacitinib for uønskede hændelser (absolut effektforskel -0,47 %-point). Upadacitinibs og adalimumabs bivirkningsprofiler er forskellige, hvor begge lægemidler kan medføre en række uønskede hændelser. Fagudvalget finder dog, at på baggrund af de rapporterede bivirkninger, er lægemidlerne sammenlignelige, hvad angår bivirkningernes sværhedsgrad.

Kliniske studier viser, at behandling med upadacitinib ikke er forbundet med øget risiko for VTE, alvorlige infektioner hos patienter ældre end 65 år, alvorlige kardiovaskulære hændelser (MACE = *Major Adverse Cardiac Events*) eller kræft, ligesom det er dokumenteret ved behandling med tofacitinib. Fagudvalget understreger, at både EMA og FDA (*U.S Food and Drug Administration*) anbefaler særlig opmærksomhed i forhold til disse hændelser ved behandling med JAK-hæmmere [27–29]. Således fremgår det i upadacitinibs produktresumé, at der er risiko for VTE og MACE [22]. Der er ikke udført post-marketing studier for upadacitinib eller baricitinib, som der er for tofacitinib. Det er fortsat uklart om disse bivirkninger er et udtryk for en klasseeffekt for JAK-hæmmere. På grund af den øgede sikkerhedsrisiko ved behandling med tofacitinib hos ældre patienter over 65 år og EMAs og FDAs opfordring til klinikerne om at udvise særlig opmærksomhed ved behandling med JAK-hæmmere [27–29], er der generelt en øget opmærksomhed blandt klinikere og patienter på sikkerheden ved behandling med JAK-hæmmere.

Livskvalitet

Som beskrevet i protokollen er effektmålet livskvalitet kritisk for vurderingen af lægemidlets værdi for patienterne, fordi patienter med PsA ofte er mærket af deres

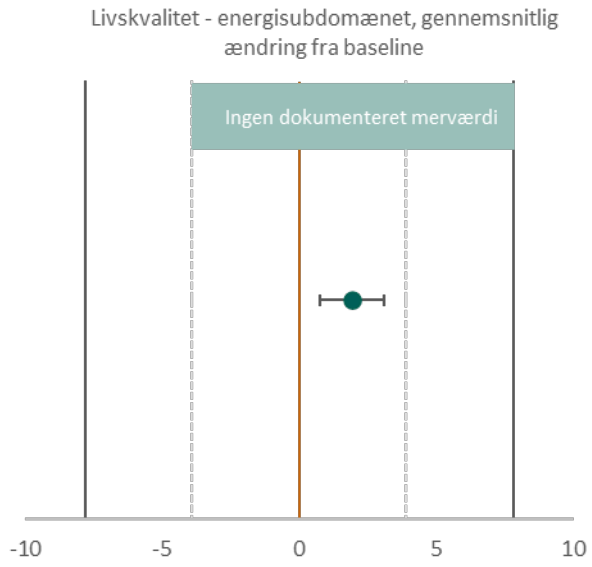
sygdom både fysisk og mentalt, og det er derfor af stor betydning, om et nyt lægemiddel kan afhjælpe dette. I protokollen har Medicinrådet defineret, at livskvalitet skal opgøres ved det generiske instrument SF-36. Effektmålet er delt op i de tre delmål: subdomænet energi (*vitality*), den sammenfattede score for de mentale komponenter og den sammenfattede score for de fysiske komponenter.

Da livskvalitetsdata opgøres på en kontinuerlig skala, kan den relative effektforskel ikke udregnes. Derfor har upadacitinib, baseret på den relative forskel, foreløbigt en værdi, der ikke kan kategoriseres efter Medicinrådets metoder vedr. alle livskvalitetsdelmål.

Subdomænet energi (*vitality*)

Fagudvalget ønsker data på subdomænet energi i SF-36, da dette betragtes som et vigtigt parameter i patienternes livskvalitet.

For patienter i upadacitinib-armen var den gennemsnitlige ændring fra baseline efter 24 uger 8,13 (7,23; 9,03) mens den gennemsnitlige ændring for patienter i adalimumab-armen var 6,20 (5,31; 7,09). Den absolutte effektforskel er vist i Figur 4 nedenfor.



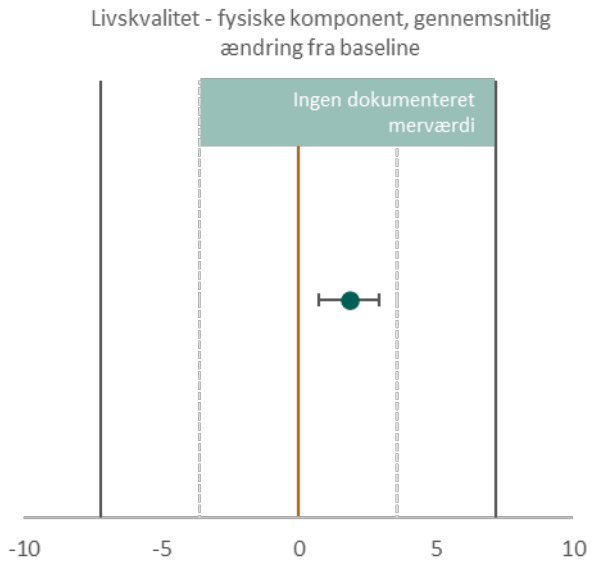
Figur 4. Punktestimat og 95 % konfidensinterval for den absolutte forskel for livskvalitet – subdomænet energi. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Fagudvalget har defineret MKRF til 7,8 point, og punktestimatet for den absolutte effektforskel på 1,93 (0,76; 3,09) afspejler derfor ikke en klinisk relevant effektforskel. Den nedre grænse for konfidensintervallet er tættere på 0 (ingen effekt) end på en negativ klinisk relevant forskel. Derfor har upadacitinib, baseret på den absolutte effektforskel, foreløbigt ingen dokumenteret merværdi vedr. livskvalitet – subdomænet energi.

Den fysiske komponent

Fagudvalget ønsker data for den sammenfattede score for de fysiske komponenter af SF-36, da dette betragtes som et vigtigt parameter i patienternes livskvalitet.

For patienter i upadacitinib-armen var den gennemsnitlige ændring fra baseline 9,66 (8,82; 10,50), mens den gennemsnitlige ændring fra baseline i adalimumab-armen var 7,84 (7,01; 8,66). For placeboarmen var den gennemsnitlige ændring 4,2 point [23]. Den absolutte forskel er vist i Figur 5 nedenfor.



Figur 5. Punktestimat og 95 % konfidensinterval for den absolutte forskel for livskvalitet – den fysiske komponent. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Fagudvalget har defineret MKRF til 7,2 point, og punktestimatet for den absolutte effektforskel på 1,83 (0,75; 2,91) afspejler derfor ikke en klinisk relevant effektforskel. Den nedre grænse for konfidensintervallet er tættere på 0 (ingen effekt) end på en negativ klinisk relevant forskel. Derfor har upadacitinib, baseret på den absolutte effektforskel, foreløbigt ingen dokumenteret merværdi vedr. livskvalitet – den fysiske komponent.

Den mentale komponent

Fagudvalget ønsker data for den sammenfattede score for den mentale komponent af SF-36, da dette betragtes som et vigtigt parameter i patienternes livskvalitet.

For patienter i upadacitinib-armen var den gennemsnitlige ændring fra baseline 4,80 (3,89; 5,70), mens den gennemsnitlige ændring fra baseline i adalimumab-armen var 4,25 (3,36; 5,14). For placeboarmen var den gennemsnitlige ændring 2,4 point [23].

Figur 6. Punktestimat og 95 % konfidensinterval for den absolutte forskel for livskvalitet – den mentale komponent. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Den absolutte forskel er vist i Figur 6 ovenfor.

Fagudvalget har fastsat MKRF til 3,1 point. Punktestimatet på 0,55 (-0,62; 1,71) for den absolutte effektforskel afspejler derfor ikke en klinisk relevant effektforskel. Den nedre grænse for konfidensintervallet er tættere på 0 (ingen effekt) end på en negativ klinisk relevant forskel. Derfor har upadacitinib, baseret på den absolutte effektforskel, foreløbigt ingen dokumenteret merværdi vedr. livskvalitet – den mentale komponent.

Samlet for effektmålet livskvalitet

Baseret på ovenstående gennemgang af effektmålet *Livskvalitet* vurderer fagudvalget, at upadacitinib for dette effektmål har **ingen dokumenteret merværdi** sammenlignet med adalimumab.

Fagudvalget lægger vægt på, at studiet ikke kan dokumentere en klinisk relevant forskel mellem upadacitinib og adalimumab på tværs af livskvalitetsdomæner. Fagudvalget vurderer derfor, at upadacitinibs effekt på patienternes livskvalitet er sammenlignelig med adalimumab.

5.1.5 Fagudvalgets konklusion

Fagudvalget vurderer, at upadacitinib til behandlingsnaive patienter med PsA uden moderat til svær plaque psoriasis sammenlignet med adalimumab har **ingen dokumenteret merværdi**.

Fagudvalgets konklusion er foretaget på baggrund af den direkte sammenligning mellem lægemidlerne i SELECT-PsA 1-studiet. Data viser, at der ikke er forskel mellem upadacitinib og adalimumab, vurderet med følgende effektmål: sygdomsaktivitet (målt

med ACR50), radiologisk progression, livskvalitet eller alvorlige uønskede hændelser. Bivirkningsprofilerne for upadacitinib og adalimumab er forskellige, men på baggrund af de rapporterede bivirkninger, er lægemidlerne sammenlignelige, hvad angår mængden af bivirkninger og bivirkningernes sværhedsgrad.

Fagudvalget understreger, at der generelt er øget opmærksomhed blandt klinikere og patienter mht. sikkerheden ved behandling med JAK-hæmmere. Der er konstateret en øget risiko for VTE, alvorlige infektioner hos ældre, risiko for alvorlige kardiovaskulære hændelser og kræft ved behandling med tofacitinib, hvilket er blevet belyst i Oral Surveillance post-marketing studiet. Fagudvalget understreger, at både EMA og FDA anbefaler særlig opmærksomhed i forhold til disse bivirkninger ved behandling med JAK-hæmmere [27–29]. Det er endnu uklart, om der er tale om, at disse bivirkninger er en klasseeffekt for JAK-hæmmere. Fagudvalget fremhæver derfor, at nye data kan ændre konklusionen vedrørende sikkerheden af upadacitinib.

5.2 Klinisk spørgsmål 2

Det kliniske spørgsmål er:

Hvilken værdi har upadacitinib sammenlignet med ixekizumab for behandlingserfarne patienter med PsA?

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 to fuldtekstartikler fra to kliniske studier, der stemmer overens med in- og eksklusionskriterierne fra Medicinrådets protokol. Artiklerne omhandler ét klinisk studie for upadacitinib (SELECT-PsA 2) [33] og ét klinisk studie for ixekizumab (SPIRIT-P2) [34] (se tabel 4). Desuden indgår EMAs EPAR og produktresuméerne for upadacitinib [22,23] og ixekizumab [35,36]. Medicinrådet har desuden suppleret datagrundlaget med publicerede artikler med resultater efter længere opfølgningstid for begge lægemidler.

Tabel 4. Oversigt over studier

Publikationer	Klinisk forsøg	NCT-nummer	Population	Intervention vs. komparator
Mease et al. 2021 [33] Mease et al. 2021 [37]	SELECT-PsA 2	NCT03162796	Behandlingserfarne patienter med aktiv psoriasisartrit	Upadacitinib vs. placebo

Publikationer	Klinisk forsøg	NCT-nummer	Population	Intervention vs. komparator
Nash et al. 2017 [34] Genovese et al. 2018 [38] Kavanaugh et al. 2019 [39]	SPIRIT-P2	NCT02349295	Behandlingserfarne patienter med aktiv psoriasisartrit	Ixekizumab vs. placebo

SELECT-PsA 2

SELECT-PsA 2 var et dobbeltblindet, randomiseret fase III-studie i patienter med aktiv PsA, som ikke havde opnået tilstrækkeligt effekt eller var intolerante overfor tidligere behandling med minimum én biologisk DMARD. SELECT-PsA 2 undersøgte effekt og sikkerhed af upadacitinib (15 mg og 30 mg) sammenlignet med placebo. Studiet inkluderede voksne patienter, som var diagnosticeret med PsA ≥ 6 måneder inden inklusionsdato og som havde nuværende eller tidligere plaque psoriasis. Patienter skulle opfylde CASPAR-kriterierne (*Classification criteria for Psoriatic Arthritis*) og have mindst tre hævede led (af 66 undersøgte) og mindst 3 ømme led (af 68 undersøgte) ved baseline. Patienter skulle have utilstrækkelig effekt eller uacceptable bivirkninger efter tidligere behandling med minimum ét biologisk DMARD. Patienter kunne modtage behandling med NSAID (non-steroide antiinflammatoriske lægemidler), kortikosteroider (svarende til ≤ 10 mg/dag prednison) og op til to csDMARDs. Samtidig behandling af psoriasis med f.eks. topikal behandling, lysterapi eller retinoider var ikke tilladt før efter uge 16. Patienter blev ekskluderet, hvis de tidligere havde modtaget behandling med JAK-hæmmere, haft fibromyalgi, haft gigt inden 17-års alderen eller andre inflammatoriske ledsygdomme udover PsA.

Patienter blev randomiseret 2:2:1:1 upadacitinib 15 mg dagligt (n = 211), upadacitinib 30 mg dagligt (n = 218) placebo efterfulgt af upadacitinib 15 mg (n = 106) eller placebo efterfulgt af upadacitinib 30 mg (n = 106). Patienter, der ikke havde opnået ≥ 20 % forbedring i ømme og hævede led sammenlignet med baseline ved uge 12 og 16, modtog ny baggrundsmedicinering eller fik justeret deres baggrundsmedicinering. Patienter, der ikke havde opnået ≥ 20 % forbedring i ømme og hævede led ved uge 36 efter to sammenhængende kontrolbesøg, stoppede i studiet. Randomiseringen var stratificeret efter graden af psoriasis (≥ 3 % vs. < 3 % påvirket kropsareal), nuværende brug af mindst et csDMARD samt tidligere antal biologiske DMARD (1 vs. > 1).

Studiet var inddelt i to perioder. Første periode varede 56 uger, hvor de første 24 uger var en dobbeltblindet, parallel-gruppe, placebokontrolleret periode, mens de efterfølgende 32 uger var en blindet periode, hvor patienter, der havde modtaget placebo de første 24 uger, skiftede til upadacitinib 15 mg eller 30 mg. Periode 2 var en ublindet opfølgningsperiode (*long-term extension*) på op til tre års samlet behandling.

Analyser for effekt blev foretaget på data fra alle randomiserede patienter (ITT-population), der havde modtaget mindst én dosis af studiemedicin. Studiets primære effektmål var andelen af patienter, der opnåede ARC20-respons ved uge 12. Sekundære effektmål (justeret for multiplicitet) af relevans er andel patienter, der opnåede ACR50 ved uge 24, gennemsnitlig ændring fra baseline i livskvalitet målt ved *short form 36* (SF-36) ved uge 24 og sikkerhed.

SPIRIT-P2

Dette er et randomiseret, dobbeltblindet fase III-studie, der undersøgte effekten og sikkerheden af ixekizumab sammenlignet med placebo hos behandlingserfarne (fortsat sygdomsaktivitet trods behandling med TNF-hæmmere) med aktiv PsA. Patienterne skulle opfylde CASPAR-kriterierne og have aktiv sygdom defineret som ≥ 3 hævede led og ≥ 3 ømme led trods tidligere behandling (1-2 TNF-hæmmere) eller intolerance overfor TNF-hæmmere. Derudover skulle patienterne have nuværende eller tidligere plaque psoriasis.

Patienterne blev randomiseret 1:1:1 til ixekizumab 80 mg hver 2. uge (IXEQ2W, n = 123), ixekizumab 80 mg hver 4. uge (IXEQ4W, n = 122) eller placebo (n = 118). Randomiseringen var stratificeret efter land og tidligere behandling med TNF-hæmmere (utilstrækkelig respons efter behandling med én TNF-hæmmer, to TNF-hæmmere eller intolerance overfor TNF-hæmmere). Patienterne skulle tidligere have været behandlet med ≥ 1 csDMARDs. Under studiets dobbeltblindede 24-ugers periode (eller op til uge 16 hos patienter, der ikke responderede på behandlingen) kunne patienter fortsætte deres stabile behandling, dog uden justering, med csDMARDs, topikale kortikosteroider (*WHO group 1 classification*), orale kortikosteroider, opiater, NSAIDs og cyclo-oxygenase-2-hæmmere. Studiet havde en 24-ugers dobbeltblindet periode, hvorefter patienter fra placeboarmene blev re-randomiseret 1:1 til enten IXEQ2W eller IXEQ4W i et ublindet ekstensionsstudie op til uge 156.

Effektanalyser op til uge 24 blev foretaget på data fra alle randomiserede patienter (ITT-population) og sikkerhedsanalyser på alle patienter, der modtog minimum én studiedosis. Studiets primære effektmål var andel patienter, der opnåede ACR20 ved uge 24. Sekundære effektmål af relevans er andel patienter, der opnåede ACR50, gennemsnitlig ændring fra baseline i livskvalitet målt ved *short form 36* (SF-36) og sikkerhed.

Tabel 5. Baselinekarakteristika fra SELECT-PsA 2 [33] **og SPIRIT-P2-studierne** [34]*

	SELECT-PsA 2	**SPIRIT-P2**
	Upadacitinib	**Ixekizumab**
	15 mg (n = 211)	**80 mg Q4W (n = 122)**
Alder, år	53,0 (12,0)	52,6 (13,6)
Mænd, antal (%)	98 (46 %)	63 (52 %)

	SELECT-PsA 2	SPIRIT-P2
	Upadacitinib 15 mg (n = 211)	Ixekizumab 80 mg Q4W (n = 122)
Etnicitet, antal (%)		
Kaukasisk	183 (87 %)	111 (91 %)
Asiatisk	19 (9 %)	7 (6 %)
Andet	9 (4 %)	4 (3,0 %)
PsA sygdomsvarighed, år	9,6 (8,4)	11,0 (9,6)
Antal hævede led, 0-66	11,3 (8,2)	13,1 (11,2)
Antal ømme led, 0-68	24,9 (17,3)	22,0 (14,1)
Baseline CRP, mg/L	11,2 (18,5)	17,0 (27,5)
Kropsoverflade berørt af psoriasis (BSA), gennemsnit	13,1 % (18,0)	12,5 % (17,0)
Psoriasis BSA ≥ 3 %, antal (%)	130 (62 %)	68 (56 %)
PASI-score, 0-72	10,1 (9,2)**	6,4 (7,9)§
Patientens vurdering af smerte	6,6 (2,1)¶	63,9 (21,4)†
Patientens globale vurdering†	NA	66,4 (20,5)
Lægens globale vurdering†	NA	60,3 (20,9)
HAQ DI (fra 0-3)	1,1 (0,6)	1,2 (0,6)
SF-36		
PCS	NA	34,8 (8,8)
MCS	NA	49,6 (11,3)
Tidligere behandling med TNF-hæmmer, antal (%)	211 (100 %)	122 (100 %)

	SELECT-PsA 2	SPIRIT-P2
	Upadacitinib 15 mg (n = 211)	Ixekizumab 80 mg Q4W (n = 122)
Én TNF-hæmmer	126 (60 %)	71 (58 %)
To TNF-hæmmere	35 (17 %)	41 (34 %)
≥ 3 TNF-hæmmere	34 (16 %)	0
Intolerance overfor TNF-Hæmmere	16 (8 %)	10 (8 %)
Behandling ved baseline, antal (%)		
csDMARDs	NA	60 (49 %)
MTX	74 (35,1 %)	48 (39 %)
MTX + anden ikke-biologisk DMARD	6 (2,8 %)	NA
Ikke-biologisk DMARD, som ikke er MTX	18 (8,5 %)	NA

*Alle værdier er opgjort som gennemsnit (SD), medmindre andet er specificeret.
**Opgjort hos patienter med Psoriasis BSA ≥ 3 %.
§ Opgjort hos patienter med psoriasis.
¶ Visuel analog skala 0-100
† Numerisk rating skala 0-10
PsA = psoriasisartrit, CRP = C-reaktiv protein, BSA = *Body Surface Area*, PASI = *Psoriasis Area Severity Index*, IGA = *Investigator Global Assessment*, SF-36 = *Short Form 36*, PCS = *Physical Component Score*, MCS = *Mental Component Score*, csDMARD = Konventionelt syntetisk *Disease Modifiying Anti-Rheumatic Drug*, MTX = methotrexat, NSAID = Non-steroide antiinflammatoriske lægemidler , NA = *Not Available*.

Fagudvalget bemærker, at der ikke er betydende forskel i patienternes baselinekarakteristika i de to studier ift. sygdomsbyrde. Der er andre mindre forskelle mellem studierne, f.eks. hvad angår baseline CRP (11,2 vs. 17,0 mg/l), sygdomsvarighed (9,6 vs. 11 år) og sværhedsgraden af psoriasis (PASI-score 10,1 vs. 6,4), men størrelsesorden af disse forskelle er små, således at det ikke forventes at påvirke effektestimaterne eller vurderingen. Overordnet afviger patientkarakteristika i studierne ikke væsentligt fra den danske patientpopulation eller patientpopulationen defineret i det kliniske spørgsmål. Patienterne har manglende eller utilstrækkelig effekt af/intolerance over for TNF-alfa-hæmmere i overensstemmelse med den relevante danske patientpopulation.

16 % af patienterne i SELECT-PsA 2-studiet havde modtaget ≥ 3 TNF-hæmmere i modsætning til SPIRIT-P2-studiet, hvor tidligere behandling med maks. 2 TNF-hæmmere var tilladt. Patienter, der skifter behandling pga. manglende effekt (primært svigt), har ofte et ringere behandlingsrespons ved senere behandlinger, hvilket muligvis kan medvirke til underestimering af effekten i SELECT-PsA 2-studiet. Denne forskel mellem studierne bidrager med usikkerhed i studiernes sammenlignelighed. Samtidigt bemærker

fagudvalget, at studiet ikke oplyser, om patientens behandlingsskift skyldes manglende effekt eller intolerance (sekundært svigt).

5.2.2 Databehandling og analyse

I dette afsnit er ansøgers datagrundlag, databehandling og analyse for hvert effektmål ved klinisk spørgsmål 2 beskrevet.

Da der ikke findes en direkte sammenligning af upadacitinib og ixekizumab til behandlingserfarne patienter med PsA, har ansøger lavet en indirekte komparativ analyse på baggrund af SELECT-PsA 2 og SPIRIT-P2-studierne, hvor den relative og absolutte forskel er estimeret ved brug af Buchers metode. Buchers metode kan anvendes, fordi studierne vurderes sammenlignelige både hvad angår studiepopulationerne og studiedesign.

Medicinrådet har ikke fundet anledning til at foretage ændringer af beregninger foretaget af ansøger eller supplere med yderligere beregninger.

Fagudvalget fremhæver følgende vedr. den indirekte sammenligning:

- Patienter med PsA er en heterogen patientpopulation med forskelle i symptombyrde i forhold til artritis, entesit og daktylit og eventuel rygsøjle involvering, hvilket betyder, at der generelt er usikkerhed forbundet med sammenligninger på tværs af studier. Derfor skal resultaterne fra den indirekte sammenligning tages med forbehold.
- Fra den indirekte sammenligning foreligger der data på ACR50, bivirkninger og livskvalitet efter opfølgningstid på 24 uger.
- Der foreligger ikke data på mTSS, da effektmålet ikke indgik i de to studier.
- Ansøger har indsendt data på alvorlige uønskede hændelser (*serious adverse events* (SAE)) fremfor alvorlige bivirkninger (*serious adverse reactions* (SAR)), som specificeret i protokollen, da der ikke foreligger data på SAR fra SELECT-PsA 2. Fagudvalget tager højde for afvigelsen i vurderingen af evidensens kvalitet.
- Poolede resultater for upadacitinib og ixekizumab fra hhv. SELECT-PsA 1+2 og SPIRIT-P1+P2 ligger til grund for den indirekte sammenligning af alvorlige uønskede hændelser. Ansøger begrunder dette i, at der ikke forventes at være forskel i bivirkninger på baggrund af patienternes tidligere (eller manglende) behandling med b/tsDMARDs. Datagrundlaget i den indirekte sammenligning vil blive styrket ved at bruge poolede resultater. Især når der er tale om sjældne hændelser ligesom alvorlige uønskede hændelser. Medicinrådet accepterer ansøgers tilgang.

5.2.3 Evidensens kvalitet

Medicinrådet har anvendt GRADE til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen. Nedenfor følger en beskrivelse af vurderingen af de væsentligste domæner for hvert klinisk spørgsmål. Vurdering af risikoen for bias ved Cochrane risk of bias tool 2.0 ved de enkelte studier fremgår af bilag 1. Den fuldstændige GRADE-vurdering og begrundelserne er samlet i en GRADE-profil (bilag 2).

Indledningsvis blev lægemidlernes direkte sammenligninger med placebo vurderet.

- Overordnet var evidensens kvalitet i SELECT-PsA 2-studiet af upadacitinib sammenlignet med placebo af lav kvalitet. Evidensen er nedgraderet på baggrund af inkonsistens (kun ét studie), indirekthed (data opgjort som alvorlige uønskede hændelser (SAE) fremfor alvorlige bivirkninger (SAR)) samt unøjagtighed (konfidensintervallet for SAE er bredt, og indeholder mulighed for flere forskellige konklusioner).
- Overordnet var evidensens kvalitet i SPIRIT-P2-studiet af ixekizumab sammenlignet med placebo af lav kvalitet. Evidensen er nedgraderet på baggrund af inkonsistens (kun ét studie), indirekthed (data opgjort som alvorlige uønskede hændelser (SAE) fremfor alvorlige bivirkninger (SAR)) samt unøjagtighed (konfidensintervallet for SAE er bredt, og indeholder mulighed for flere forskellige konklusioner).

Da merværdien af upadacitinib sammenlignet med ixekizumab er vurderet via indirekte sammenligninger, er der for alle effektmål yderligere nedjusteret for indirekte evidens. Den samlede evidenskvalitet for klinisk spørgsmål 2 er vurderet ud fra det lavest vurderede kritiske effektmål (alvorlige uønskede hændelser ved både SELECT-PsA 2- og SPIRIT-P2-studierne).

Evidensens kvalitet er meget lav, hvilket betyder, at nye studier med høj sandsynlighed kan ændre konklusionen.

5.2.4 Effektestimater og kategorier

I tabellen herunder fremgår de absolutte og relative effektforskelle, de foreløbige og aggregerede kategorier, den samlede kategori og den samlede kvalitet af evidensen for klinisk spørgsmål 2.

Tabel 6. Resultater for klinisk spørgsmål 2 – upadacitinib sammenlignet med ixekizumab til behandlingserfarne patienter med PsA uden moderat til svær plaque psoriasis ved uge 24

Effektmål	Målenhed (MKRF)	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi for effektmålet
			Forskel (95 % CI)	Foreløbig værdi	Forskel (95 % CI)	Foreløbig værdi	
Sygdomsaktivitet - ledaffektion	Andel patienter, der oplever respons på ACR50 (MKRF: 15 %-point)	Kritisk	[redacted]	Kan ikke kategoriseres	[redacted]	Kan ikke kategoriseres	Kan ikke kategoriseres
	Andel patienter uden progression, jf. mTSS (MKRF: 10 %-point)		NA	Kan ikke kategoriseres	NA	Kan ikke kategoriseres	
Bivirkninger	Andel patienter, der oplever alvorlige bivirkninger (MKRF: 5 %-point)	Kritisk	[redacted]	Kan ikke kategoriseres	[redacted]	Kan ikke kategoriseres	Kan ikke kategoriseres
	Gennemgang af bivirkningsprofil		Se nedenfor				
Livskvalitet	Gennemsnitlig ændring fra baseline på SF-36, energi-subdomæne (MKRF: 7,8 point))	Kritisk	[redacted]	Kan ikke kategoriseres	Kan ikke estimeres*	Kan ikke kategoriseres*	Kan ikke kategoriseres
	Gennemsnitlig ændring fra baseline på SF-36, den fysiske komponent summary (MKRF: 7,2 point)		[redacted]	Ingen dokumenteret merværdi	Kan ikke estimeres*	Kan ikke kategoriseres*	

Effektmål	Målenhed (MKRF)	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi for effektmålet
			Forskel (95 % CI)	Foreløbig værdi	Forskel (95 % CI)	Foreløbig værdi	
	Gennemsnitlig ændring fra baseline på SF-36, den mentale komponent summary (MKRF: 3,1 point)		[redacted]	Kan ikke kategoriseres	Kan ikke estimeres*	Kan ikke kategoriseres*	

Konklusion	
Samlet kategori for lægemidlets værdi	Kan ikke kategoriseres efter Medicinrådets metoder
Kvalitet af den samlede evidens	Meget lav

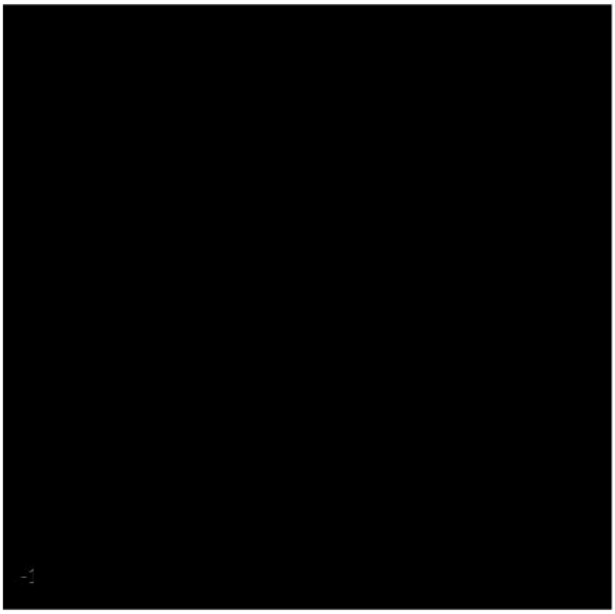
CI = konfidensinterval, HR = Hazard Ratio, OR = Odds Ratio, RR = relativ risiko, NA = *Not Available*
*Det er ikke muligt at regne relativ risiko for effektmål opgjort på en kontinuerlig skala. Derfor kan den foreløbige værdi ikke kategoriseres.

Sygdomsaktivitet - ledaffektion

Se afsnit 5.1.4 for definition af effektmålet *Sygdomsaktivitet-ledaffektion*.

ACR50

Efter 24 ugers opfølgning havde 81 ud af 211 patienter (38,4 %) opnået ACR50 i upadacitinib-armen i SELECT-PsA 2-studiet [33], hvilket var tilfældet for 43 ud af 122 patienter (35,2 %) i ixekizumab-armen i SPIRIT-P2-studiet [34]. For placeboarmene var andelen 9,4 % og 5 % i hhv. SELECT-PsA 2 og SPIRIT-P2-studierne. Den absolutte forskel fra den indirekte sammenligning er vist i figur 7 nedenfor.



Figur 7. Punktestimat og 95 % konfidensinterval for den absolutte forskel for andel patienter, der oplever respons på ACR50. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Fagudvalget har i protokollen defineret MKRF til 15 %-point. Punktestimatet for den absolutte effektforskel på [redacted] afspejler dermed ikke en klinisk relevant effektforskel, da det ligger under den mindste klinisk relevante forskel på 15 %-point. Konfidensintervallet er bredt, hvilket betyder, at det rummer muligheden for, at upadacitinib har en positiv, ingen og negativ værdi. Derfor kan den foreløbige værdi af upadacitinib vedr. ACR50, baseret på den absolutte effektforskel, ikke kategoriseres efter Medicinrådets metoder.

Baseret på den relative effektforskel, opgjort som en relativ risiko på [redacted] (fremgår af tabel 6), har upadacitinib foreløbigt en værdi, som ikke kan kategoriseres vedr. ACR50.

Efter 56 ugers opfølgning havde 40,8 % af patienterne i upadacitinib-armen i SELECT-PsA 2 opnået ACR50 [37] – og dermed lidt flere end ved 24 uger (38,4 %). I SPIRIT-P2-studiet havde 41,8 % af patienterne i ixekizumab-armen opnået ACR50 efter 52 ugers opfølgning, som ligeledes er lidt flere end ved 24 uger (35,2 %) [38]. Fagudvalget

vurderer derfor, at effekten af begge lægemidler ved ACR50 er vedvarende i mindst ét år.

mTSS

Ansøger har ikke indsendt en analyse på delmålet, da mTSS ikke indgik i de to studier. Den foreløbige værdi af upadacitinib vedr. delmålet kan dermed ikke kategoriseres.

Samlet for effektmålet *Sygdomsaktivitet - ledaffektion*

Baseret på ovenstående gennemgang af effektmålet *Sygdomsaktivitet-ledaffektion*, målt med ACR50, vurderer fagudvalget, at upadacitinib sammenlignet med ixekizumab **ikke kan kategoriseres** på dette effektmål efter Medicinrådets metoder.

Den indirekte sammenligning tyder på, at der ikke er forskel mellem upadacitinib og ixekizumab, hvad angår ACR50, da den absolutte effektforskel er lav (-1 %-point) og ikke af klinisk betydning.

Overordnet vurderer fagudvalget, at på baggrund af usikkerheden ved den indirekte sammenligning, er det ikke muligt at konkludere, om der er en klinisk relevant forskel mellem upadacitinib og ixekizumab, hvad angår sygdomsaktivitet målt som ACR50.

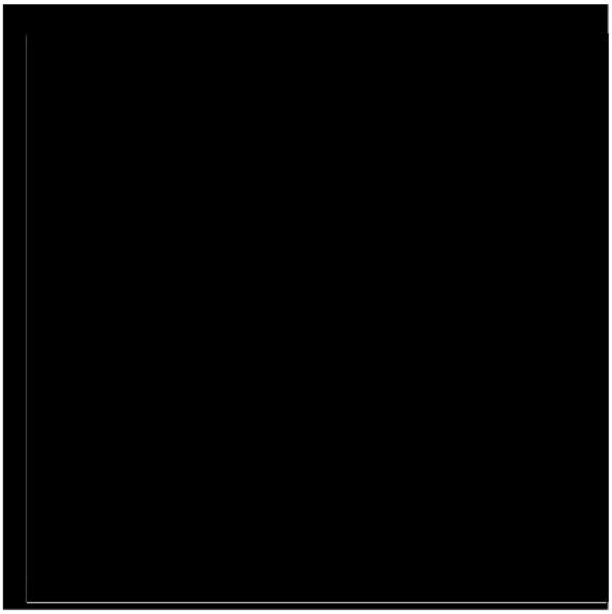
Bivirkninger

Se afsnit 5.1.4 for definition af effektmålet *Bivirkninger*.

Andel patienter, der oplever alvorlige bivirkninger

Ansøger har indsendt data på andel patienter, der oplever alvorlige uønskede hændelser (SAE), da der ikke foreligger data på alvorlige bivirkninger (SAR) fra upadacitinib-studierne. Data stammer fra poolede resultater fra SELECT-PsA 1+2-studierne og SPIRIT-P1+2-studierne.

Efter 24 ugers opfølgning havde [redacted] oplevet en uønsket hændelse i upadacitinib-armene i SELECT-PsA 1+2-studierne [20,33], hvilket var tilfældet for [redacted] i ixekizumab-armene i SPIRIT-P1+2-studierne [35]. For placeboarmene var andelen [redacted] i begge poolede resultater. Den absolutte forskel fra den indirekte sammenligning er vist i figur 8 nedenfor.



Figur 8. Punktestimat og 95 % konfidensinterval for den absolutte forskel for *andel patienter, der oplever SAE*. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Fagudvalget har i protokollen defineret MKRF til 5 %-point. Punktestimatet for den absolutte effektforskel på [redacted] afspejler dermed ikke en klinisk relevant effektforskel. Konfidensintervallet er bredt, hvilket betyder, at det rummer muligheden for, at upadacitinib har en positiv, ingen og negativ værdi. Derfor kan den foreløbige værdi af upadacitinib vedr. alvorlige uønskede hændelser, baseret på den absolutte effektforskel, ikke kategoriseres efter Medicinrådets metoder.

Baseret på den relative effektforskel på [redacted], som fremgår af tabel 6, har upadacitinib foreløbig en værdi vedr. alvorlige uønskede hændelser, der ikke kan kategoriseres. X

Gennemgang af bivirkningsprofilen

Gennemgangen af bivirkningsprofilen tager udgangspunkt i lægemidlernes produktresuméer, hvor bivirkningerne er sammenlagt fra de underliggende kliniske studier [22,36].

Upadacitinib

Se gennemgangen af bivirkningsprofilen ved klinisk spørgsmål 1, afsnit 5.1.4.

Ixekizumab

De hyppigst rapporterede bivirkninger er reaktioner på injektionsstedet (udslæt (erytem) og smerte) og øvre luftvejsinfektioner (oftest forkølelse (nasopharyngitis)). Behandling med ixekizumab er forbundet med en øget forekomst af infektioner, f.eks. infektion i øvre luftveje, svamp i munden (oral candidiasis), øjenbetændelse (konjunktivitis) og svampeinfektioner i huden (dermatofytose). Alvorlige overfølsomhedsreaktioner er rapporteret, og der er blevet rapporteret om tilfælde af nyopstået eller forværret

inflammatorisk tarmsygdom ved behandling med ixekizumab, hvilket, fagudvalget bemærker, er alvorligt for patienten [36].

Nedenstående tabel giver et overblik over de rapporterede bivirkninger fra de underliggende upadacitinib-studier (poolede resultater fra SELECT-PsA 1+2) samt SPIRIT-P2.

Tabel 7. Oversigt over bivirkninger ved 24 uger fra SELECT-PsA 2 og SPIRIT-P2

	SELECT-PsA 1+2		SPIRIT-P2	
	Placebo	Upadacitinib	Placebo	Ixekizumab Q4W
Uønskede hændelser (AE)	61,6 %	65,9 %	64 %	68 %
Alvorlige uønskede hændelser (SAE)	2,7 %	4,1 %	3 %	2 %
Infektioner	33,5 %	37,5 %	30 %	39 %
Alvorlige infektioner	0,8 %	0,9 %	0 %	0 %
Behandlingsophør grundet AE	3,8 %	4,4 %	5,0 %	4,0 %
Forhøjet alanin aminotransferase	2 %	3,3 %	NA*	NA*
Forhøjet aspartat aminotransferase	1,4 %	2,2 %	NA*	NA*
Nasopharyngitis	6 %	4,8 %	3 %	7 %
Øvre luftvejsinfektion	6,9 %	8,9 %	8 %	9 %

*Hepatic events 2 % i både placebo- og ixekizumab-armene.

Sammenligning af opgørelser over uønskede hændelser i forskellige studier skal tages med forbehold, da der kan være forskel på, hvordan uønskede hændelser bliver opgjort i forskellige studier. Fagudvalget kan ikke med sikkerhed konkludere, om der er forskel i bivirkninger mellem upadacitinib og ixekizumab til patienter med PsA på baggrund af ovenstående data.

Samlet for effektmålet bivirkninger

Baseret på ovenstående gennemgang af effektmålet *Bivirkninger* vurderer fagudvalget, at upadacitinib **ikke kan kategoriseres** efter Medicinrådets metoder på dette effektmål sammenlignet med ixekizumab.

Den indirekte sammenligning tyder på, at der ikke er forskel mellem upadacitinib og ixekizumab, hvad angår alvorlige uønskede hændelser, da den absolutte effektforskel er lav (0 %-point) og ikke af klinisk betydning. Upadacitinibs og ixekizumabs bivirkningsprofiler er forskellige, hvor begge lægemidler kan medføre en række uønskede hændelser. Fagudvalget finder dog, at på baggrund af de rapporterede bivirkninger, er lægemidlerne sammenlignelige, hvad angår bivirkningernes sværhedsgrad.

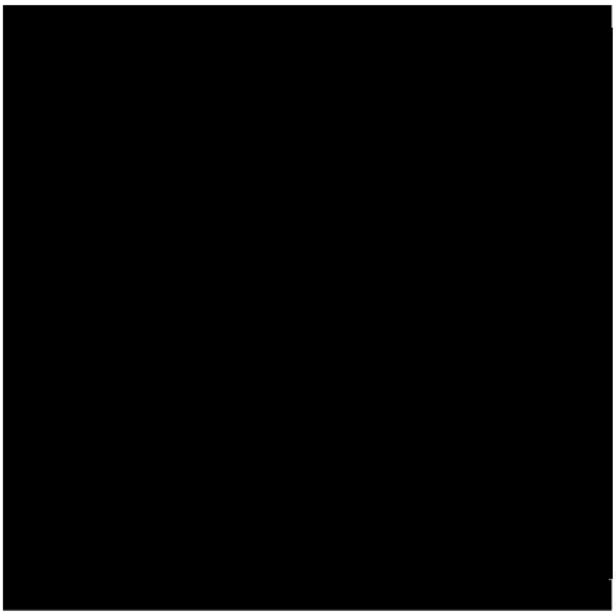
Jf. gennemgangen i afsnit 5.1.4 omkring den særlige opmærksomhed, som både EMA og FDA anbefaler ved behandling med JAK-hæmmere [27–29], understreger fagudvalget, at der generelt er øget opmærksomhed blandt klinikere og patienter mht. sikkerheden ved behandling med JAK-hæmmere.

Livskvalitet
Se afsnit 5.1.4 for definition af effektmålet *Livskvalitet*.

Da livskvalitetsdata opgøres på en kontinuer skala, kan den relative effektforskel ikke udregnes. Derfor har upadacitinib, baseret på den relative forskel, foreløbigt en værdi, der ikke kan kategoriseres efter Medicinrådets metoder vedr. alle livskvalitetsdelmål.

Subdomænet energi (*vitality*)
For patienter i upadacitinib-armen i SELECT-PsA 2-studiet var den gennemsnitlige ændring fra baseline efter 24 uger 10,7 (8,1; 13,2) [33], mens den gennemsnitlige ændring for patienter i ixekizumab-armen i SPIRIT-P2-studiet var 14,4 [39]. For placeboarmene var den gennemsnitlige ændring fra baseline 3,0 (0,3; 5,7) og 5,5 i hhv. SELECT-PsA 2 og SPIRIT-P2-studierne.

Den absolutte forskel fra den indirekte sammenligning er vist i figur 9 nedenfor.



Figur 9. Punktestimat og 95 % konfidensinterval for den absolutte forskel for livskvalitet – subdomænet energi. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

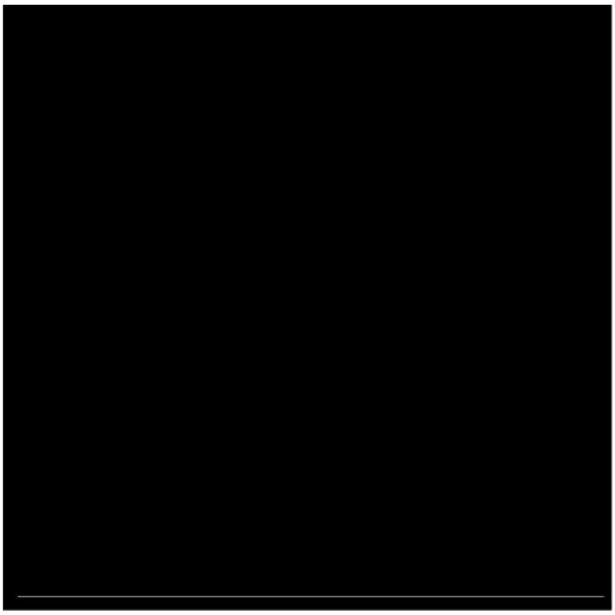
Fagudvalget har defineret MKRF til 7,8 point, og punktestimatet for den absolutte effektforskel på [redacted] afspejler derfor ikke en klinisk relevant effektforskel. Konfidensintervallet er bredt, hvilket betyder, at det rummer muligheden for, at upadacitinib har en positiv, ingen og negativ værdi. Derfor kan den foreløbige

værdi af upadacitinib vedr. SF-36 – energi-subdomæne, baseret på den absolutte effektforskel, ikke kategoriseres efter Medicinrådets metoder.

Den fysiske komponent

For patienter i upadacitinib-armen i SELECT-PsA 2-studiet var den gennemsnitlige ændring fra baseline efter 24 uger 6,38 (5,28; 7,48) [33], mens den gennemsnitlige ændring for patienter i ixekizumab-armen i SPIRIT-P2-studiet var 8,9 (6,35; 11,45) [34]. For placeboarmene var den gennemsnitlige ændring fra baseline 1,34 (0,19; 2,49) og 3,3 (0,56; 6,04) i hhv. SELECT-PsA 2 og SPIRIT-P2-studierne.

Den absolutte forskel fra den indirekte sammenligning er vist i figur 10 nedenfor.



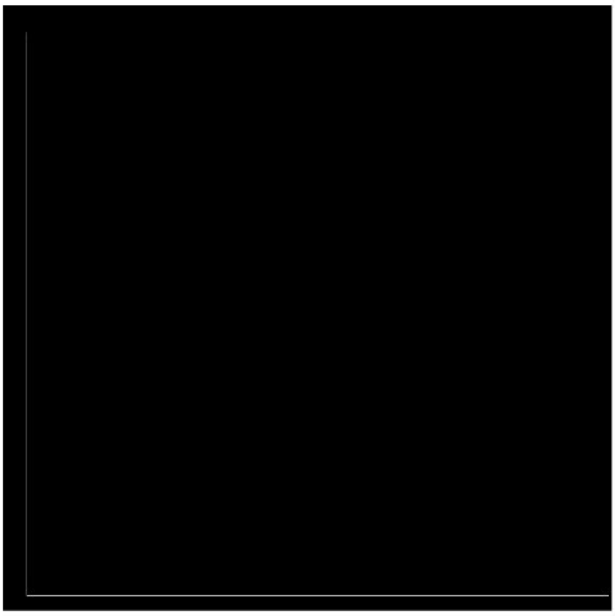
Figur 10. Punktestimat og 95 % konfidensinterval for den absolutte forskel for livskvalitet – den fysiske komponent. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Fagudvalget har defineret MKRF til 7,2 point, og punktestimatet for den absolutte effektforskel på [redacted] afspejler derfor ikke en klinisk relevant effektforskel. Den nedre grænse for konfidensintervallet er tættere på 0 (ingen effektforskel) end på en negativ klinisk relevant forskel. Derfor er den foreløbige værdi af upadacitinib, baseret på den absolutte effektforskel, ingen dokumenteret merværdi vedr. SF-36 – den fysiske komponent summary.X

Den mentale komponent

For patienter i upadacitinib-armen i SELECT-PsA 2-studiet var den gennemsnitlige ændring fra baseline efter 24 uger 2,25 (0,98; 3,52) [33], mens den gennemsnitlige ændring for patienter i ixekizumab-armen i SPIRIT-P2-studiet var 3,6 [34]. For placeboarmene var den gennemsnitlige ændring fra baseline 0,37 (-0,95; 1,70) og 0,9 i hhv. SELECT-PsA 2 og SPIRIT-P2-studierne.

Den absolutte forskel fra den indirekte sammenligning er vist i figur 11 nedenfor.



Figur 11. Punktestimat og 95 % konfidensinterval for den absolutte forskel for livskvalitet – den mentale komponent. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Fagudvalget har defineret MKRF til 3,1 point, og punktestimatet for den absolutte effektforskel på [redacted] afspejler derfor ikke en klinisk relevant effektforskel. Konfidensintervallet er bredt, hvilket betyder, at det rummer muligheden for, at upadacitinib har en positiv, ingen og negativ værdi. Derfor kan den foreløbige værdi af upadacitinib vedr. SF-36 – **den mentale komponent summary**, baseret på den absolutte effektforskel, ikke kategoriseres efter Medicinrådets metoder.X

Samlet for effektmålet livskvalitet

Baseret på ovenstående gennemgang af effektmålet *Livskvalitet* vurderer fagudvalget, at upadacitinib **ikke kan kategoriseres efter Medicinrådets metoder på dette effektmål sammenlignet med ixekizumab**.

Den indirekte sammenligning tyder på, at der ikke er forskel mellem upadacitinib og ixekizumab, hvad angår livskvalitet, da den absolutte effektforskel for alle livskvalitetsdomæner er lav og ikke af klinisk betydning.

Overordnet vurderer fagudvalget, at på baggrund af usikkerheden ved den indirekte sammenligning, er det ikke muligt at konkludere, om der er en klinisk relevant forskel mellem upadacitinib og ixekizumab, hvad angår livskvalitet.

5.2.5 Fagudvalgets konklusion

Fagudvalget vurderer, at den samlede værdi af upadacitinib sammenlignet med ixekizumab til behandlingserfarne patienter med PsA uden moderat til svær plaque psoriasis **ikke kan kategoriseres** efter Medicinrådets metoder.

Den indirekte sammenligning tyder på, at der ikke er forskel mellem upadacitinib og ixekizumab, hvad angår sygdomsaktivitet målt med ACR50, livskvalitet eller alvorlige uønskede hændelser. Der foreligger ikke data på radiologisk progression, hvilket vanskeliggør en vurdering af lægemidlets effekt på dette effektmål. Bivirkningsprofilerne for upadacitinib og ixekizumab er forskellige, men på baggrund af de rapporterede bivirkninger er lægemidlerne sammenlignelige, hvad angår bivirkningernes sværhedsgrad.

Resultaterne fra den indirekte sammenligning har meget brede konfidensintervaller, hvilket vanskeliggør at konkludere entydigt på værdien af upadacitinib. Derudover skal der tages forbehold for, at patienter med PsA er en heterogen patientpopulation, hvilket betyder, at sammenligninger på tværs af studier generelt er behæftet med usikkerhed. Derfor finder fagudvalget, at det indirekte sammenligningsgrundlag er utilstrækkelig til at drage konklusioner i forhold til effekt og bivirkninger. Fagudvalget bemærker, at nye studier vil kunne ændre konklusionen.

Pga. den særlige opmærksomhed, som både EMA og FDA anbefaler ved behandling med JAK-hæmmere [27–29], understreger fagudvalget, at der er generelt øget opmærksomhed blandt klinikere og patienter mht. sikkerheden ved behandling med JAK-hæmmere. Det er endnu uklart, om der er tale om, at disse bivirkninger er en klasseeffekt for JAK-hæmmere. Fagudvalget fremhæver derfor, at nye data kan ændre konklusionen vedrørende sikkerheden af upadacitinib.

6. Relation til behandlingsvejledning

Medicinrådet besluttede den 20. november 2020 at udarbejde en behandlingsvejledning vedr. psoriasisartrit mhp. at erstatte nuværende RADS-behandlingsvejledning for anvendelse af biologisk behandling af psoriasisartrit [19]. Medicinrådet har besluttet, at RADS-lægemiddelrekommandationen derfor ikke længere vil blive opdateret [40].

Af den grund vil Medicinrådet først tage stilling til evt. indplacering af upadacitinib i en behandlingsvejledning i forbindelse med udarbejdelsen af Medicinrådets behandlingsvejledning vedr. psoriasisartrit.

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8. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende gigtsygdomme

Sammensætning af fagudvalg	
Formand	**Indstillet af**
Annemarie Lyng Svensson *Overlæge*	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
Salome Kristensen *Overlæge*	Region Nordjylland
Lars Erik Bartels *Afdelingslæge*	Region Midtjylland
Hanne M. Lindegaard *Overlæge, klinisk lektor*	Region Syddanmark
Thomas Adelsten *Uddannelsesansvarlig overlæge*	Region Sjælland
Maria Krogstrup *Afdelingslæge*	Region Hovedstaden
Per Damkier *Professor, overlæge*	Dansk Selskab for Klinisk Farmakologi
Ane Hornbæk Mortensen *Farmaceut*	Dansk Selskab for Sygehusapoteksledelse
Dorte Vendelbo Jensen *Overlæge, sekretariatsleder*	DANBIO
Philip Bennett *Overlæge*	Dansk Reumatologisk Selskab
Annette de Thurah *Klinisk sygeplejespecialist*	Dansk Sygepleje Selskab
Connie Ziegler *Patient/patientrepræsentant*	Danske Patienter

Sammensætning af fagudvalg	
Lene Mandrup Thomsen *Patient/patientrepræsentant*	Danske Patienter
Tidligere medlemmer, som har bidraget til arbejdet	**Udpeget af**
Thomas Loof Hedegård *Farmaceut*	Dansk Selskab for Sygehusapoteksledelse

Medicinrådets sekretariat

Medicinrådet

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9. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.2	8. februar 2022	Præcisering af en enkelt sætning omkring dosisafhængig risiko for VTE på side 21.
1.1	7. februar 2022	Forkert reference på side 21 er blevet rettet til.
1.0	26. januar 2022	Godkendt af Medicinrådet.

10. Bilag

Bilag 1: Cochrane – risiko for bias

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

Tabel 8. Vurdering af risiko for bias McInnes et al., 2021, SELECT-PsA 1, NCT03104400

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiseringsprocessen	**Lav**	Patienter blev randomiseret vha. et interaktivt-responsesystem. Randomiseringen var stratificeret efter graden af psoriasis, nuværende brug/ikke brug af mindst ét ikke-biologisk DMARD, tilstedeværelse af dactylitis og tilstedeværelse af enthesitis. Patienter blev randomiseret 1:1:1:1 til upadacitinib 15 mg p.o. eller 30 mg p.o. en gang dagligt, placebo efterfulgt af upadacitib 15 mg eller 30 mg en gang dagligt (1:1) eller adalimumab 40 mg s.c. hver anden uge.
Effekt af tildeling til intervention	**Lav**	Studiet var et placebo-kontrolleret, dobbelt-blindet studie. Investigator, involverede sites, patienter og sponsor var blindede i den 24 uger lange placebokontrollerede periode. Patienter, der var randomiseret til upadacitinib eller placebo, modtog placebo s.c. hver anden uge, mens patienter, der var randomiseret til adalimumab eller placebo, modtog placebo p.o. dagligt. Resultater blev analyseret på en modificeret ITT-population, som inkluderede alle patienter, der havde modtaget mindst én dosis upadacitinib, placebo eller adalimumab.
Manglende data for effektmål	**Lav**	Der foreligger data for alle effektmål, der er beskrevet i studieprotokollen. For ACR20, 50 og 70 blev manglende data registreret som non-response. For kontinuerlige endepunkter blev der anvendt en *mixed-effect model repeated measurement*, hvor "missing data at random" blev antaget.
Risiko for bias ved indsamlingen af data	**Lav**	Dobbeltblindet, placebo-kontrolleret studie.
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Lav**	Alle effektmål er analyseret som specificeret i protokollen.
Overordnet risiko for bias	**Lav**	Den overordnede risiko for bias er lav, da alle domæner har lav risiko for bias.

Tabel 9. Vurdering af risiko for bias Mease et al., 2021, SELECT-PsA 2, NCT03162796

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	**Lav**	Patienter blev randomiseret ved et interaktivt respons-system. Randomiseringen var stratificeret efter graden af psoriasis, nuværende brug af mindst én DMARD og antal tidligere biologiske DMARDs uden succes. Patienter blev randomiseret 2:2:1:1 til upadacitinib 15 mg p.o. én gang dagligt, upadacitinib 30 mg p.o. én gang dagligt, placebo p.o. efterfulgt af upadacitinib 15 mg p.o. én gang dagligt ved uge 24 eller placebo p.o. efterfulgt af upadacitinib 30 mg p.o. én gang dagligt ved uge 24.
Effekt af tildeling til intervention	**Lav**	Dobbeltblindet studie, hvor deltagere, care providere, investigatorer og outcomes assessor alle var blindede i den placebokontrollere periode, som varede 24 uger. Resultater blev analyseret på en modificeret ITT-population, som inkluderede alle patienter, der havde modtaget mindst én dosis upadacitinib eller placebo. 84,6 % af deltagerne fuldførte studiets første 24 uger. Frafald var jævnt fordelt mellem studiearmene med samme fordeling i årsagerne til frafald.
Manglende data for effektmål	**Lav**	Alle effektmål var præspecificerede i protokollen. Manglende data blev registeret som non-response. For kontinuerlige endepunkter blev der anvendt en *mixed-effect model repeated measurement*.
Risiko for bias ved indsamlingen af data	**Lav**	Effektmål er målt på den måde, som er standard indenfor feltet. Studiet er dobbeltblindet og placebokontrolleret.
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Lav**	Effektmål er præspecificeret i protokol og statistisk analyseplan.
Overordnet risiko for bias	**Lav**	Den overordnede risiko for bias er lav, da alle domæner har lav risiko for bias.

Tabel 10. Vurdering af risiko for bias Nash et al., 2017, SPIRIT-P2, NCT02349295

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiseringsprocessen	**Lav**	Randomisering foretaget ved brug af en computer-genereret *random sequence*. Randomiseringen var stratificeret efter region og tidligere behandling med TNF-hæmmere (utilstrækkelig respons efter behandling med én TNF-hæmmer, to TNF-hæmmere eller intolerance overfor TNF-hæmmere). Patienterne blev randomiseret 1:1:1 til ixekizumab 80 mg hver 2. uge, ixekizumab 80 mg hver 4. uge eller placebo.
Effekt af tildeling til intervention	**Lav**	Dobbeltblindet studie, hvor både investigator, site personale og deltagere var blindede til den allokerede behandling. Forudfyldte, identiske sprøjter. Studiet havde en 24-ugers dobbeltblindet periode, hvorefter patienter fra placeboarmene blev re-randomiseret 1:1 til enten IXEQ2W eller IXEQ4W i et ublindet ekstensionsstudie op til uge 156.
Manglende data for effektmål	**Lav**	Data er opgjort på ITT-populationen, og der foreligger data på de effektmål, der er beskrevet i studieprotokollen. Non-responder imputation blev brugt ved manglende data. For kontinuerlige endepunkter blev der anvendt en *mixed-effect model repeated measurement*.
Risiko for bias ved indsamlingen af data	**Lav**	Dobbeltblindet, placebo-kontrolleret studie.
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Lav**	Der foreligger data på de effektmål, der er beskrevet i studieprotokollen, og der er ingen indikation om selektiv rapportering.
Overordnet risiko for bias	**Lav**	Den overordnede risiko for bias er lav, da alle domæner har lav risiko for bias.

Bilag 2: GRADE

Klinisk spørgsmål 1 – upadacitinib sammenlignet med adalimumab til behandling af psoriasisartrit uden moderat til svær plaque psoriasis

Tabel 11. GRADE evidensprofil for klinisk spørgsmål 1, SELECT-PsA 1, upadacitinib vs. adalimumab

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Upadacitinib	Adalimuab	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
ACR50, 24 uger												
1	RCT	Ingen	Alvorlig[a]	Ingen	Ingen	Ingen	225/429	190/429	RR: 1,2 (1,03; 1,36)	8,2 %-point (1,5; 14,8)	⨁⨁⨁◯ MODERAT	KRITISK
mTSS, 24 uger												
1	RCT	Ingen	Alvorlig[a]	Ingen	Ingen	Ingen	371/387	371/391	RR: 1,01 (0,98; 1,04)	1,0 %-point (-2; 3,9)	⨁⨁⨁◯ MODERAT	KRITISK
SAE, 24 uger												
1	RCT	Ingen	Alvorlig[a]	Alvorlig[b]	Alvorlig[c]	Ingen	14/429	16/429	RR: 0,88 (0,43; 1,77)	-0,47 %-point (-2; 3,9)	⨁◯◯◯ MEGET LAV	KRITISK
SF-36 – subdomænet energi, 24 uger												

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Upadacitinib	Adalimuab	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
1	RCT	Ingen	Alvorlig[a]	Ingen	Ingen	Ingen	8,13 point (7,23; 9,03)	6,20 point (5,31; 7,09)	-	1,93 point (0,76; 3,09)	⨁⨁⨁◯ MODERAT	KRITISK
SF-36 - den fysiske komponent summary, 24 uger												
1	RCT	Ingen	Alvorlig[a]	Ingen	Ingen	Ingen	9,66 point (8,82; 10,50)	7,84 point (7,01; 8,66)	-	1,83 point (0,75; 2,91)	⨁⨁⨁◯ MODERAT	KRITISK
SF-36 - den mentale komponent summary, 24 uger												
1	RCT	Ingen	Alvorlig[a]	Ingen	Ingen	Ingen	4,80 point (3,89; 5,70)	4,25 point (3,36; 5,14)	-	0,55 point (-0,62; 1,71)	⨁⨁⨁◯ MODERAT	KRITISK
Kvalitet af den samlede evidens	MEGET LAV[d]											

[a] Der er nedgraderet ét niveau, da der kun var ét studie.

[b] Der er nedgraderet ét niveau, da konfidensintervallet indeholder en beslutningsgrænse.

[c] Data opgjort som alvorlige uønskede hændelser (*serious adverse events* (SAE)) fremfor alvorlige bivirkninger (*serious adverse reactions* (SAR)).

[d] Den samlede evidenskvalitet er vurderet ud fra den laveste kvalitet af de kritiske effektmål.

Klinisk spørgsmål 2 – upadacitinib sammenlignet med ixekizumab til behandling af psoriasisartrit uden moderat til svær plaque psoriasis

Tabel 12. GRADE evidensprofil for klinisk spørgsmål 2, SELECT-PsA 2, upadacitinib vs. placebo

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Upadacitinib	Placebo	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
ACR50, 24 uger												
1	RCT	Ingen	Alvorlig[a]	Ingen	Ingen	Ingen	81/211	20/212	RR: 4,07 (2,59; 6,39)	29 %-point (21,3-; 36,6)	⊕⊕⊕◯ MODERAT	KRITISK
mTSS, 24 uger – ingen data												
-	-	-	-	-	-	-	-	-	-	-	-	KRITISK
SAE, 24 uger, poolet fra SELECT-PsA 1+2												
1	RCT	Ingen	Ingen	Alvorlig[b]	Alvorlig[c]	Ingen	[redacted]	[redacted]	[redacted]	[redacted]	⊕⊕◯◯ LAV	KRITISK
SF-36 – subdomænet energi, 24 uger												
1	RCT	Ingen	Alvorlig[a]	Ingen	Ingen	Ingen	10,7 point (8,1; 13,2)	3,0 point (0,3; 7,09)	-	7,7 point (4,0; 11,4)	⊕⊕⊕◯ MODERAT	KRITISK

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Upadacitinib	Placebo	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
SF-36 - den fysiske komponent summary, 24 uger												
1	RCT	Ingen	Alvorlig[a]	Ingen	Ingen	Ingen	6,38 point (5,28; 7,48)	1,34 point (0,19; 2,49)	-	5,04 point (3,45; 6,63)	⨁⨁⨁◯ MODERAT	KRITISK
SF-36 - den mentale komponent summary, 24 uger												
1	RCT	Ingen	Alvorlig[a]	Ingen	Ingen	Ingen	2,25 point (0,98; 3,52)	0,37 point (-0,95; 1,70)	-	1,88 point (0,05; 3,71)	⨁⨁⨁◯ MODERAT	KRITISK
Kvalitet af den samlede evidens			LAV[d]									

[a] Der er nedgraderet ét niveau, da der kun var ét studie.

[b] Data opgjort som alvorlige uønskede hændelser (*serious adverse events* (SAE)) fremfor alvorlige bivirkninger (*serious adverse reactions* (SAR)).

[c] Der er nedgraderet ét niveau, da konfidensintervallet indeholder en beslutningsgrænse.

[d] Den samlede evidenskvalitet er vurderet ud fra den laveste kvalitet af de kritiske effektmål.

Tabel 13. GRADE evidensprofil for klinisk spørgsmål 2, SPIRIT-P2, ixekizumab vs. placebo

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Ixekizumab	Placebo	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
ACR50, 24 uger												
1	RCT	Ingen	Alvorlig[a]	Ingen	Ingen	Ingen	43/122	6/118	RR: 6,93 (3,07; 15,67)	30,2 %-point (20,8-; 39,5)	⊕⊕⊕◯ MODERAT	KRITISK
mTSS, 24 uger – ingen data												
-	-	-	-	-	-	-	-	-	-	-	-	KRITISK
SAE, 24 uger, poolet fra SPIRIT-P1+2												
2	RCT	Ingen	Ingen	Alvorlig[b]	Alvorlig[c]	Ingen	[redacted]	[redacted]	[redacted]	[redacted]	⊕⊕◯◯ LAV	KRITISK
SF-36 – subdomænet energi, 24 uger										[redacted]		
1	RCT	Ingen	Alvorlig[a]	Ingen	Ingen	Ingen	14,4 point	5,5 point	-	8,9 point [0,27-17,52]	⊕⊕⊕◯ MODERAT	KRITISK

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Ixekizumab	Placebo	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
SF-36 - den fysiske komponent summary, 24 uger												
1	RCT	Ingen	Alvorlig[a]	Ingen	Ingen	Ingen	8,9 point [6,35; 11,45]	3,3 point [0,56; 6,04]	-	5,6 point [3,2-8,0]	⨁⨁⨁◯ MODERAT	KRITISK
SF-36 - den mentale komponent summary, 24 uger												
1	RCT	Ingen	Alvorlig[a]	Ingen	Ingen	Ingen	3,6 point	0,9 point	-	2,7 point [0,4-5,0]	⨁⨁⨁◯ MODERAT	KRITISK
Kvalitet af den samlede evidens	LAV[d]											

[a] Der er nedgraderet ét niveau, da der kun var ét studie.

[b] Data opgjort som alvorlige uønskede hændelser (*serious adverse events* (SAE)) fremfor alvorlige bivirkninger (*serious adverse reactions* (SAR)).

[c] Der er nedgraderet ét niveau, da konfidensintervallet indeholder en beslutningsgrænse.

[d] Den samlede evidenskvalitet er vurderet ud fra den laveste kvalitet af de kritiske effektmål.

abbvie

Application for the assessment of clinically added value of Rinvoq™ (upadacitinib) for psoriatic arthritis

1 Basic information

TABLE 1: CONTACT INFORMATION

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TABLE 2: OVERVIEW OF THE PHARMACEUTICAL

Proprietary name	Rinvoq
Generic name	Upadacitinib
Marketing authorization holder in Denmark	AbbVie Deutschland GmbH & Co. KG
ATC code	L04AA44
Pharmacotherapeutic group	Janus kinase inhibitor (JAK)
Active substance(s)	Upadacitinib
Pharmaceutical form(s)	Prolonged-release tablet
Mechanism of action	Upadacitinib is a selective and reversible JAK inhibitor. In human cellular assays, upadacitinib preferentially inhibits signaling by JAK1 or JAK1/3 with functional selectivity over cytokine receptors that signal via pairs of JAK2
Dosage regimen	The recommended dose of upadacitinib is 15 mg once daily.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	RINVOQ is indicated to treatment of psoriatic arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs). RINVOQ may be used as monotherapy or in combination with methotrexate.
Other approved therapeutic indications	Treatment of moderate to severe active rheumatoid arthritis (RA) Treatment of active ankylosing spondylitis (AS)
Will dispensing be restricted to hospitals?	Yes

Combination therapy and/or co-medication	Monotherapy or in combination with methotrexate
Packaging – types, sizes/number of units, and concentrations	Each pack contains 28, 15mg prolonged-release tablets
Orphan drug designation	No

2 Abbreviations

ACR	American College of Rheumatology
ACR20/50/70	American College of Rheumatology criteria 20%/50%/70%
ADA	Adalimumab
AE	Adverse Event
BL	Baseline
BSA	Body Surface Psoriasis
CI	Confidence Interval
CI_low	Lower confidence Interval
CI_high	Higher confidence Interval
CRP	C Reactive Protein
CPK	Creatine Phosphokinase
csDMARD	Conventional synthetic Disease Modifying Antirheumatic Drug
DAS(28)(CRP)	28-joint disease activity Score Based on C-reactive protein
DMARD	Disease Modifying Antirheumatic Drug
DSS	Dactylitis Severity Score
EMA	European Medicines Agency
EOW	Every other week
EPAR	European public assessment report
EAER	Exposure Adjusted Event Rate
HAQ-DI	Health Assessment Questionaire Disability Index
HBV	Hepatitis B virus
HSTCL	Hepatosplenic T-cell Lymphoma
IV	Intravenous
JAK	Janus Kinase

MACE	Major Adverse Cardiovascular Event
MCID	Minimal clinically important difference
mTSS	modified Total Sharp Score
MTX	Methotrexate
NRI	Non-responder imputation
OR	Odds Ratio
PASI	Psoriasis Area Severity Index
PASI75	Psoriasis Area Severity Index score 75%
PBO	Placebo
PsA	Psoriatic arthritis
RCT	Randomized controlled trial
RR	Relative Risk
SAE	Serious Adverse Event
SC	Subcutaneously
SD	Standard Deviation
SDAI	Simplified Disease Activity Index
SE	Standard Error
SF-36	Short Form 36 health survey
SmPC	Summary of product Characteristics
TB	Tuberculosis
TNF	Tumor Necrosis Factor

3 Summary

Psoriatic arthritis (PsA) is a common inflammatory arthritis of the peripheral and axial skeleton.(1) PsA can be distinguished from other spondyloarthropathies by the presence of peripheral arthritis, asymmetrical distribution of axial involvement, with lower levels of pain, and movement limitation.(2) Almost one-third of patients with psoriasis will also develop PsA approximately 10 years after initial psoriasis diagnosis. However, in 15% of cases, arthritis and psoriasis occur at the same time, or even precedes psoriasis.(3) PsA is associated with many comorbidities and extra-articular manifestation and besides psoriasis cardiovascular disease, inflammatory bowel disease, uveitis, diabetes, osteoporosis, depression, and anxiety are common. The disease heterogeneity has a major negative impact on both the patient and the health care resources needed by the patient group. The hallmark of PsA consists of the coexisting progression of joint disease and skin inflammation, where joint pain is the most important parameter hampering daily activities for patients.

The prevalence in Denmark is difficult to estimate due to unclear diagnostic criteria, however it is estimated to be between 6.000 - 25.000 of the Danish population (4),(5). PsA normally develops in early 40s and 50s, with no difference between genders.

Current treatment recommendations for PsA in Denmark, updated 15 January 2021, differentiate between patients with or without concomitant moderate to severe plaque psoriasis and former or existing uveitis or former or existing inflammatory bowel disease (IBD) (6).For all these groups, the TNF inhibitor adalimumab is ranked highest and recommended as 1st choice. After that, for patients with or without concomitant plaque psoriasis the treatment choice is another TNF inhibitor, IL-17 inhibitors or IL12/23 inhibitor. For patients with former or existing comorbidities, uveitis or IBD (Ulcerative colitis, Crohn's disease), options are limited. The only choice for patients with uveitis is another TNF inhibitor and for patients with IBD another TNF-inhibitor or IL12/23 inhibitor (Crohn's disease only) (6).

Currently no JAK inhibitors are in the guidelines for PsA as tofacitinib was removed from the treatment guidelines due to safety concerns regarding VTE. Therefore, there is a need in Denmark for new treatment options with a proven efficacy and a well-defined safety profile.

This application is concerning the JAK-inhibitor upadacitinib as a treatment option for patients with PsA in Denmark. Upadacitinib was approved by the European Commission on January 25th 2021 for the treatment of psoriatic arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs). RINVOQ is administered orally once daily and may be used as monotherapy or in combination with methotrexate. Rinvoq is also approved by EMA for the treatment of rheumatoid arthritis and ankylosing spondylitis.

The 26th of April AbbVie received a protocol from the Danish Medicines Council (DMC) which form the basis for this application. The protocol stated two clinical questions to assess the clinical value of upadacitinib:

1. What is the clinical added value of upadacitinib vs. adalimumab for bio-naïve patients with PsA?
2. What is the clinical added value of upadacitinib vs. ixekizumab for bio-experienced patients with PsA?

The outcomes measure of interest was stated to be:

- Proportion of patients achieving American College of Rheumatology 50% response (ACR50).
- Proportion of patients without progression (mTSS).
- Proportion of patients who experienced severe adverse events.
- Mean change from baseline on SF-36 (vitality, physical component and mental component).
- Narrative assessment of adverse events. Specifically, it was also asked for an assessment of Rinvoq's safety regarding risk for Venous Thromboembolism (VTE), serious infections for patients above 65 years, as well as for Rinvoqs toxicity regarding reproduction and malignity.

The clinical efficacy and safety of upadacitinib in PsA have been established in an extensive clinical program which contains two dedicated phase III, randomized, double blind studies that assessed upadacitinib in both a bDMARD-naïve

population vs. placebo and the active comparator adalimumab (SELECT PsA-1) and bDMARD-experienced population vs. placebo (SELECT PsA-2). Both studies demonstrated upadacitinib to provide significantly greater improvement compared with placebo in all measurements, and in SELECT PsA-1 significantly greater score vs. adalimumab on several important joint and axial measurements, such as ACR20/50/70, physical function, and pain at week 24 was shown, with at least similar responses regarding psoriasis.

Results from the SELECT PsA-1 trial at week 24 have been used to assess the clinically added value of upadacitinib vs. adalimumab for the bio-naïve population, based on outcomes defined in the DMC protocol. Results from the analysis shows better results for upadacitinib vs. adalimumab on all outcomes (ACR50, modified total Sharp/van der Heijde Score, serious adverse events and SF-36 subdomains) although the difference is not bigger than the minimal clinically important difference defined by DMC. Upadacitinib has therefore demonstrated to be at least as good as adalimumab for this population.

For the bio-experienced population there exist no head-to head trial of upadacitinib vs. ixekizumab but results from an indirect treatment comparison (ITC), using the Bucher's method, have been used to assess the relative efficacy of upadacitinib vs. ixekizumab at week 24. The ITC use results from two randomized clinical trials including bio-experienced patients (SELECT PsA-2 for upadacitinib and SPIRIT-P2 for ixekizumab), and compares the efficacy of upadacitinib and ixekizumab on ACR50, SF36-vitality,- mentally component (MCS) and – physical component (PCS). The assessment of clinically added value based on all outcomes show a very similar response and suggest that upadacitinib provide similar clinical value as Ixekizumab for the treatment of bio-experienced patients with PsA.

The observed safety profile for upadacitinib from the SELECT PsA program was generally consistent with what has been observed in the robust RA clinical studies and the AS study SELECT AXIS-1, and no new safety signals were observed.(7) In the randomized controlled period of the SELECT PsA-1 trial (up to 24 weeks), 3,3% of patients on upadacitinib experienced serious infections and none experienced MACE or VTE's. In contrast, 3,7% of patients in the adalimumab arm experienced serious infections, 2 experienced MACE and 2 experienced VTE. Furthermore, long term integrated safety analyses from the SELECT PsA program shows that rates of serious infections, VTE's and malignancies are comparable to that of adalimumab. As opposed to another JAK-inhibitor with a different selectivity profile, tofacitinib, there has not been identified any dose relationship with upadacitinib and risk of VTE's. Since the safety profile has been evaluated and is consistent in a robust clinical program across several indications (RA, PsA, and AS), upadacitinib has demonstrated a balanced risk-benefit profile. A narrative assessment of the safety profiles between upadacitinib and ixekizumab for the bio-experienced population was also done. Results indicate that upadacitinib has a higher rate of serious infections compared to placebo, while ixekizumab has a lower rate compared to placebo. However, this is a naïve comparison and results should be interpreted with caution. First of all, it is unusual for an active treatment to have a lower rate of infections compared to placebo and there are differences in the populations assessed. Patients in SPIRIT-P2 were diagnosed with PsA for a shorter amount of time and included only patients who had previously been treated with one or two TNFIs, whereas 16% of patients in SELECT PsA-2 had previously been treated with 3 or more bDMARDs. Overall, the safety profile of upadacitinib have been clearly defined and long-term safety analyses suggest that rates of adverse events are consistent with that of adalimumab without identification of the same safety concerns as seen in other JAKis with a different selectivity profile.

To summarize, there still remains an unmet need for patients with PsA in the treatment landscape today. During the 21st annual international Advances in Targeted Therapies meeting, more than 100 scientists and clinical researchers identified several areas of unmet need in the treatment of rheumatological diseases, including PsA(8). The most pressing unmet needs were related to the need for improved efficacy, especially related to joint outcomes, higher achievement of minimal disease activity (MDA), a favorable safety profile and formulations that can offer greater patient convenience(8). Furthermore, there is currently a need for new mode of actions as no JAK-inhibitors exist in the Danish treatment guidelines for PsA. Upadacitinib has through an extensive clinical trial program demonstrated to have the ability to meet these needs. Upadacitinib has a well-characterized safety profile from an extensive clinical trial program, and there were no new safety signals detected in the pivotal clinical trials for PsA. The assessment of clinically added value shows that upadacitinib offers at least similar value as adalimumab and ixekizumab for the bio-naïve and bio-experienced population, respectively.

Furthermore, upadacitinib is the only novel therapy that offers oral administration once a day without the need for methotrexate. This simplifies the treatment routine for patients and can require less healthcare resources, compared with treatment administered via infusions or injections, such as ixekizumab and adalimumab. The oral administration of upadacitinib also provides another treatment option for patients who are ineligible/do not want to use infusion and/or injection treatment. Considering the current COVID-19 pandemic, a simple oral treatment can provide an additional benefit with the reduced health care contacts, and thus reduction of risk of infection via close contact, compared to injection/infusion treatments.

4 Clinical questions and outcomes defined in protocol

Q1: What is the value of upadacitinib compared to adalimumab for bDMARD therapy naive patients with psoriatic arthritis?

Population: bDMARD therapy naive patients with PsA

Intervention: Upadacitinib, oral 15 mg once daily

Comparator: adalimumab 40mg every other week

Outcomes: defined in table 3

Q2: What is the value of upadacitinib compared to ixekizumab for bDMARD therapy experienced patients with psoriatic arthritis?

Population: bDMARD therapy experienced patients with PsA

Intervention: Upadacitinib, oral 15 mg once daily

Comparator: ixekizumab, s.c. 160 mg week 0, 80 mg every fourth Week

Outcomes: defined in table 3

TABLE 3: CLINICAL OUTCOMES SPECIFIED IN THE MEDICINES COUNCIL PROTOCOL ON 26 APRIL 2021

Outcome	Importance	Group of outcomes	Unit	MCID	Adjusted MCID
American College of Rheumatology 50 % response, ACR50	critical	Quality of life, severe symptoms and adverse events	Proportion responders on ACR50	15%	7.5%
			Proportion of patients without progression (mTSS)	10%	5%
Adverse events	Critical	Quality of life, severe symptoms, and adverse events	Proportion who experienced severe adverse events	5%	2.5%
			Qualitative examination of side effect profile		
Quality of Life	Critical	Quality of life, severe symptoms, and adverse events	Mean change from baseline on SF-36 – physical function	7,2 point	

			Mean change from baseline on SF-36 – vitality	7,8 point	
			Mean change from baseline on SF-36 – mental component summary	3,1 point	

Note: MCID - Minimal clinically important difference

For all outcomes the longest feasible time horizon/follow up was of interest as defined in the protocol.

5 Literature search

In the protocol, DMC stated that it was not necessary to do a literature search for question 1 since the Select PsA-1 study included adalimumab as an active comparator.

A systematic literature search was conducted on May 17th 2021 according to the criteria set out by the Medicines Council protocol to reveal data to answer the clinical question 2. See 7.1 for details on the literature search, including inclusion and exclusion criteria, search terms and strategy.

See appendix 7.2 for links to EPARs for upadacitinib, adalimumab and ixekizumab.

Results of literature search:

A total of 53 potentially relevant references were identified through searching MEDLINE and CENTRAL (see appendix 7.1). A total of 8 reference duplicates were identified and 45 references were subsequently screened, 34 records were excluded based on titles and abstracts and 11 published full-text papers were subsequently assessed for eligibility. Of these, 4 references were excluded in full text review. In total, 7 references reporting results from 3 studies were included. The PRISMA flow diagram is shown in appendix 7.1.1. Of these 7 references, 3 references, each reporting primary and secondary efficacy endpoints from the randomized trial period (SELECT PsA 1 for bio-naïve, SELECT PsA-2 and SPIRIT-P2 for bio-experienced) were found relevant to assess the clinical outcomes for question 1 and 2 defined in the DMC protocol. The other 4 references included results from the extension period from these studies (except for SELECT PsA-1). See Table 4 for the studies included in the assessment and appendix 7.1.3 for all references identified in the systematic literature search.

5.1 Relevant studies

TABLE 4: RELEVANT STUDIES INCLUDED IN THE ASSESSMENT

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevance for clinical questions
Trial of Upadacitinib and Adalimumab for Psoriatic Arthritis, McInnes et al, N Engl J Med 2021.	Select-PSA 1	NCT03104400	**Start**: April 27, 2017 **Primary completion:** September 26, 2019 **Study completion**: August 4, 2024	1
Upadacitinib for psoriatic arthritis refractory to biologics: SELECT-PsA 2, Mease et al, Ann Rheum Dis. 2021.	Select-PSA 2	NCT03104374	**Start**: April 17, 2017 **Primary completion:** July 23, 2019 **Study completion**: April 22, 2022	2
Ixekizumab for the treatment of patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors: results from the 24-week randomised, double-blind, placebo-controlled period of the SPIRIT-P2 phase 3 trial. Nash P et al: Lancet, 2017.	SPIRIT-P2	NCT02349295	**Start**: December 31, 2014 **Primary completion:** September 9, 2016 **Study completion**: June 26, 2019	2

5.2 Main characteristics of the relevant upadacitinib studies

The clinical program in PsA for upadacitinib contains two dedicated phase III studies that assessed the effect of upadacitinib in both patients previously failing non-biological or biological DMARD failures, with the SELECT-PsA 1 study being a head-to-head study against adalimumab. The studies showed upadacitinib being statistically significant greater results compared with placebo in both studied cohorts in all measurements and significantly greater than adalimumab in several important joint and axial measurements, with at least similar responses regarding psoriasis.

The therapeutic potential of upadacitinib has been demonstrated in clinical trials and is currently approved for the treatment of RA, PsA and AS (9). Data from studies of upadacitinib in RA have supported the rationale for a straight-to-phase III approach for upadacitinib in PsA. The efficacy and safety of upadacitinib 15 mg QD and 30 mg QD in PsA was investigated in two ongoing Phase III trials; SELECT PsA-1 and SELECT PsA-2 (10), (11).

SELECT PsA-1 is investigating the efficacy and safety of upadacitinib 15 mg QD and 30 mg QD compared with placebo and adalimumab in patients with active PsA who have an inadequate response to at least one non-biologic DMARD (DMARD-IR) (10).

SELECT PsA-2 is investigating efficacy and safety of upadacitinib 15 mg QD and 30 mg QD compared with placebo in participants with active PsA who have a history of inadequate response to at least one biologic DMARD (bDMARD-IR) (11).

TABLE 5: PHASE 3 STUDY PROGRAM FOR UPADACITINIB IN PSA PHASE 3 STUDY PROGRAM FOR UPADACITINIB IN PSA

	SELECT PsA-1 study (NCT03104400) (12)				SELECT PsA-2 (NCT03104374) (13)			
Study duration	152 weeks (Period 1:56 weeks; Period 2:96 weeks)				152 weeks (Period 1:56 weeks; Period 2:96 weeks)			
Study population	• Adults with active PsA • Fullfilled CASPAR criteria; ≥3 swollen joints and ≥3 tender joints at screening and baseline visits • Diagnosis or history of plaque psoriasis • DMARD-IR (lack of efficacy after a minimum 12-week duration of therapy to at least one non-biologic DMARD) or intolerant or contraindicated to DMARDs • bDMARD-naive				• Adults with active PsA • Fullfilled CASPAR criteria; ≥3 swollen joints and ≥3 tender joints at screening and baseline visits • Diagnosis or history of plaque psoriasis • bDMARD-IR (lack of efficacy after a minimum 12-week duration of therapy to at least one non-biologic DMARD) or intolerance to at least 1 bDMARD			
Trial design	Randomized ✓	Double-blind ✓	Placebo-controlled ✓	Active-controlled ✓	Randomized ✓	Double-blind ✓	Placebo-controlled ✓	Active-controlled ■
Enrolment	N=1,705				N=642			
Study arms	1. Oral upadacitinib 15 mg or 30 mg once daily 2. Active control: ADA 40 mg every other week 3. Placebo (Optional non-biologic concomitant medication)				1. Oral upadacitinib 15 mg or 30 mg once daily 2. Placebo (Optional non-biologic concomitant medication)			
Primary endpoint(s)	ACR20 at Week 12				ACR20 at Week 12			
Status	Primary Completion September 20 2019; estimated study completion August 2022.				Primary Completion July 17 2019; estimated study completion April 2022.			

Note: ADA = adalimumab

Based on the Medicines Council protocol on 26 April 2021, the data included for upadacitinib in the application is from the studies SELECT-PSA 1 and SELECT-PSA 2.

The main characteristics of included studies are summarized in appendix 7.1.4.

5.2.1 SELECT-PSA 1

SELECT PsA-1 is a phase III, randomized, double-blind, study in patients with PsA that previously failed ≥1 non-biologic DMARD.

Updacitinib 15 mg demonstrated a statistically significant higher proportion of patients who achieved the primary endpoint of ACR20 at Week 12 compared to placebo. Importantly upadacitinib also achieved the secondary endpoint of non-inferiority compared with adalimumab for ACR20 at week 12 and was numerically better on the other assessed outcomes. At week 24 upadacitinib 15mg also demonstrated significant improvements on PsARC, ACR20/50/70, enthesitis, axial improvement, physical function, and pain compared with adalimumab. At week 12 upadacitinib also demonstrated significant improvements compared with both placebo and adalimumab ($p<0.05$) for SF-36. Patients treated with upadacitinib showed substantial improvements in QoL with upadacitinib demonstrating significant improvements compared to both placebo ($p<0.001$) and adalimumab ($p<0.05$) at week 12. Upadacitinib showed significantly greater MDA response compared with placebo at week 24, and a numerical higher, although non-significant, MDA response compared with adalimumab. A summary of the results is shown in Table 7.

The study also showed the risk profile to be in line with the clinical program for upadacitinib across indications, with no new safety signals detected.

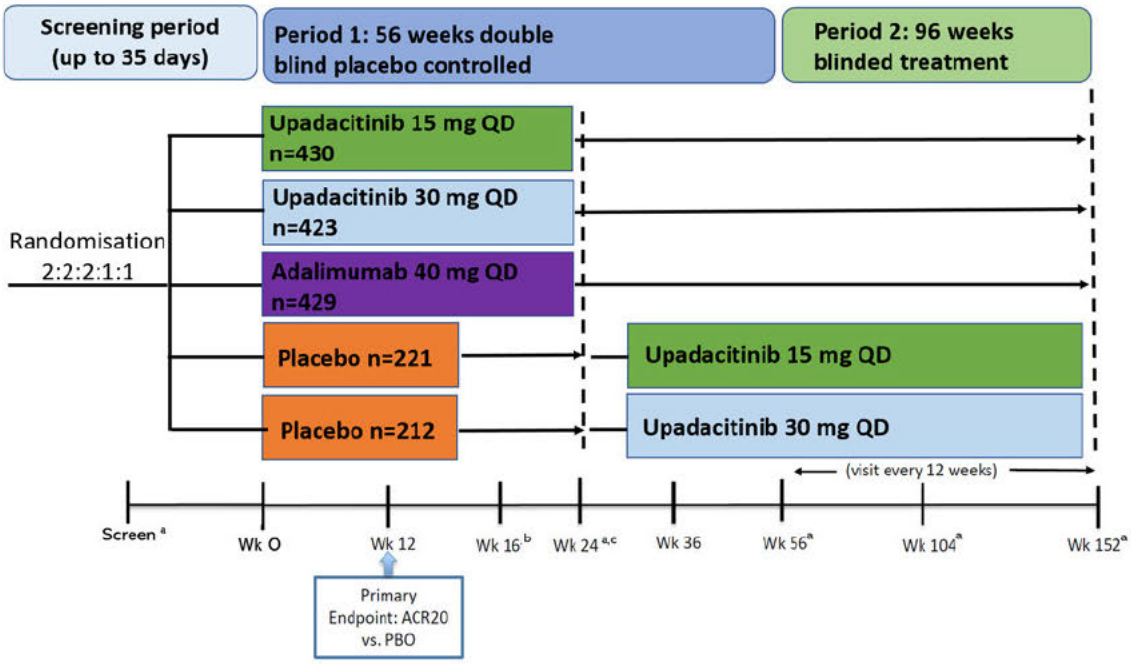
The study was divided into two periods. Period 1 is 56 weeks and includes a 24-week randomized, double-blind, parallel-group, placebo-controlled and active comparator-controlled period followed by an additional 32 weeks of blinded, active comparator-controlled treatment (Weeks 24 – 56). Period 1 is designed to compare the safety, tolerability, and efficacy of upadacitinib 15 mg QD and 30 mg QD versus placebo and adalimumab 40 mg every other week (eow) for the treatment of signs and symptoms of subjects with moderately to severely active PsA who have an inadequate response or DMARD-IR. Period 1 is also designed to compare the efficacy of upadacitinib 15 mg and 30 mg versus placebo for the prevention of structural progression. Period 2 is an open label (blinded until the last subject completes the last visit of Period 1), long-term extension of up to a total treatment duration of approximately 3 years to evaluate the safety, tolerability and efficacy of upadacitinib 15 mg QD and 30 mg QD in subjects with PsA who have completed Period 1.

At the baseline, all eligible subjects were randomized in a 2:2:2:1:1 ratio to one of the following five treatment groups (Figure 1):

- Group 1: Upadacitinib 15 mg QD, N = 429
- Group 2: Upadacitinib 30 mg QD, N = 423
- Group 3: Adalimumab (40 mg eow), N = 429
- Group 4: Placebo followed by upadacitinib 15 mg QD, N= 211
- Group 5: Placebo followed by upadacitinib 30 mg QD, N= 212

Based on the benefit:risk assessment of 15 mg and 30 mg for PsA patients only the 15 mg upadacitinib dose was submitted in PsA. Hence, the results of the PsA clinical trials focus on the 15 mg QD dose.

FIGURE 1: SELECT-PSA 1 STUDY DESIGN



Source: AbbVie data-on-file 2020; At Week 36, patients could change or initiate background DMARD therapy. [a]All subjects will receive x-rays of hands and feet at Screening, Wk 24, Wk 56, Wk 104, and Wk 152. [b]At Week 16 rescue therapy will be offered to subjects classified as non-responders (defined as not achieving at least 20% improvement in either or both tender joint count [TJC] and swollen joint count [SJC] at both Week 12 and Week 16). [c]At Week 24, all placebo subjects will switch to upadacitinib regardless of response.

Patient characteristics:

The key demographics and baseline characteristics in SELECT PsA-1 are reported in Table 6.

TABLE 6: SELECT PSA-1 PATIENT CHARACTERISTICS

Key Demographic and Baseline Characteristics Mean (SD) or n (%)	PLACEBO (N=423)	ADALIMUMAB 40 MG EOW (N=429)	UPADACITINIB 15 MG QD (N=429)
Female	211 (49.9%)	222 (51.7%)	238 (55.5%)
Age (years)	50.4 (12.2)	51.4 (12.0)	51.6 (12.2)
Duration of PsA diagnosis, years	6.2 (7.0)	5.9 (7.1)	6.2 (7.4)
TJC68	20.0 (14.3)	20.1 (13.8)	20.4 (14.7)
SJC66	11.0 (8.6)	11.6 (8.8)	11.6 (9.3)
HAQ-DI	1.12 (0.6)	1.12 (0.6)	1.15 (0.7)
≥3% BSA-Ps	211 (49.9%)	211 (49.2%)	214 (49.9%)
LEI > 0	241 (57.0%)	265 (61.8%)	270 (62.9%)
LEI[a]	2.7 (1.5)	2.5 (1.4)	2.6 (1.6)
LDI>0	126 (29.8%)	127 (29.6%)	136 (31.7%)
LDI[b]	87.7 (114.8)	99.0 (163.1)	89.0(106.5)
Number of prior DMARDs used			
0	0	2 (0.5)	1 (0.2)
1	274 (64.8%)	286 (66.7%)	274 (63.9%)
2	105 (24.8%)	112 (26.1%)	112 (26.1%)
≥3	44 (10.4%)	29 (6.8%)	42 (9.8%)

Source: (10)

[a]Leeds Enthesitis Index (LEI)>0; [b]Leeds Dactylitis Index (LDI)>0.

Endpoints:

The primary endpoint of SELECT PsA-1 is the proportion of patients achieving ACR20 response for upadacitinib vs. placebo by Week 12 (10). The key ranked secondary endpoints for upadacitinib vs. placebo at week 12 (unless stated differently) are:

1. Change in HAQ-DI from Baseline
2. sIGA 0/1 and ≥2-point improvement from Baseline (Week 16)
3. Proportion of patients achieving PASI 75 (Week 16)
4. Change in Modified PsA Sharp/van der Heijde Score (mTSS) from Baseline (Week 24)
5. Proportion of patients achieving MDA (Week 24)
6. Resolution of enthesitis (LEI=0) (Week 24)
7. ACR20 response rate (noninferiority vs. adalimumab)
8. Change from Baseline in SF-36 PCS
9. Change from Baseline in FACIT-Fatigue Questionnaire
10. ACR20 response rate (superiority vs. adalimumab)
11. Resolution of dactylitis (LDI=0) (Week 24)
12. Change in Patient's Assessment of Pain NRS from Baseline (superiority vs. adalimumab)
13. Change in HAQ-DI from Baseline (superiority vs. adalimumab)
14. Change from Baseline in Self-Assessment of Psoriasis Symptoms Questionnaire (Week 16)

Study results:

Updacitinib 15 mg demonstrated a statistically significant higher proportion of patients who achieved the primary endpoint of ACR20 at Week 12 compared to placebo and was significantly better than placebo on all other outcomes. Importantly upadacitinib also achieved the secondary endpoint of non-inferiority compared with adalimumab for ACR20 at week 12 and was numerically better on the other key ranked secondary outcomes versus adalimumab. At week 24 upadacitinib 15mg also demonstrated statistically significant improvements on PsARC, ACR20/50/70, enthesitis, axial improvement, physical function, and pain compared with adalimumab ($p<0.05$). See Table 7 below for details on primary and ranked key secondary endpoints and 6.1.2 for more information on outcomes at week 24.

TABLE 7 - EFFICACY RESULTS OF SELECT PSA-1

Ranked endpoints		Endpoint	Placebo (N=423)	Adalimumab 40 mg EOW (N=429)	Upadacitinib 15 mg QD (N=429)
Primary		ACR20 (Week 12)	36.2%	65.0%	70.6% (p<0.0001) †
Ranked Key Secondary	1	HAQ-DI (Week 12)	-0.14	-0.34	-0.42 (p<0.0001) †
	2	sIGA (Week 16)[b]	10.9%	38.5%	41.9% (p<0.0001) †
	3	PASI 75 (Week 16)[c]	21.3%	53.1%	62.6% (p<0.0001) †
	4	mTSS (Week 24)	0.25	0.01	-0.04 (p=0.0002) †
	5	MDA (Week 24)	12.3%	33.3%	36.6% (p<0.0001) †

	6	Enthesitis Resolution LEI = 0 (Week 24)[d]	32.4%	47.2%	53.7% (p<0.0001) †
	7	ACR20 NI versus ADA (Week 12) [e]	36.2%	65.0%	70.6% (p<0.0001) †
	8	SF-36 PCS (Week 12)	3.2	6.8	7.86 (p<0.0001) †
	9	FACIT-F (Week 12)	2.8	5.7	6.3 (p<0.0001) †
	10	ACR20 Sup. versus ADA (Week 12) [f]	36.2%	65.0%	70.6% (p=0.0815)
	11	Dactylitis resolution (Week 24)[g]	39.7%	74.0%	76.5% (p<0.0001)
	12	Pain Sup. versus ADA (Week 12) [f]	-0.9	-2.3	-2.3 (p=0.8970)
	13	HAQ-DI Sup. versus ADA (Week 12) [f]	-0.14	-0.34	-0.42 (0.0162)
	14	SAPS (Week 16)	-8.2	-22.7	-25.3 (p<0.0001)
Other Key Secondary		ACR50 (Week 12)	13.2%	37.5%	37.5% (p<0.0001)
		ACR70 (Week 12)	2.4%	13.8%	15.6% (p<0.0001) †
		ACR20 (Week 2)	12.1%	30.3%	28.2% (p<0.0001) †

Source: McInnes et al 2021 (10)

Note: The nominal p-values are provided in parentheses. *, Achieved statistical significance using graphical multiple testing procedure controlling the overall type I error rate at 2-sided 0.0499 level. Note that 0.0001 was spent at the interim futility analysis; †Multiplicity controlled endpoints that were met. [a], Results for binary endpoints are based on NRI analysis. Results for MDA and enthesitis resolution at week 24 are based on non-responder imputation with additional rescue handling, where subjects rescued at week1 6 are imputed as non-responders. Results for dactylitis resolution at Week 24 is based on NRI with additional rescue handling, where subjects rescued at week 16 are imputed as non-responders. Results for continuous endpoints are based on MMRM model with fixed effects of treatment, visit, treatment-by-visit interaction, the stratification factor of current DMARD use (yes/no) and baseline measurement. [b], Summarized for subjects with baseline sIGA ≥ 2; N(PBO) = 313, N(ADA) = 330, N(UPA_{15}) = 322, N(UPA_{30}) = 324. [c], Summarized for subjects with baseline BSA affected by psoriasis ≥ 3%; N(PBO) = 211, N(ADA) = 211, N(UPA_{15}) = 214, N(UPA_{30}) = 210. [d], Summarized for subjects with baseline LEI >0; N(PBO) = 241, N(ADA) = 265, N(UPA_{15}) = 270, N(UPA_{30}) = 267. [e]Non-inferiority test of upadacitinib versus adalimumab, preserving 50% of adalimumab effect. [f], Superiority test of upadacitinib versus adalimumab. [g], Summarized for subjects with baseline LDI >0; N(pbo) = 126, N(ADA) = 127, N(UPA_{15}) = 136, N(UPA_{30}) = 127.

5.2.2 SELECT-PSA 2

SELECT PsA-2 is a phase III, randomized, double-blind study comparing upadacitinib to placebo in subjects with active PsA who have a history of inadequate response to at least one bDMARD (bDMARD-IR). The study met its primary endpoint with a significantly higher proportion of patients achieving ACR20 compared with placebo at week 12. Upadacitinib 15 mg was significantly greater compared with placebo for all other measurements, including the highly important measures PsARC, MDA, and HAQ-DI, with similar response rates regardless of the number of previous biological DMARDS used. A summary of the results is shown in Table 9.

The study also showed the risk profile to be in line with the clinical program for upadacitinib across indications, with no new safety signal detect.

The study was initiated in April 2017 and the primary completion date was July 2019, with a final estimated study final completion date in April 2022.(13).

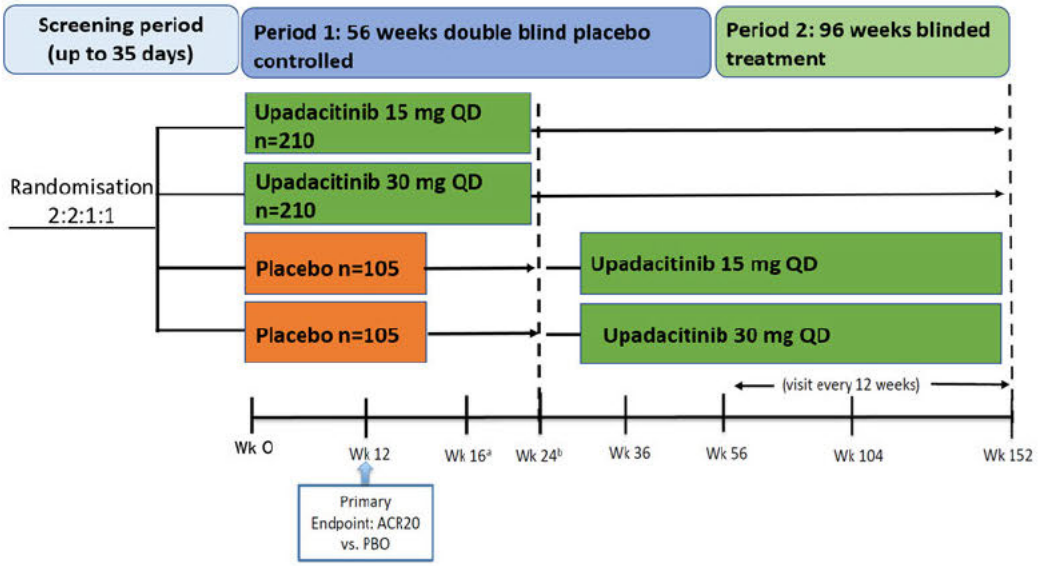
The study was divided into two periods. Period 1 was 56-weeks in duration and includes a 24-week randomized, double-blind, parallel-group, placebo-controlled period followed by an additional 32 weeks of blinded treatment (Weeks 24–56). Period 1 was designed to compare the safety, tolerability, and efficacy of upadacitinib 15 mg QD and 30 mg QD versus placebo in subjects with moderately to severely active PsA who have bDMARD-IR. Period 2 is an open label (blinded until the last subject completes the last visit of Period 1) long-term extension of up to a total treatment duration of approximately 3 years to evaluate the safety, tolerability and efficacy of upadacitinib 15 mg QD and 30 mg QD in subjects with PsA who have completed Period 1.(14) Patients were enrolled in sites in North America, eastern and western Europe, Asia, and Oceania in accordance with the inclusion and exclusion criteria described below.

At the baseline visit, all eligible patients were randomized in a 2:2:1:1 ratio (FIGURE 2). (11)

- Group 1: Upadacitinib 15 mg QD (N = 210) (Period 1) → Upadacitinib 15 mg QD (Period 2)
- Group 2: Upadacitinib 30 mg QD (N = 210) (Period 1) → Upadacitinib 15 mg QD (Period 2)
- Group 3: Placebo (N = 105) (Period 1) → Upadacitinib 15 mg QD (Period 2)
- Group 4: Placebo (N = 105) (Period 1) → Upadacitini 30 mg QD (Period 2)

Based on the benefit:risk assessment of 15 mg and 30 mg for PsA patients only the 15 mg upadacitinib dose was submitted in PsA. Hence, the results of the PsA clinical trials focus on the 15 mg QD dose.

FIGURE 2: SELECT-PSA 2 STUDY DESIGN



[a]At week 16 rescue therapy offered to subjects classified as non-responders (defined as not achieving at least 20% improvement in either tender joint count (TJC) and swollen joint count (SJC) at both week 12 and week 16). At Week 16 changes to psoriasis therapies permitted. [b]At week 24, all placebo subjects switch to upadacitinib regardless of response.

Patient characteristics:

The key demographics and baseline characteristics in SELECT PsA-2 are reported in Table 8.

TABLE 8: SELECT PSA-2 PATIENT CHARACTERISTICS

Key Demographic and Baseline Characteristics Mean (SD) or n (%)	Placebo (N=212)	Upadacitinib 15 mg QD (N=211)
Female	120 (57)	113 (54)
Age (years)	54.1 (11.5)	53.0 (12.0)
Duration of PsA Symptoms, years	14.6 (11.7)	12.2 (8.8)
TJC68	25.3 (17.6)	24.9 (17.3)
SJC66	12.0 (8.9)	11.3 (8.2)
HAQ-DI	1.23 (0.7)	1.10 (0.6)
≥3% BSA-Ps	131 (62)	130 (62)
PASI (for baseline BSA-Ps ≥3%)	11.7 11.4)	10.1 (9.2)
Presence of enthesitis[a]	173 (82)	173 (82)
Enthesitis count[b] (out of those with presence of enthesitis)	7.7 (82)	173 (82)
Presence of dactylitis[c]	64 (30)	55 (26)
Dactylitis count[d] (out of those with presence of dactylitis)	4.2 (4.3)	3.8 (4.1)
Number of prior bDMARDs failed		
0[e]	18 (8.5)	16 (7.6)
1	135 (63.7)	126 (59.7)
2	35 (16.5)	35 (16.6)
≥3	24 (11.3)	34 (16.1)
Current use of ≥1 non-biologic DMARD	100 (47.2)	98 (46.4)

Source: (11); [a]Leeds Enthesitis Index (LEI)>0, [b]Of 18 sites, [c]Leeds Dactylitis Index (LDI)>0, [d]Of 20 digits, [e]Indicates subjects enrolled due to intolerance to bDMARD therapy

Endpoints:

The primary efficacy endpoint is the proportion of patients achieving ACR20 response at Week 12 (11). The key multiplicity adjusted secondary efficacy endpoints (each dose of upadacitinib versus placebo) at week 12 (unless stated differently) are:

1. Change in HAQ-DI from Baseline
2. sIGA 0/1 and ≥2-point improvement from Baseline (Week 16)
3. Proportion of patients achieving PASI 75 (Week 16)
4. Change from Baseline in SF-36
5. Change from Baseline in FACIT-Fatigue Questionnaire
6. Proportion of patients achieving MDA (Week 24)
7. Change from Baseline in Self-Assessment of Psoriasis Symptoms Questionnaire (Week 16)

Study results:

Upadacitinib demonstrated a significantly higher proportion of patients who achieved the primary endpoint of ACR20 at Week 12 compared with placebo. Results for all ranked secondary endpoints were met as well (all with multiplicity-adjusted p<0.0001 compared with placebo). Results from SELECT PsA-2 are summarized in Table 9.

TABLE 9 - EFFICACY RESULTS FOR SELECT PSA-2[A]

Ranked endpoints		Endpoint	Placebo (N=212)	Upadacitinib 15 mg QD (N=211)
Primary		ACR20 Week 12	24.1%	56.9%
Ranked Key Secondary	1	HAQ-DI Week 12	-0.10	-0.30
	2	sIGA Week 16	9.2%	36.8%
	3	PASI 75 Week 16	16.0%	52.3%
	4	SF-36 Week 12	1.62	5.15
	5	FACIT-F Week 12	1.3	5.0
	6	MDA Week 24	2.8%	25.1%
	7	SAPS Week 16	-1.5	-24.4

Source: (11); [a]All endpoints listed were multiplicity adjusted and significant compared to placebo (p<0.0001)

For more details on study characteristics, see appendix 7.1.4.

5.3 Main characteristics of the relevant comparator studies

5.3.1 SPIRIT–P2

SPIRIT-P2 investigated the efficacy and safety of ixekizumab in patients who have had an inadequate response to tumor necrosis factor inhibitors, distinguished by being refractory to therapy or had loss of efficacy, or were intolerant to tumor necrosis factor (15). The primary objective was to compare the proportion of patients treated with ixekizumab who attained an at least 20% improvement in the American College of Rheumatology response criteria (ACR-20) response at week 24 versus placebo.

Study design:

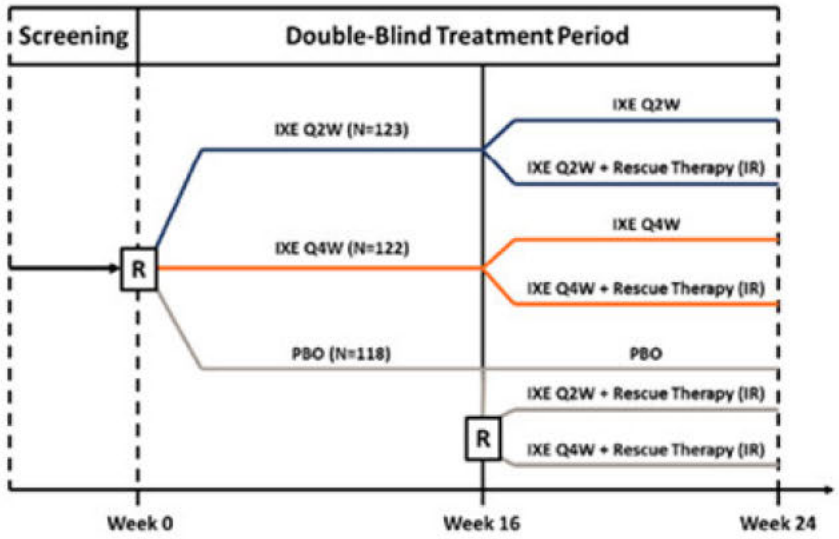
The study was double-blind, multicentre, randomised, placebo-controlled, phase 3 study. Patients were recruited from 109 centres across ten countries in Asia, Australia, Europe, and North America. Patients were randomly assigned (1:1:1) by a computer-generated random sequence to receive a subcutaneous injection of 80 mg ixekizumab every 4 weeks or every 2 weeks after a 160 mg starting dose or placebo.

Patients in all treatment groups with an inadequate response at week 16, distinguished by predefined tender and swollen joint count criteria (ie, inadequate responders), were required to add or modify concomitant drugs. The investigators, study site personnel, and patients were blinded to the inadequate response criteria. Inadequate responders continued taking their originally assigned dose of ixekizumab or, if receiving placebo, were re-randomized to ixekizumab every 2 weeks or every 4 weeks in a 1:1 ratio.

Arms:

- IXE Q2W: Ixekizumab 80 mg every 2 weeks (n=123)
- IXE Q4W: Ixekizumab 80 mg every 4 weeks (n=122)
- PBO: Placebo (n=118

FIGURE 3: SPIRIT-P2 STUDY DESIGN



Patient characteristics:

The key demographics and baseline characteristics in SPIRIT-P2 are reported in Table 10.

TABLE 10: SPIRIT-P2 PATIENT CHARACTERISTICS

Key Demographic and Baseline Characteristics Mean (SD) or n (%)	Placebo n=118	Ixekizumab n=122 (every 4 weeks)	Ixekizumab n=123 (every 2 weeks)
Age	51.5 (10.4)	52.6 (13.6)	51.7 (11.9)
Sex			
Male	56 (47%)	63 (52%)	50 (41%)
Female	62 (53%)	59 (48%)	73 (59%)
Weight (kg)	91.0 (22.1)	89.9 (22.0)	85.2 (20.7)
BMI (kg/m2)	31.6 (7.6)	30.9 (7.1)	30.1 (6.8)
Race			
White	108 (92%)	111 (91%)	113 (93%)
Asian	7 (6%)	7 (6%)	7 (6%)
Other	3 (3%)	4 (3%)	2 (2%)
Time since psoriatic arthritis diagnosis (years)	9.2 (7.3)	11.0 (9.6)	9.9 (7.4)
Time since psoriasis diagnosis (years)	15.3 (12.6)	15.7 (12.3)	16.5 (13.0)
Present use of cDMARD	52 (44%)	60 (49%)	73 (59%)
Present use of methotrexate	40 (34%)	48 (39%)	61 (50%)
Previous TNFi treatment			
Inadequate response to one TNFi	68 (58%)	71 (58%)	65 (53%)
Inadequate response to two TNFi	41 (35%)	41 (34%)	46 (37%)
Intolerance to a TNFi*	9 (8%)	10 (8%)	12 (10%)
Patients with specific disease characteristics			
Present psoriasis†	108 (92%)	118 (97%)	113 (92%)
Psoriasis ≥3% of body surface area†	67 (57%)	68 (56%)	68 (55%)
Fingernail psoriasis†	73 (62%)	89 (73%)	74 (60%)
Dactylitis‡	14 (12%)	28 (23%)	20 (16%)
Enthesitis§	69 (58%)	68 (56%)	84 (68%)
Baseline disease and quality of life scores			
Tender joint count (68 joints)	23.0 (16.2)	22.0 (14.1)	25.0 (17.3)
Swollen joint count (66 joints)	10.3 (7.4)	13.1 (11.2)	13.5 (11.5)
HAQ-DI	1.2 (0.7)	1.2 (0.6)	1.2 (0.6)
Patient-reported pain¶	63.9 (20.1)	63.9 (21.4)	62.7 (20.9)
Patient-assessed global disease¶	64.1 (21.5)	66.4 (20.5)	66.0 (20.5)
Physician-assessed global disease¶	58.9 (20.7)	60.3 (20.9)	64.6 (16.8)
C-reactive protein (mg/L)	12.1 (19.6)	17.0 (27.5)	13.5 (26.1)
28-joint Disease Activity Score with C-reactive protein	5.0 (1.1)	5.1 (1.1)	5.1 (1.1)
LEI§	2.9 (1.7)	2.9 (1.4)	3.0 (1.7)
LDI Basic‡	37.3 (25.2)	31.5 (33.8)	53.9 (37.6)
Psoriasis body surface area involved (%)||	9.0 (13%)	12.5 (17%)	11.6 (19%)

PASI total score||	5.2 (6.3)	6.4 (7.9)	6.2 (8.7)
NAPSI**	18.7 (18.8)	20.5 (20.0)	21.0 (22.0)
SF-36 physical component summary score	33.9 (9.0)	34.8 (8.8)	34.3 (9.1)
SF-36 mental component summary score	48.0 (13.1)	49.6 (11.3)	49.1 (11.5)
Data are mean (SD) or n (%). BMI=body-mass index. cDMARD=conventional disease-modifying antirheumatic drug. TNFi=tumour necrosis factor inhibitor. HAQ-DI=Health Assessment Questionnaire-Disability Index. LDI=Leeds Dactylitis Index. LEI=Leeds Enthesitis Index. PASI=Psoriasis Area and Severity Index Improvement. NAPSI=Nail Psoriasis Severity Index. SF-36=Short Form (36 Items) Health Survey. *Patients had previously received a TNFi and had discontinued. †Qualitatively assessed by the investigator at baseline. ‡Defined as LDI>0. §Defined as LEI>0. ¶Visual analogue scale 0–100. ||Assessed only in patients with psoriasis. **Assessed only in patients with fingernail psoriasis.			

Source: (15)

Description of endpoints:

The primary objective was to compare the proportion of patients treated with ixekizumab who attained an at least 20% improvement in the American College of Rheumatology response criteria (ACR-20) response at week 24 versus placebo. ACR 20 is defined as a 20% or more improvement in ACR criteria from baseline.

Secondary endpoints included the following:

- Proportion of patients who attained at least 50% improvement in the American College of Rheumatology response criteria (ACR-50) or at least 70% improvement in the American College of Rheumatology response criteria (ACR-70) responses;
- Proportion of patients who attained a Psoriasis Area and Severity Index score improvement of 75% (PASI-75), 90% (PASI-90), or 100% (PASI-100);
- Proportion of patients attaining a minimal disease activity (defined as fulfilling at least five of the following seven domains: tender joint count ≤1, swollen joint count ≤1, PASI ≤1 or body surface area ≤3, Patient's Assessment of Pain Visual Analogue Scale ≤15, Patient's Global Assessment of Disease Activity Visual Analogue Scale ≤20, Health Assessment Questionnaire-Disability Index [HAQ-DI] ≤0·5, and tender entheseal points ≤1);
- Change from baseline in the HAQ-DI;
- Change from baseline in 28-joint Disease Activity Score using C-reactive protein (DAS28-CRP);
- Change from baseline in Short Form (36 items) Health Survey (SF-36) Physical and Mental Component Summary Scores.

Summary of results:

The primary endpoint and major secondary endpoints were assessed in a graphical approach that used a sequential testing order. The proportion of patients who attained an ACR-20 response at week 24, the primary endpoint, was higher for patients who received ixekizumab every 4 weeks (65 [53%] patients; effect size vs placebo 33.8% [95% CI 22.4–45.2]; p<0.0001) and in patients who received ixekizumab every 2 weeks (59 [48%] patients; effect size vs placebo 28.5% [95% CI 17.1–39.8]; p<0.0001) than in patients treated with placebo (23 [20%]).

TABLE 11: SPIRIT-P2 RESULTS ON KEY RANKED ENDPOINTS

Ranked endpoints		Endpoint	Placebo (N=118)	IXE Q4w (n=122)	IXE Q2w (n=123)
Primary		ACR20 Week 24	19%	53%	48%
Ranked Key Secondary	1	HAQ-DI Week 24	-0.2	-0.6	-0.4
	2	ACR20 Week 12	22%	50%	48%
	3	ACR50 Week 24	5%	35%	33%
	4	ACR70 Week 24	0%	22%	12%
	5	PASI-75 Week 12	10.4%	57.4%	61.8%
	6	MDA Week 24	3%	28%	24%

	7	LEI=0 Week 24	22%	35%	31%

Source: (15)

See 6.2.4 for results on all key and secondary outcomes from SPIRIT-P2.

5.4 Indirect treatment comparison of upadacitinib vs. ixekizumab

Due to the lack of direct comparisons between upadacitinib and several relevant comparators an indirect treatment comparison (ITC) using the Bucher's method was undertaken to indirectly compare the relative efficacy of upadacitinib to ixekizumab for a range of outcome measures at week 24. The ITC's is conducted for the treatment comparison of patients with prior biologics use (bDMARD-experienced).

Results from the indirect comparison shows that there is no significant difference between upadacitinib and ixekizumab for the efficacy and safety outcomes defined in the protocol.

An ITC was conducted using the Bucher's methods, to answer the questions in the DMC's protocol for upadacitinib to PsA.

The efficacy and safety of upadacitinib and ixekizumab was measured by the following assessment criteria, assessed at week 24:

- Proportion of patients achieving 50% improvement per the ACR criteria (ACR50)
- SF36-Vitality
- SF36-MCS
- SF36-PCS
- Serious adverse events (SAE)

Two studies (SPIRIT-P2 and SELECT-PSA-2) was included for the efficacy outcomes (ACR50, SF36-Vitality, -MCS, -PCS) in the bio-experienced population. For the outcome SAE four studies (SPIRIT-P1, SELECT-PSA-1, SPIRIT-P2 and SELECT-PSA-2) was included to assess the safety between Ixekizumab and upadacitinib. This was to include higher patient numbers and more representative results on the safety outcome.

Due to differences in outcomes reported and study design in SPIRIT-P2 and SELECT-PSA-2, it was not possible to assess the relative effectiveness for the outcome mTSS specified in the DMC's protocol.

For the purposes of this submission and the protocol from The Danish Medicines Council this indirect comparison will be used to assess the comparative efficacy of upadacitinib vs. ixekizumab for the biologic-experienced population for the outcomes ACR50, SAE, SF36-Vitality, -PCS, and -MCS.

The comparison between upadacitinib and ixekizumab is based on the results from the SELECT PsA-2 study for upadacitinib and the SPIRIT-P2 study for ixekizumab, also identified in the literature search.

The results of the indirect comparison between upadacitinib and ixekizumab will be presented in part [redacted]

6 Clinical questions

6.1 Clinical question 1

Following the Medicines Council protocol of 26th april 2021 the first clinical question was:

Q1: What is the value of upadacitinib compared to adalimumab for bDMARD therapy naïve patients with psoriatic arthritis?

Population: bDMARD therapy naïve patients with psoriatic arthritis

Intervention: Upadacitinib, oral 15 mg once daily

Comparator: Adalimumab, subcutaneous 40 mg every other week

Outcomes:

- Proportion of patients having ACR50 response
- Proportion of patients without progression as measured by mTSS
- Proportion of patients who experienced severe adverse events
- Change from baseline on SF-36 (vitality, physical component and mental component)
- Narrative assessment of side effect profile

The protocol specified that data for the longest feasible time horizon was required.

6.1.1 Summary of relevant study – SELECT PsA-1

SELECT PsA-1 is a phase III, randomized, double-blind, study in patients with PsA that previously failed ≥1 non-biologic DMARD. Upadacitinib 15 mg demonstrated a significantly higher proportion of patients who achieved the primary endpoint of ACR20 at Week 12 compared to placebo. Importantly upadacitinib also achieved the secondary endpoint of non-inferiority compared with adalimumab for ACR20 at week 12 and was numerically better on the other assessed outcomes. At week 24 upadacitinib 15mg also demonstrated statistically significant improvements on PsARC, ACR20/50/70, enthesitis, axial improvement, physical function, and pain compared with adalimumab. At week 12 upadacitinib also demonstrated significant improvements compared with both placebo and adalimumab ($p<0.05$) for SF-36 at week 12. Patients treated with upadacitinib showed substantial improvements in QoL with upadacitinib demonstrating significant improvements compared to both placebo ($p<0.001$) and adalimumab ($p<0.05$) at week 12. Upadacitinib showed significantly greater MDA response compared with placebo at week 24, and a numerical higher, although non-significant, MDA response compared with adalimumab.

The study also showed the risk profile to be in line clinical program for upadacitinib across indications, with no new safety signal detect.

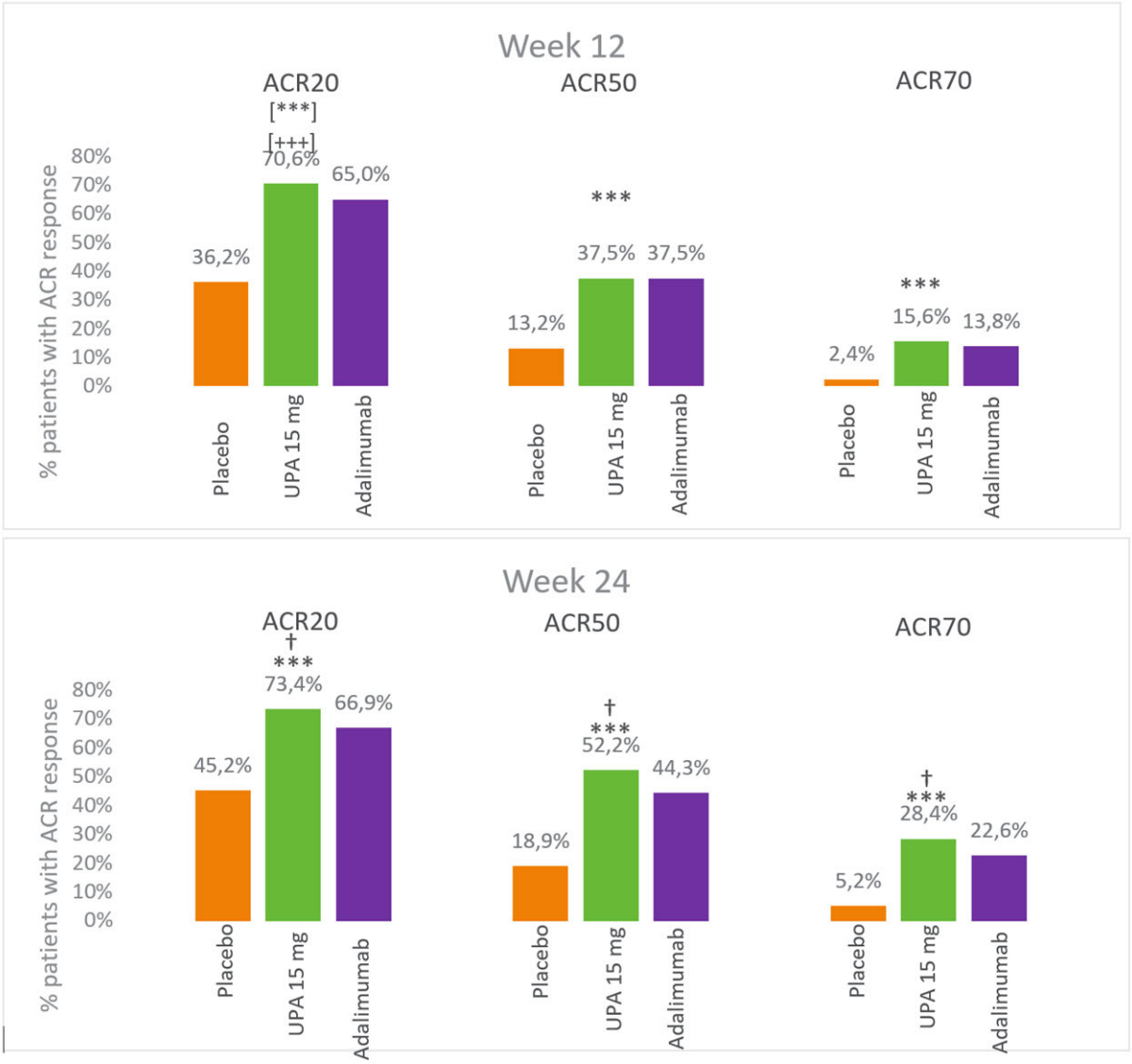
Below we only present a more detailed overview of the results from the SELECT PsA-1 study. Please see 5.2.1 and 7.1.4 for further descriptions of the SELECT PsA-1 study.

6.1.2 Description of results from SELECT-PSA 1

Peripheral arthritis

The study achieved the primary endpoint, since a significantly greater proportion of patients treated with upadacitinib 15 mg achieved ACR20 response rate (NRI) compared with placebo at week 12 (Figure 4). Additionally, at week 12, statistical significance was achieved for non-inferiority (NI) of ACR20 response for upadacitinib versus adalimumab(10). Although not ranked endpoints, response rates for ACR50 and ACR70 showed similar comparative efficacy for upadacitinib versus adalimumab at week 12 (10). At week 24, a statistically significant larger proportion of patients treated with upadacitinib 15 mg achieved response rates for ACR20/50/70 compared with patients treated with adalimumab ($p<0.05$ for each measurement) and placebo ($p<0.0001$ for each measurement).(10)

FIGURE 4: ACR RESPONSE RATES FOR PATIENTS TREATED WITH PLACEBO, UPADACITINIB 15 MG, AND ADALIMUMAB AT WEEK 12 AND WEEK 24 USING NRI



Source: McInnes et al. 2021 (10)

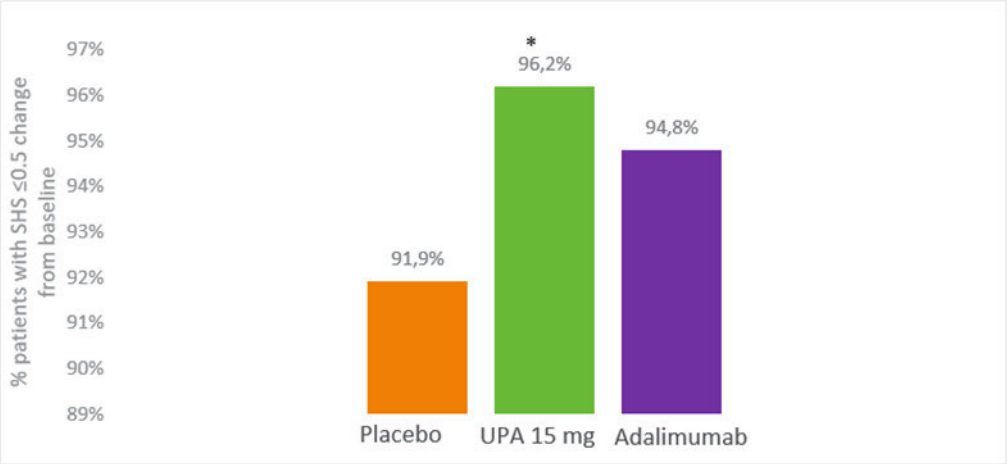
***p<0.0001 for UPA versus placebo; +++p≤0.001 for non-inferiority of UPA versus ADA; †p≤0.05 UPA versus ADA; §Statistically significant in the multiplicity-controlled analysis.

Radiographic data

At Week 24, upadacitinib demonstrated a significant change in modified PsA Sharp/van der Heijde Score (mTSS) from baseline vs. placebo (see Table 7).

Furthermore, a significantly higher proportion of patients treated with upadacitinib 15 mg showed no radiographic progression (proportion with SHS ≤0.5 from baseline), compared with placebo (p≤0.05). Upadacitinib 15 mg also demonstrated a numerically higher proportion of patients showing no or low progression (SHS ≤0.5 change from baseline) compared with adalimumab (10) (Figure 5).

FIGURE 5: PATIENTS WITH ≤0.5 SHS CHANGE FROM BASELINE WHEN TREATED WITH PLACEBO, UPADACITINIB 15 MG, AND ADALIMUMAB AT WEEK 24[A]

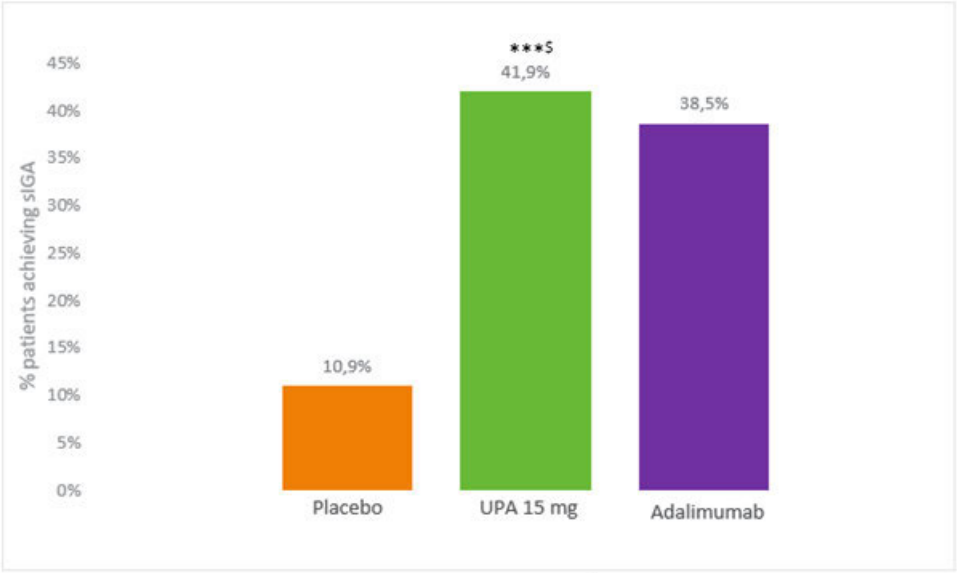


Source: McInnes et al 2021 (10) ; SHS: Sharp/van der Heijde Score; [a]Based on linear extrapolation; Comparisons unadjusted for multiplicity: *p≤0.05 for UPA versus PBO.

Skin disease

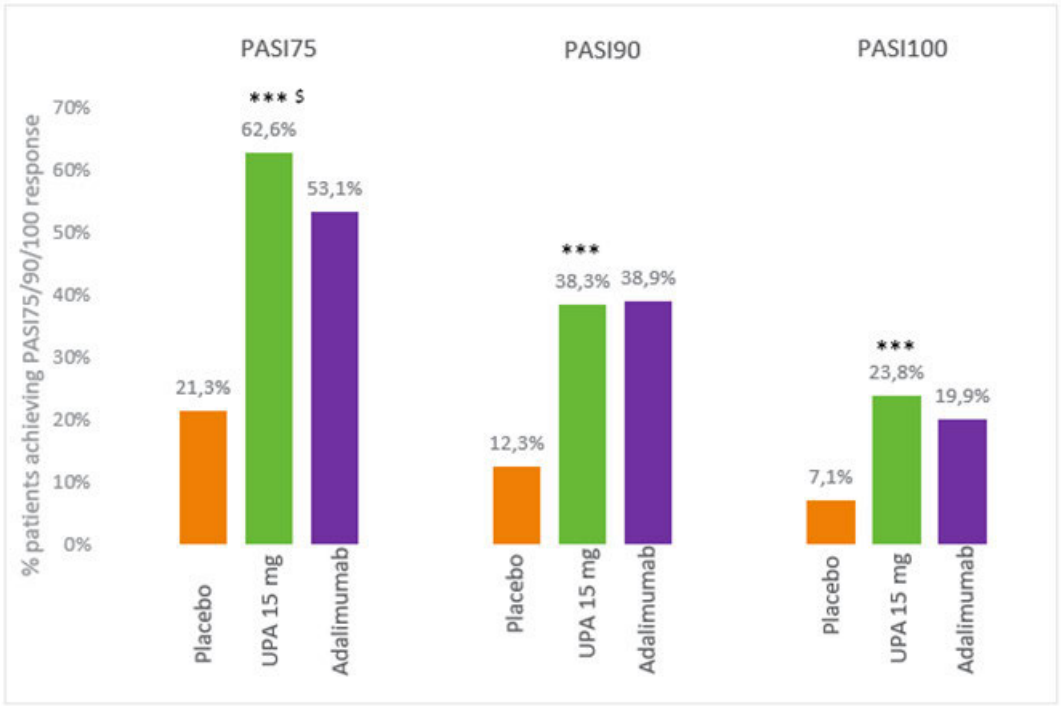
Patients with PsA treated with upadacitinib 15 mg demonstrated significant improvements in psoriasis. At week 16, a significantly higher proportion of patients treated with upadacitinib 15 mg demonstrated a sIGA response rate of 0 or 1 with at least a 2-point improvement from baseline compared with placebo (p<0.0001) (10) (Figure 6). Similarly a higher proportion of patients treated with upadacitinib 15 mg showed a 75%, 90%, or 100% improvement in the PASI score in patients with ≥3% BSA psoriasis at baseline, compared with placebo (p≤0.001) at Week 16 (Figure 7).(7) Upadacitinib also demonstrated a numerical benefit relative to adalimumab on sIGA response (U: 41,9% v. A: 38,5%), PASI 75 (U: 62,6% v. A: 53,1%) and PASI 100 (U: 23,8% v. A: 19,9%) with a minor difference on PASI 90 (U: 38,3% v. A: 38,9%) at week 16.

FIGURE 6: SIGA RESPONSE RATES IN PATIENTS TREATED WITH PLACEBO, UPADACITINIB 15 MG AND ADALIMUMAB AT WEEK 16[A]



Source: McInnes et al 2021 (10); [a]sIGA calculated for subjects with baseline sIGA ≥2; [$]Statistically significant in the multiplicity-controlled analysis. ***, p<0.0001 for UPA versus placebo.

FIGURE 7: PASI 75/90/100 RESPONSE RATES IN PATIENTS TREATED WITH PLACEBO, UPADACITINIB 15 MG, AND ADALIMUMAB AT WEEK 16[A]

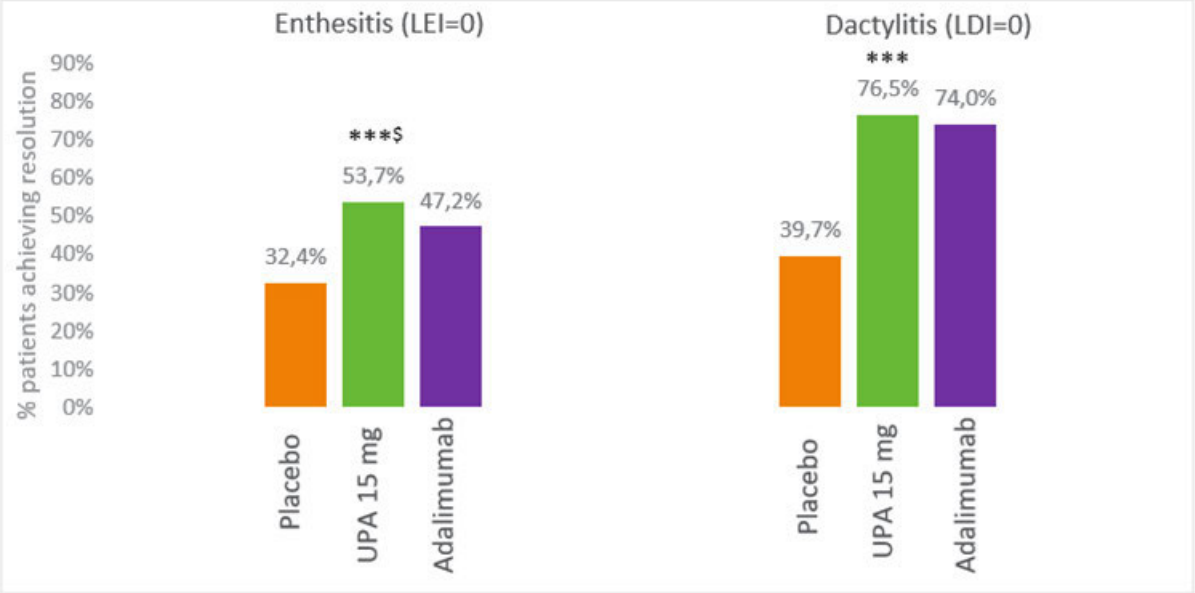


Source: McInnes et al 2021 (10) ; [a]For subjects with ≥3% BSA psoriasis at baseline; ***, p≤0.001 for UPA versus PBO; [$]Statistically significant in the multiplicity-adjusted analysis.

Enthesitis and dactylitis

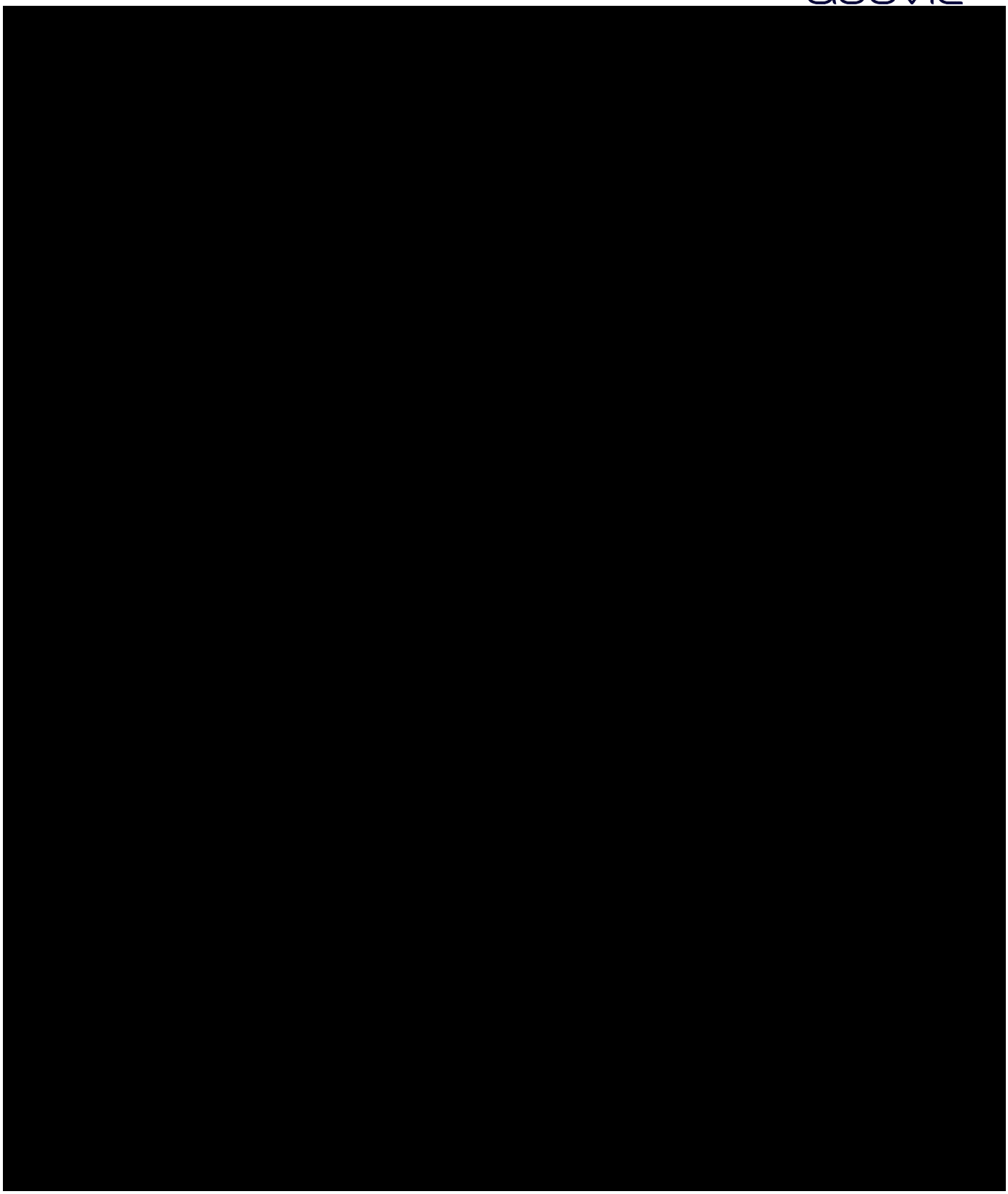
Upadacitinib 15 mg demonstrated a significantly higher proportion of patients achieving resolution of enthesitis (LEI=0) and a higher proportion resolution of dactylitis (LDI=0) compared with placebo at week 24 (p≤0.001) (10) (Figure 8). Upadacitinib also demonstrated a numerical benefit relative to adalimumab on both resolution of enthesitis (U: 53,7% v. A: 47,2%) and resolution of dactylitis (U: 76,5% v. A: 74%) at week 24.

FIGURE 8: PROPORTION OF PATIENTS ACHIEVING RESOLUTION OF ENTHESITIS AND DACTYLITIS WHEN TREATED WITH PLACEBO, UPADACITINIB 15 MG, AND ADALIMUMAB AT WEEK 24[A,B]



Source: McInnes et al 2021 (10); [a]LEI evaluates the presence or absence of tenderness in 6 entheseal sites and LDI evaluates the size and tenderness of each of 20 fingers; [b]For patients with enthesitis and dactylitis, respectively at baseline; resolution of enthesitis defined as LEI=0; resolution of dactylitis defined as LDI=0; ***, p≤0.001 for UPA versus PBO; [$]Statistically significant in the multiplicity-controlled analysis.

[redacted]

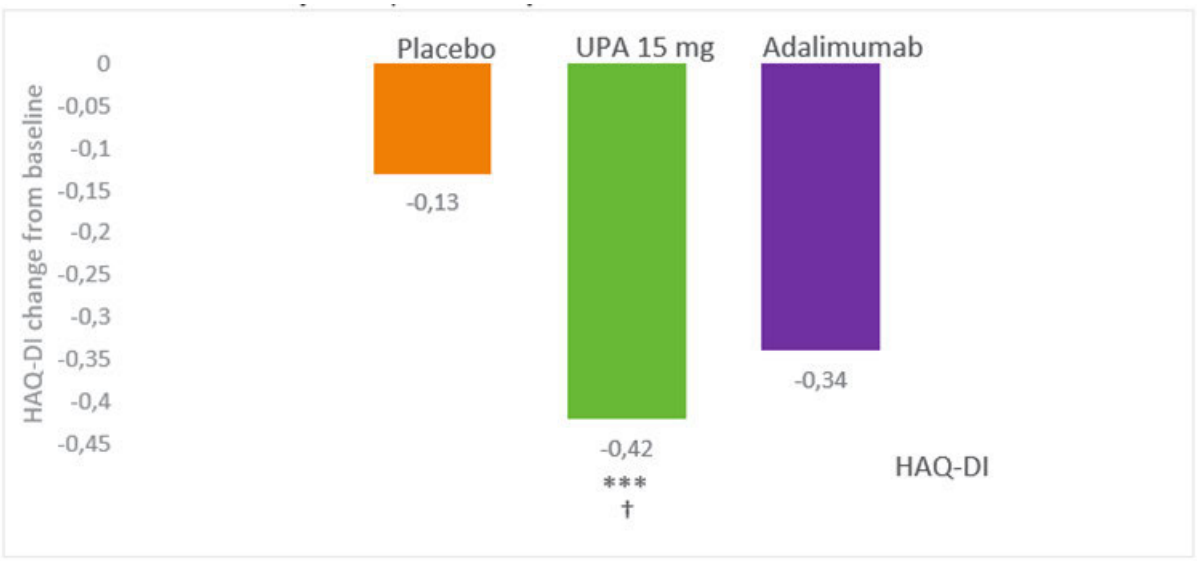


[redacted]

Pain and physical function

Patients treated with upadacitinib 15 mg showed a significantly greater improvement (change from baseline) in physical function (HAQ-DI) compared with placebo at week 12 ($p<0.0001$) (Figure 12). Upadacitinib also demonstrated statistically significant improvements compared with adalimumab ($p<0.05$) (10). These results were maintained through to week 24 (PBO: -0,19; ADA: -0,39; UPA: -0,51) (10).

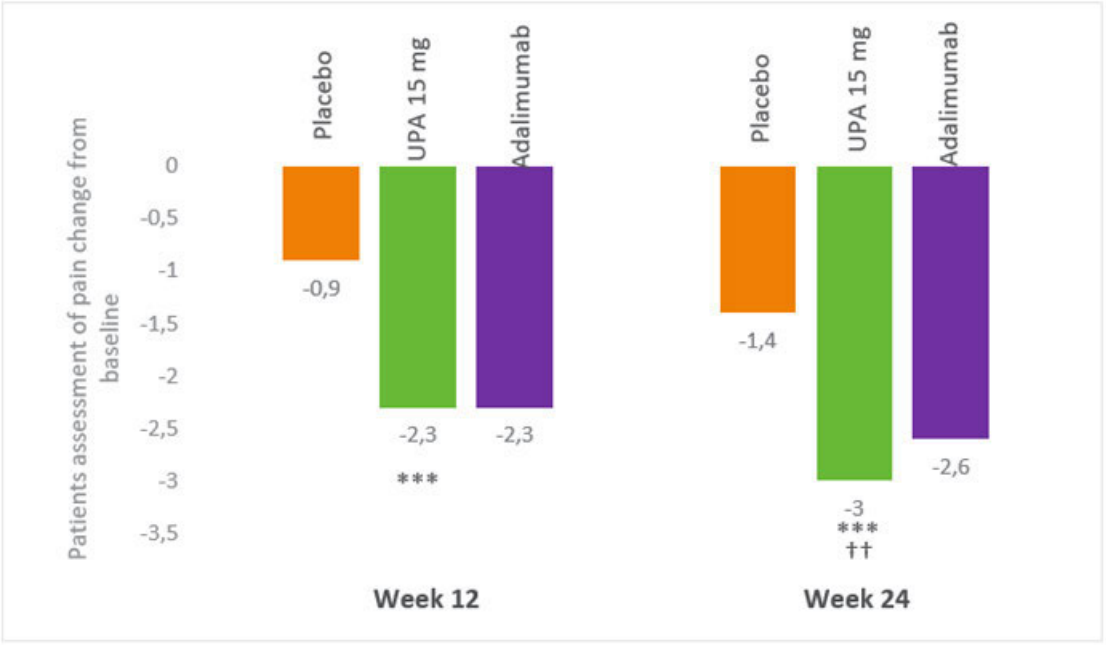
FIGURE 12: HAQ-DI CHANGE FROM BASELINE IN PATIENTS TREATED WITH PLACEBO UPADACITINIB 15 MG AND ADALIMUMAB AT WEEK 12



Source: McInnes et al 2021 (10); ***, $p<0.0001$ for UPA versus placebo; †, $p<0.05$ for UPA versus ADA.

At week 12, the predefined multiplicity-adjusted p-values were not significant for superiority of upadacitinib versus adalimumab for patient's assessment of pain(10). [redacted] Figure 13).

FIGURE 13: CHANGE FROM BASELINE IN PATIENT'S ASSESSMENT OF PAIN (NRS) WHEN TREATED WITH PLACEBO, UPADACITINIB 15 MG, AND ADALIMUMAB AT WEEK 12 AND 24

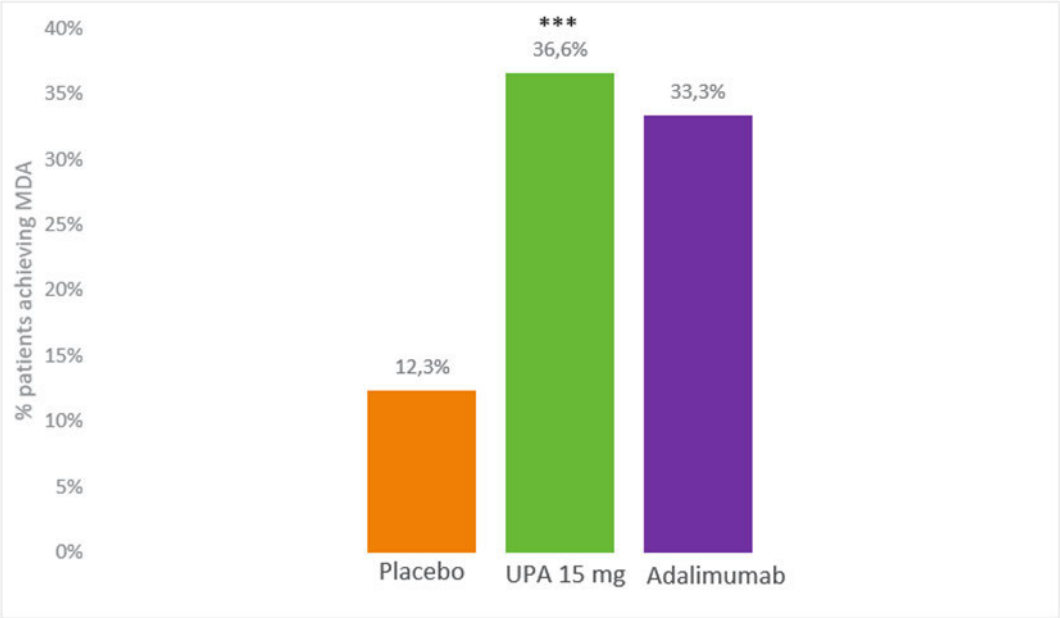


Source: McInnes et al 2021 (10) (week 12 data) [redacted]; ***, p≤0.001 for UPA versus PBO; ††, p≤0.01 for UPA versus ADA

MDA, PsARC, and composite measures

At week 24, a significantly higher proportion of patients achieved MDA compared with placebo (p<0.0001) (Figure 14). (10)

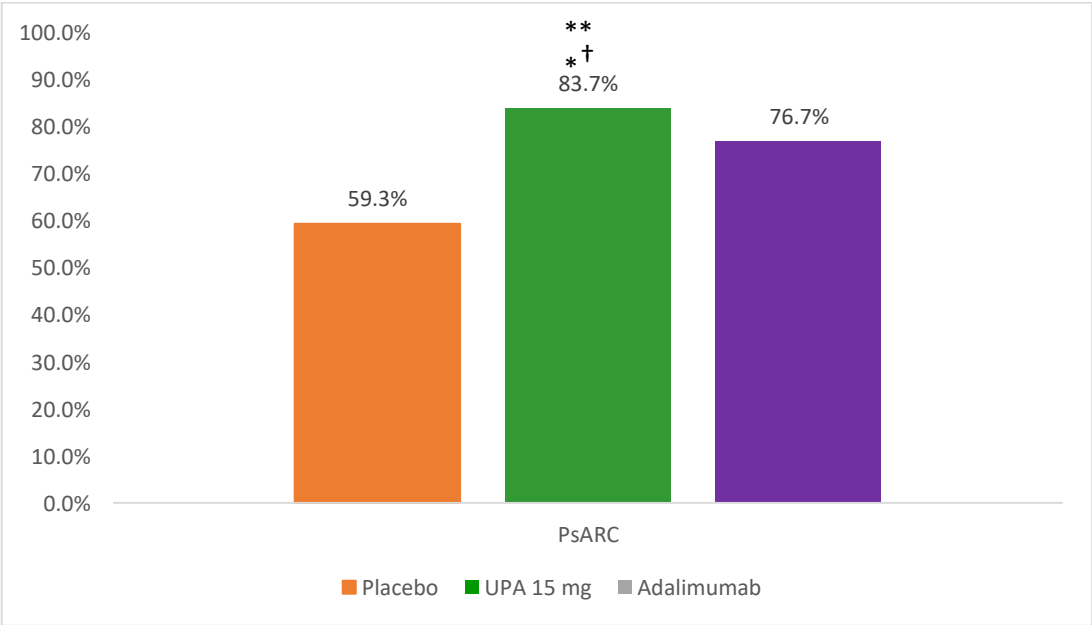
FIGURE 14: PROPORTION OF PATIENTS ACHIEVING MDA WHEN TREATED WITH PLACEBO, UPADACITINIB 15 MG, AND ADALIMUMAB AT WEEK 24



Source: McInnes et al 2021 (10); ***, p<0.0001 vs. placebo; MDA: achieve five of seven outcome measures: TJC ≤1; SJC ≤1; PASI ≤1 or BSA-Ps ≤3%; patient assessment of pain ≤1.5 (0–10 NRS); PtGA-disease activity ≤2 (0–10 NRS); HAQ-DI score ≤0.5; and tender entheseal points ≤1.

Significantly more patients treated with upadacitinib 15 mg achieved PsARC at week 24 compared with both placebo (p<0.0001) and adalimumab (p<0.05) (Figure 15) (16).

FIGURE 15 - PROPORTION OF PATIENTS ACHIEVING PSARC WHEN TREATED WITH PLACEBO, UPADACITINIB 15 MG, AND ADALIMUMAB AT WEEK 24

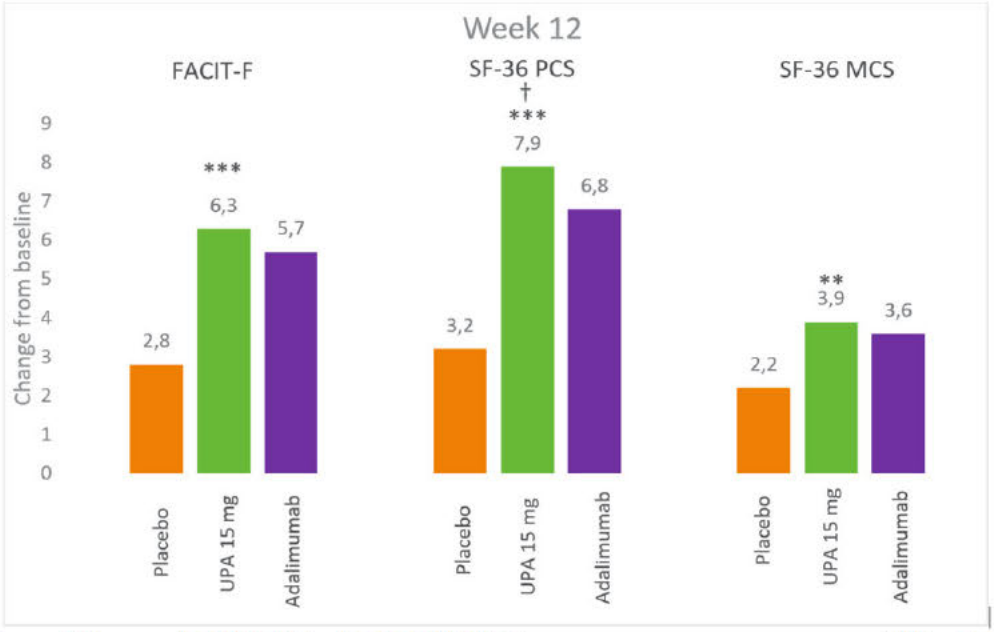


Source: Coates et al 2021 (16); ***: p<0.0001 vs. placebo;†: p<0.05 vs. adalimumab ; PsARC: Achieve at least 2 of 4 criteria: ≥30% improvement in TJC or SJC, ≥1 (1-5 scale) PtGA, or ≥1 (1-5 scale) PhGA, and no worsening in any criteria.

Other patient reported outcomes

Patients treated with upadacitinib showed substantial improvements in fatigue and QoL, as indicated through greater improvement in FACIT-F and SF-36 (PCS [redacted] compared with placebo (p<0.0001 or [redacted] at week 12 (Figure 16). For SF-36 (PCS), upadacitinib demonstrated significant improvements compared with adalimumab (p<0.05) at week 12.(7, 10)

FIGURE 16 - FACIT-F AND SF-36 PCS CHANGE FROM BASELINE IN PATIENTS TREATED WITH PLACEBO, UPADACITINIB 15 MG, AND ADALIMUMAB AT WEEK 12



Source: McInnes et al 2021 (FACIT-F and SF-36 PCS) (10) PCS, [redacted]; ***, p<0.0001 for UPA versus placebo; **, p<0.001 for UPA versus placebo; †, p<0.05 for UPA versus ADA.

6.1.3 Narrative description of safety profile of upadacitinib and adalimumab from SELECT PsA-1

The observed safety profile for upadacitinib in SELECT PsA-1 study (**Table 12 - Overview of AEs in SELECT PsA-1 through to Week 24 (placebo-controlled analysis set)**Table 12**Error! Reference source not found.**) was generally consistent with that observed in the robust RA clinical studies and the AS study SELECT AXIS-1, and no new safety signals were observed. As the safety profile has now been evaluated in the robust clinical programs for RA, PsA, and AS it is well defined.(10)

The rates of serious AEs, severe AEs, and AEs that resulted in drug discontinuation were comparable between the upadacitinib 15 mg and the placebo groups. The number of AEs of special interest were comparable between the placebo and upadacitinib 15 mg groups except for hepatic disorder and creatine phosphokinase (CPK) elevation, where upadacitinib had higher rates compared with placebo. The rates of hepatic disorders were higher in the upadacitinib group compared with placebo, but lower compared with the adalimumab group. Lower rates of herpes zoster, CPK elevation, and lymphopenia were observed in patients treated with adalimumab compared with those treated with upadacitinib. No active TB, lymphoma, or GI perforation were reported in any treatment groups.

There was one death in the placebo group, one MACE in placebo group, two MACE in the adalimumab group, one VTE in the placebo group, and two VTE in the adalimumab group. In contrast, there were no deaths, no MACE, and no VTE in the upadacitinib group.

TABLE 12 - OVERVIEW OF AES IN SELECT PSA-1 THROUGH TO WEEK 24 (PLACEBO-CONTROLLED ANALYSIS SET)

	Placebo (N=423)		Adalimumab 40mg EOW (N=429)		Upadacitinib 15 mg QD (N=429)	
Subjects with:	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Any Adverse Event (AE)	252	(59.6)	278	(64.8)	287	(66.9)
Any Serious AE	13	(3.1)	16	(3.7)	14	(3.3)
Any AE Leading to Discontinuation of Study Drug	13	(3.1)	22	(5.1)	13	(3.0)
Any Severe AE	16	(3.8)	27	(6.3)	21	(4.9)
Any AE With Reasonable Possibility of Being Related to Study Drug	120	(28.4)	167	(38.9)	157	(36.6)
Deaths	1	(0.2)	0		0	
Occurring ≤30 days (for ADA 70 days) after last dose)	1	(0.2)	0		0	
Occurring >30 days (for ADA 70 days) after last dose)	0		0		0	
Any Infection	140	(31.1)	146	(34.0)	169	(39.4)
Any Serious Infection	4	(0.9)	3	(0.7)	5	(1.2)
Any Opportunistic Infection excluding TB and herpes zoster	0		0		1	(0.2)
Any possible malignancy	1	(0.2)	4	(0.9)	3	(0.7)
Any Malignancy	1	(0.2)	3	(0.7)	1	(0.2)
Any Non-Melanoma Skin Cancer (NMSC)	1	(0.2)	0		0	
Any malignancy other than NMSC	0		3	(0.7)	1	(0.2)
Any Lymphoma	0		0		0	
Any Hepatic Disorder	16	(3.8)	67	(15.6)	39	(9.1))
Any Gastrointestinal Perforation	0		0		0	
Any Anemia	4	(0.9)	1	(0.2)	3	(0.7)
Any Neutropenia	1	(0.2)	10	(2.3)	4	(0.9)
Any Lymphopenia	5	(1.2)	1	(0.2)	6	(1.4)
Any herpes zoster	3	(0.7)	0		4	(0.9)
Any Creatine Phosphokinase (CPK) Elevation	6	(1.4)	24	(5.6)	38	(8.9)
Any Renal Dysfunction	1	(0.2)	0		0	
Any active tuberculosis	0		0		0	
Any Adjudicated MACE*	1	(0.2)	2	(0.5)	0	
Any Adjudicated VTE **	1	(0.2)	2	(0.5)	0	

Source: McInnes et al 2021 (10)

*MACE, Major adverse cardiovascular events, defined as cardiovascular death (includes fatal acute myocardial infarction, sudden cardiac death, heart failure, cardiovascular procedure-related death, death due to cardiovascular hemorrhage, fatal stroke, pulmonary embolism and other cardiovascular causes), non-fatal mdyocardial infarction and non-fatal stroke.

**Venous Thromboembolic Events (VTE) include deep vein thrombosis (DVT) and pulmonary embolism (PE).

[redacted]

Additionally, an integrated safety analysis of the SELECT PsA program through week 24, including both SELECT PsA-1 and SELECT PsA-2 studies is shown in table Table 14 below. The overall safety profile was generally consistent with that of adalimumab, and the rates of any serious infections was consistent between the upadacitinib group, the placebo group and the adalimumab group (17). The most common reported serious infection was pneumonia. (17)

TABLE 14: INTEGRATED SAFETY DATA FROM THE SELECT-PSA PROGRAM THROUGH WEEK 24.

	Placebo		Upadacitinib 15 MG QD		Adalimumab 40 mg EOW	
Subjects with:	n	(%)	n	(%)	n	(%)
Any Adverse Event (AE)	391	61.6	422	65.9	278	64.8
Any Serious AE	17	2.7	26	4.1	16	3.7
Any AE Leading to Discontinuation of Study Drug	24	3.8	28	4.4	22	5.1
Deaths	2	0.3	0	0	0	0
Any Infection	213	33.5	240	37.5	146	34
Any Serious Infection	5	0.8	6	0.9	3	0.7

Any Opportunistic Infection	0	0	1	0.2	0	0
Herpes Zoster	5	0.8	7	1.1	0	0
Tuberculosis	0	0	0	0	0	0
Non-melanoma skin cancer	1	0.2	1	0.2	0	0
Malignancy other than NMSC	0	0	3	0.5	3	0.7
Any Adjudicated MACE	1	0.2	1	0.2	2	0.5
Any Adjudicated VTE	1	0.2	1	0.2	2	0.5
Any Gastrointestinal Perforation	0	0	0	0	0	0
Hepatic disorder	19	3.0	43	6.7	67	15.6
Any Anemia	6	0.9	7	1.1	1	0.2
Any Neutropenia	2	0.8	6	0.9	10	2.3
Any Lymphopenia	5	0.8	10	3.5	1	0.5
Any Creatine Phosphokinase (CPK) Elevation	10	1.6	42	6.6	24	5.6
Any Renal Dysfunction	2	0.3	0	0	0	0

Source: (17)

Long term results of the integrated safety analysis on patients treated up to three years will be presented on The European Alliance of Associations for Rheumatology (EULAR) congress in June 2021. The results of this long-term integrated safety analysis confirms that the rates of serious infections are comparable between upadacitinib 15mg and adalimumab also in the long term (Exposure-adjusted Event Rates/100 patient years [95%CI]: 2.3 [1.5, 3.2] for UPA15mg; 1.3 [0.3, 2.2] for ADA), with the most common serious infection being pneumonia (18).

6.1.4 Study results by outcomes defined in the protocol.

Select PsA-1 assessed the efficacy and safety of upadacitinib vs. placebo and adalimumab in patients with PsA that have failed ≥1 non-biologic DMARD. In Table 15, the results of upadacitinib 15 mg vs. adalimumab 40mg EOW on outcomes defined in the protocol are presented.

In the protocol DMC specified that they wanted comparative data on serious adverse reactions (SAR). Unfortunately, AbbVie does not have data on SAR as that was not collected or analyzed in the Select PsA-1 study. Therefore, AbbVie has instead included data on serious adverse events (SAE) which was reported in the study as that is the best data AbbVie has to this date.

TABLE 15: STUDY RESULTS FROM SELECT PSA-1 FOR UPADACITINIB AND ADALIMUMAB FOR BIO-NAIVE PATIENTS WITH PSA AT WEEK 24, BY OUTCOMES DEFINED IN THE PROTOCOL.

	Upadacitinib 15mg		**Adalimumab 40mg EOW**		**Absolute difference (UPA vs. ADA)**	**Relative Risk (UPA vs. ADA)**
Binary outcomes (proportion of patients)						
Outcome	**n (N)**	**Response rate (95% CI)**	**n (N)**	**Response rate (95% CI)**	**AD (CI_low, CI_high)**	**RR (CI_low, CI_high)**
ACR50	225 (429)	52,4 (47.7, 57.2)	190 (429)	44.3 (39.6, 49.0)	8.2% (1.5%, 14.8%)	1.2 (1.03, 1.36)
Serious AE's	14	3.3	16	3.7	-0.47%	0.88

	(429)	(1.7, 5.4)	(429)	(2.1, 6.0)	(-2.12%, 2.87%)	(0.43, 1.77)
mTSS (Proportion showing ≤0,5 SHS CFB)	371 (387)	95.9 (93.9, 97.8)	371 (391)	94.9 (92.7, 97.1)	1.0% (-2%, 3.9%)	1.01 (0.98, 1.04)

The absolute difference between upadacitinib and adalimumab for the outcomes ACR50, serious AE's and proportion of patients showing no radiographc inhibition (≤0,5 SHS change from baseline) are 8,2%, –0,47% and 1 %respectively. The MCID for these outcomes is 15% (adjusted 7,5%), 5% (adjusted 2,5%) and 10% (adjusted 5%) points, respectively.

	Upadacitinib 15mg		**Adalimumab 40mg EOW**		**Absolute difference (UPA vs. ADA)**	**Relative Risk (UPA vs. ADA)**
Continuous outcomes (change from baseline, CFB)						
Outcome	**N**	**(95% CI)**	**N**	**(95% CI)**	**(95% CI)**	
SF-36 physical component summary	398	9.66 (8.82, 10.50)	403	7.84 (7.01, 8.66)	1.83 (0.75, 2.91)	NA
SF-36 vitality	398	8.13 (7.23, 9.03)	305	6.20 (5.31, 7.09)	1.93 (0.76, 3.09)	NA
SF-36 mental component summary	398	4.80 (3.89, 5.70)	403	4.25 (3.36, 5.14)	0.55 (-0.62, 1.71)	NA

The absolute difference between upadacitinib and adalimumab for the patient reported outcomes SF-36 PCS, SF-36 Vitality and SF-36 MCS, are 1,83, 1,93 and 0,55, respectively. The MCID defined in the protocol for these outcomes are 7.2, 7.8 and 3.1 points, respectively.

In summary, the results demonstrate better outcomes for upadacitinib vs. adalimumab on the outcomes defined the protocol, albeit not being bigger than the MCID threshold. Upadacitinib has therefore shown to have similar clinical value as adalimumab for the bio-naïve population.

6.2 Clinical question 2

Following the Medicines Council protocol of 26th of april 2021 the second clinical question was:

Q2: What is the value of upadacitinib compared to ixekizumab for bDMARD therapy experienced patients with psoriatic arthritis?

Population: bDMARD therapy experienced patients with psoriatic arthritis

Intervention: Upadacitinib, oral 15 mg once daily

Comparator: ixekizumab, s.c. 160 mg week 0, 80 mg every fourth Week

Outcomes requested:

- Proportion of patients having ACR50 response
- Proportion of patients without progression as measured by mTSS (no relative comparison)
- Proportion of patients who experienced severe adverse events
- Narrative assessment of side effect profile
- Change from baseline on SF-36

The protocol specified that data for the longest feasible time horizon was required.

Due to lack of direct comparative data of upadaditinib v.s ixekiuzmab for the bio-experienced population, AbbVie performed an indirect treatment comparison using the Bucher's method. The ITC compares the efficacy of upadacitinib vs. ixekizumab on efficacy outcomes such as ACR50 and SF36. Unfortunately, mTSS data was not collected in any of the studies. Also, serious adverse events are based on both bio naïve population and bio experienced population, to get a more representative results on the safety outcome including a higher patient numbers and therefore more robust results. See more information in chapter 5.4 regarding the indirect comparison.

6.2.1 Presentation of relevant studies

Upadacitinib in patients with PsA that previously have shown inadequate response or intolerance to at least one biologic DMARD was studied in the SELECT-PSA-2 study. The primary endpoint was ACR20 at week 12 vs. placebo.

The comparator, ixekizumab, was studied in patients who have had an inadequate response to tumor necrosis factor inhibitors, distinguished by being refractory to therapy or had loss of efficacy, or were intolerant to tumor necrosis factor in the SPIRIT-P2 study. The primary endpoint was ACR20 at week 24.

There exist no head-to-head trials between upadacitinib and ixekizumab and therefore an indirect treatment comparison (ITC) between upadacitinib and ixekizumab on several clinical outcomes have been performed, utilizing data from SELECT PsA-2 for upadacitinib and SPIRIT-P2 for ixekizumab.

SELECT PsA-2 is a phase III, randomized, double-blind, study in patients with PsA that previously failed ≥1 biologic DMARD vs. placebo. The study met its primary endpoint with a significantly higher proportion of patients achieving ACR20 compared with placebo (11). Upadacitinib 15 mg was significantly greater compared with placebo for all other measurements, including the highly important measures PsARC, MDA, and HAQ-DI, with similar response rates regardless of the number of previous biological DMARDS used. A summary of the results is shown in Table 9. The study also showed the risk profile to be in line with the clinical program for upadacitinib across indications, with no new safety signals detected (11). See 5.2.2 for more information.

SPIRIT-P2 was a double blind, multicentre, randomized, placebo controlled, phase 3 study and followed a 1:1:1 randomization where patients received either a subcutaneous injection of 80 mg ixekizumab every 4 weeks or every 2 weeks after 160 mg starting dose or placebo. The study reached its primary endpoint with a higher proportion of patients attaining ACR 20 with ixekizumab every 4 weeks (65 [53%] patients; effect size vs placebo 33·8% [95% CI 22·4–45·2]; p<0·0001) at week 24 (15). See 0 for more information.

The ITC indirectly compared the relative efficacy of upadacitinib vs. ixekizumab for a range of outcome measures at week 24, for patients with prior biologics use (bio experienced).

Outcomes assessed in the ITC were:

- Proportion of patients achieving 50% improvement per the ACR criteria (ACR50)
- SF36-vitality
- SF36-MCS
- SF36-PCS

Data from SELECT-PsA-1, SLECT-PsA-2, SPIRIT-P1 and SPIRIT-P2 were used in an ITC for the outcome assessed:

- SAE

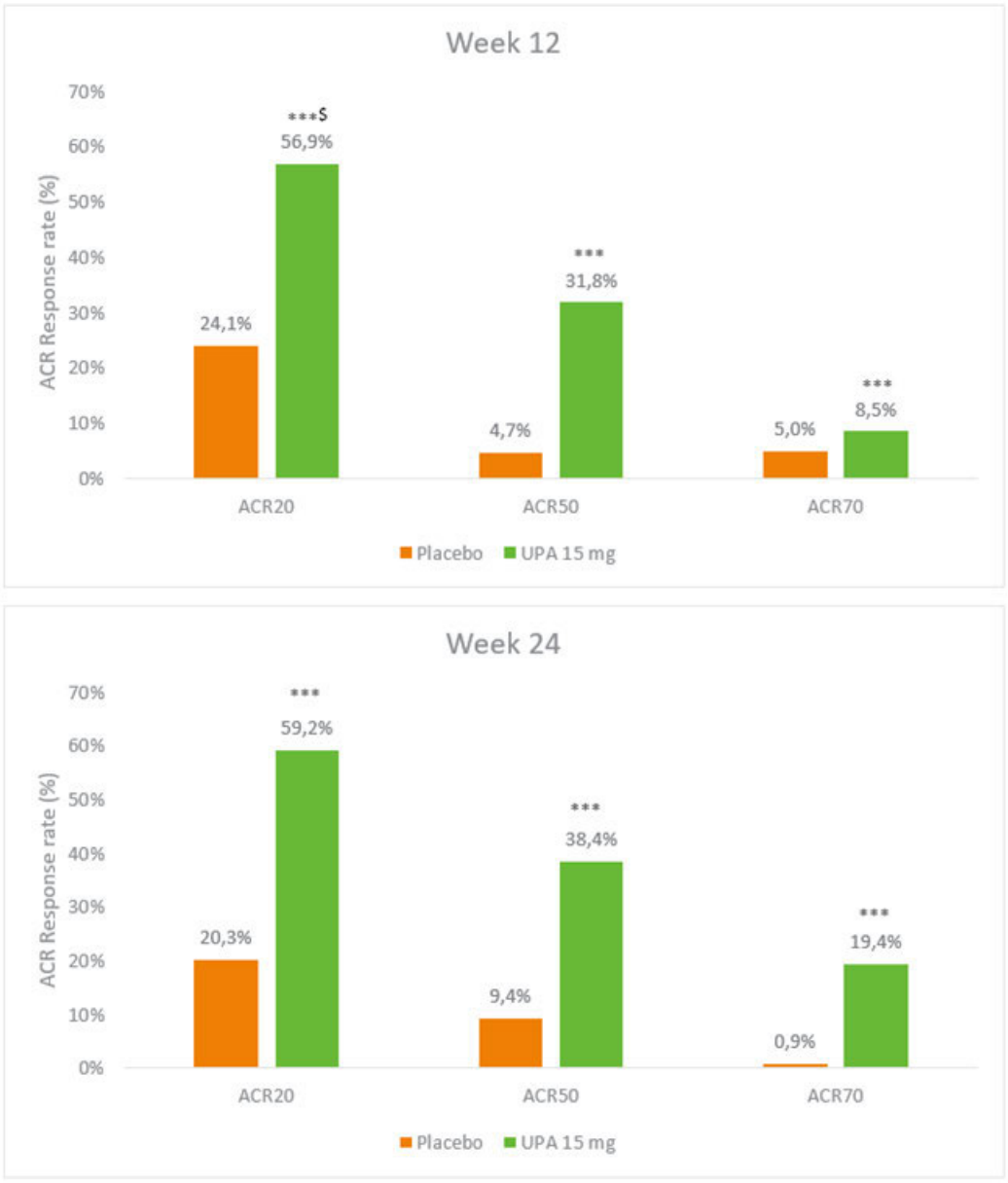
The ITC demonstrated no statistically significant differences between upadacitinib and ixekizumab, suggesting that upadacitinib is at least as good as ixekizumab for the treatment of biologic-experienced patients with PsA. See 6.2.5 for more details on the results.

6.2.3 Description of results SELECT-PSA 2

Peripheral arthritis

A significantly greater proportion of patients treated with upadacitinib achieved the primary endpoint of ACR20 response rate compared with placebo at week 12, using NRI (Figure 17). Results was also significantly better for upadacitinib vs. placebo at week 24 for all ACR outcomes (Figure 17).

FIGURE 17 - ACR RESPONSE RATES AT WEEK 12 AND 24 SELECT PSA-2

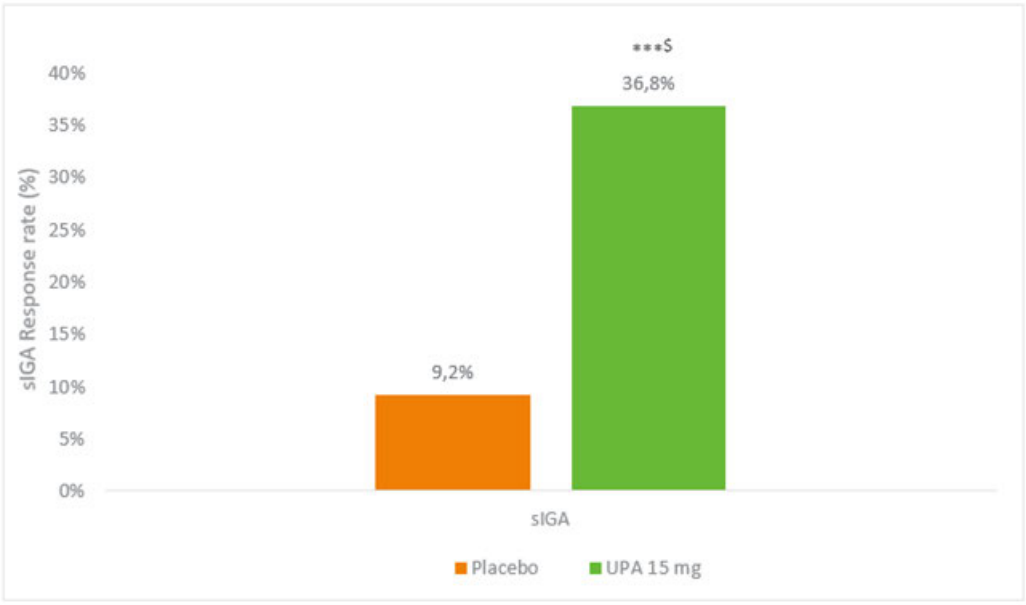


Source: Mease et al 2020 (11) ***p≤0.001 for UPA versus PBO; $Statistically significant in the multiplicity-controlled analysis.

Skin involvement

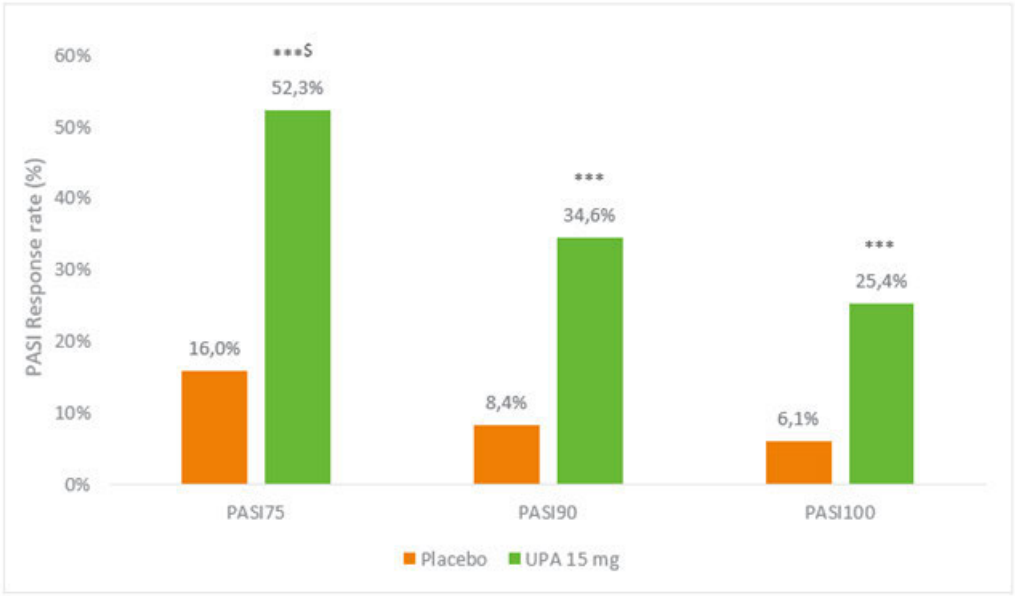
sIGA response rates at week 16 were also significantly greater for upadacitinib compared with placebo (p<0.001) (Figure 18) (11). Additionally, all PASI responses (PASI 75/90/100) were greater for upadacitinib compared with placebo across all time points up to week 24 (p<0.001; nominal for PASI 90/100, multiplicity-adjusted for PASI 75), indicating 75% , 90%, and 100% improvement in psoriasis area severity, respectively (week 16; Figure 19) (11).

FIGURE 18 - SIGA 0/1 RESPONSE RATES AT WEEK 16[A]



Source: Mease et al 2020 (11); [a]sIGA calculated for subjects with baseline sIGA ≥2; ***, p≤0.001 for UPA versus PBO; [$], Statistically significant in the multiplicity-controlled analysis.

FIGURE 19 – PASI 75/90/100 RESPONSE RATE AT WEEK 16[A]

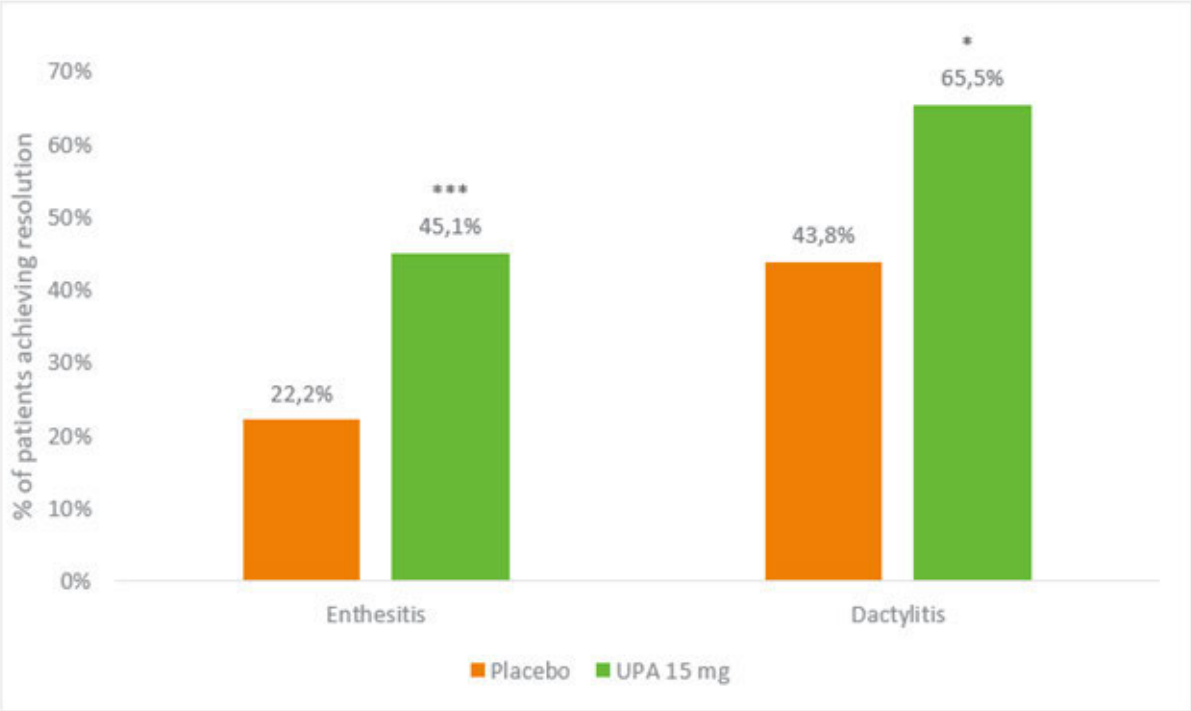


Source: Mease et al 2020 (11); [a]PASI calculated for subjects with ≥3% BSA psoriasis at baseline; ***, p≤0.001 for UPA versus PBO; [$], Statistically significant in the multiplicity-controlled analysis.

Enthesitis and dactylitis

A number of non-ranked secondary endpoints were also greater for upadacitinib 15 mg vs. placebo.(11) The proportion of patients with resolution of enthesitis (LEI=0; p≤0.001) or dactylitis (LDI=0; p<0.05) were significantly greater for upadacitinib compared with placebo through week 24 (week 24; Figure 20) (11).

FIGURE 20 - RESOLUTION OF ENTHESITIS AND DACTYLITIS AT WEEK 24[A]



Source: Mease et al 2020 (11); [a], Patients with enthesitis at baseline; resolution of enthesitis defined as LEI=0; Patients with dactylitis at baseline; resolution of dactylitis defined as LDI=0, respectively; *, p≤0.05; ***, p≤0.001 for UPA versus PBO.

Axial involvement

[redacted]

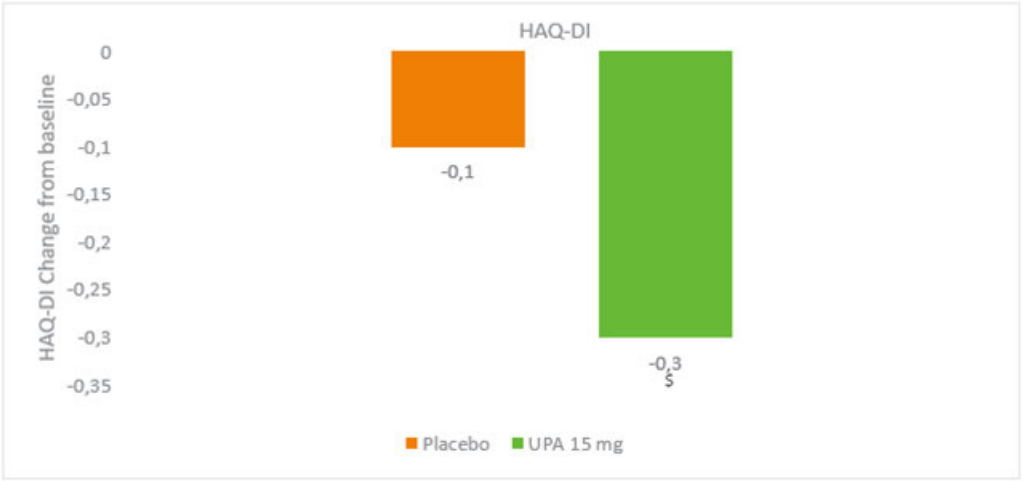
[redacted]

[redacted]

Pain and physical function

Patients treated with upadacitinib 15 mg showed a significantly greater improvement (change from baseline) in signs and symptoms of PsA (as measured by HAQ-DI) compared with placebo ($p<0.05$; multiplicity-controlled) at week 12 (Figure 24). (11) The improvement stayed consistent through week 24 (11).

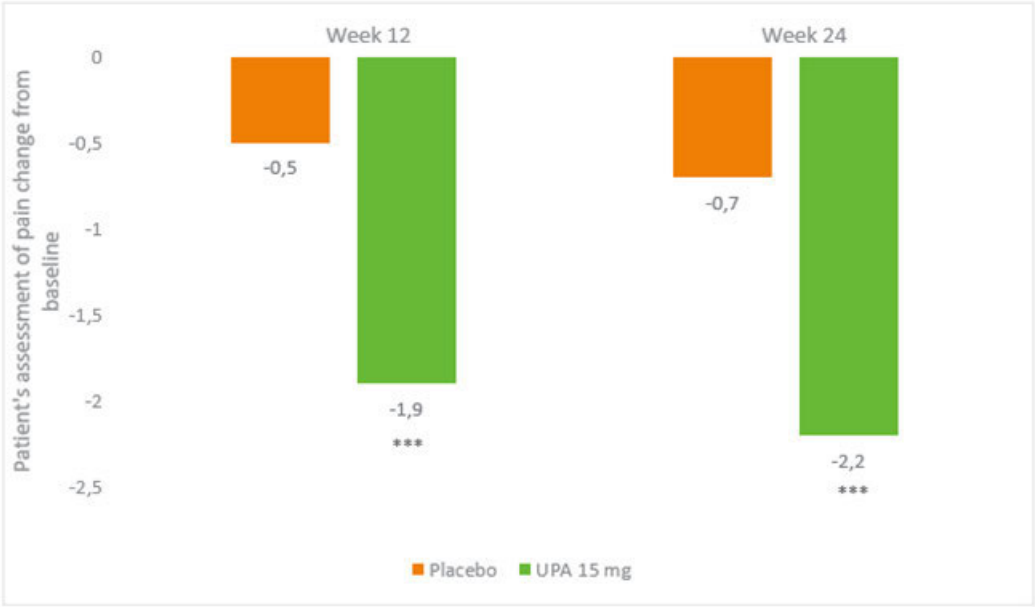
FIGURE 24 - HAQ-DI CHANGE FROM BASELINE AT WEEK 12



Source: Mease et al 2020 (11); $Statistically significant in the multiplicity-controlled analysis.

Additionally, patients treated with upadacitinib 15 mg reported significantly greater improvement in pain (change from baseline) through the patient's assessment of pain (NRS) score compared with placebo at week 12 and 24 (Figure 25).(11)

FIGURE 25 - IMPROVEMENT IN PAIN (PATIENTS' ASSESSMENT NRS) AT WEEK 12 AND 24

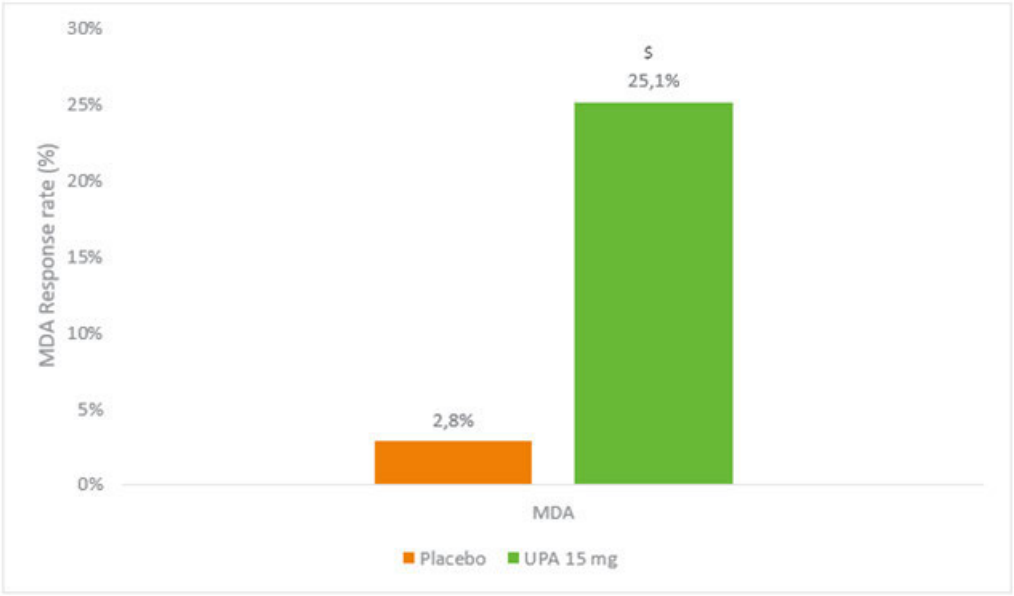


Source: Mease et al 2020 (11); ***, p≤0.001 for UPA versus PBO

MDA, PsARC, and composite indices

The proportion of patients who achieved MDA at week 24 was significantly greater for patients treated with upadacitinib 15 mg compared with placebo (p<0.05; multiplicity-controlled) (Figure 26).(11)

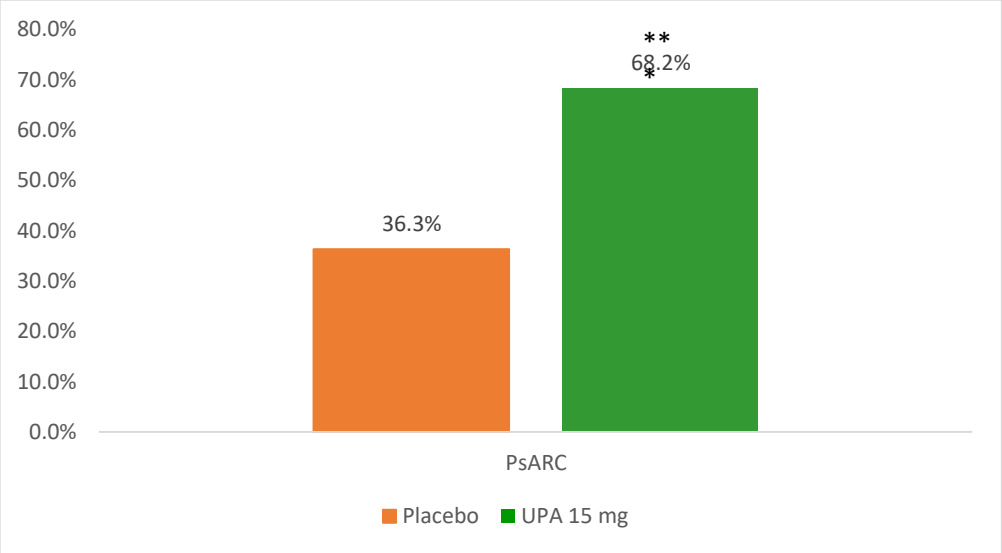
FIGURE 26 - MDA RATES AT WEEK 24 SELECT PSA-2



Source: Mease et al 2020 (11); $, p<0.05 in the multiplicity-adjusted analysis; MDA: Achieve 5 of 7 outcome measures: TJC ≤ 1; SJC ≤ 1; PASI ≤ 1 or BSA-Ps ≤ 3%; patient assessment of pain ≤ 1.5 (0 – 10 NRS); PtGA-disease activity ≤ 2 (0 – 10 NRS); HAQ-DI score ≤ 0.5; and tender entheseal points ≤ 1.

Significantly more patients treated with upadacitinib 15 mg achieved PsARC at week 24 compared with placebo (p<0.0001) (Figure 27). (16)

FIGURE 27 - PSARC RATES AT WEEK 24 SELECT PSA-2

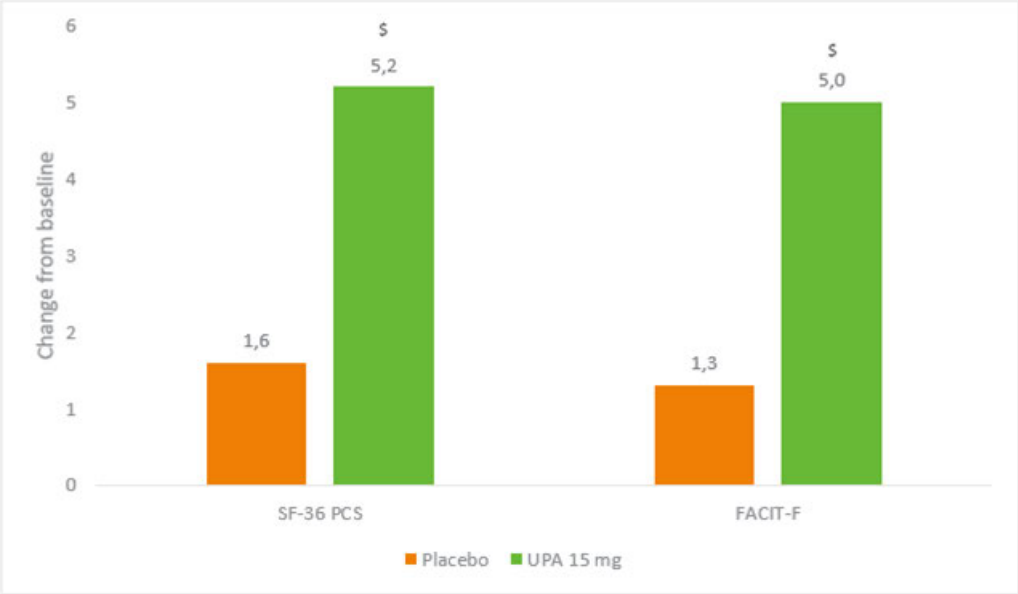


Source: Coates et al 2021 (16); ***: p<0.0001 vs. placebo; PsARC: Achieve at least 2 of 4 criteria: ≥30% improvement in TJC or SJC, ≥1 (1-5 scale) Patient's Global Assessment, or ≥1 (1-5 scale) Physician Global Assessment, No worsening in any criteria

Patient reported outcomes

Upadacitinib showed significant efficacy compared with placebo in multiple key secondary endpoints.(11) Patients treated with upadacitinib showed substantial improvements in fatigue and physical QoL, as indicated through larger scores in FACIT-F and SF-36 (PCS), respectively, compared with placebo (p<0.05 for both; multiplicity-controlled) at week 12 (Figure 28). The improvement stayed consistent through week 24 (11).

FIGURE 28 - SF-36 (PCS) AND FACIT-F CHANGE FROM BASELINE AT WEEK 12



Source: Mease et al 2020 (11); $, p<0.05 for UPA versus PBO in the multiplicity-controlled analysis

Week 56 follow-up data from SELECT PsA-2

Recently, a study reporting 56-week follow-up data from the SELECT PsA-2 trial was published (20). The study found that the efficacy of upadacitinib across manifestations of PsA remained consistent or improved through 56 weeks, and that patients who switched from placebo to upadacitinib at week 24 showed improvements at week 56 that approached or were similar to those in patients originally randomized to upadacitinib (20).

Safety profile of upadacitinib from Select PsA-2

The safety profile of upadacitinib in the 24-week double blind period of SELECT PsA-2 was consistent with that seen in previous clinical studies for upadacitinib across indications (RA, AS, and SELECT-PsA 1), with no new safety signals detected (Table 16).(11) There was one death in the placebo group, one VTE event, and one non-fatal MACE event in the upadacitinib group.(11)

By Week 56, the observed safety profile was comparable with that observed in the 24-week double blind period and in the study program for RA (20).

TABLE 16 - OVERVIEW OF ADVERSE EVENTS IN SELECT PSA-2 THROUGH WEEK 24

	Placebo (N=212)		Upadacitinib 15 mg (N=211)	
Subjects with:	**n**	**(%)**	**n**	**(%)**
Any Adverse Event (AE)	139	(65.6)	135	(64.0)
Any Serious AE	4	(1.9)	12	(5.7)
Any AE Leading to Discontinuation of Study Drug	11	(5.2)	15	(7.1)
Any Severe AE	8	(3.8)	13	(6.2)
Any AE With Reasonable Possibility of Being Related to Study Drug	17	(18.1)	27	(29.0)
Deaths	1	(0.5)	0	
Any Infection	76	(34.4)	71	(33.6)
Any Serious Infection	1	(0.5)	1	(0.5)
Any Opportunistic Infection	0		1	(0.5)
Herpes Zoster	2	(0.9)	3	(1.4)
Tuberculosis	0		0	
Any Malignancy	0		3	(1.4)
Any Non-Melanoma Skin Cancer (NMSC)	0		1	(0.5)
Any Lymphoma	0		1[a]	(0.5)
Any Hepatic Disorder	3	(1.4)	4	(1.9)
Any Gastrointestinal Perforation	0		0	
Any Anemia	2	(0.9)	4	(1.9)
Any Neutropenia	1	(0.5)	2	(0.9)
Any Lymphopenia	0		2	(0.9)
Any Creatine Phosphokinase (CPK) Elevation	4	(1.9)	4	(1.9)
Any Renal Dysfunction	1	(0.5)	0	
Any Adjudicated MACE	0		1	(0.5)
Any Adjudicated VTE	0		1	(0.5)

Source: Mease et al 2020 (11). [a]AE of Atypical Lymphocytes

By Week 56, the observed safety profile was comparable with that observed in the 24-week double blind period and in the study program for RA (20). 1 death was reported in the placebo group due to a motor vehicle accident. The most commonly reported AEs were nasopharyngitis and upper respiratory tract infection. Opportunistic infections (excluding tuberculosis and herpes zoster) were infrequent and consisted mostly of mucosal candidiasis along with coccidioidomycosis. No cases of active tuberculosis were reported. The EAERs of neutropenia, lymphopenia, and renal dysfunction were relatively low. One case of adjudicated pulmonary embolism was reported in a patient receiving upadacitinib 15mg that was non-fatal and occurred in a patient who had risk factors for VTE. The incidence rate of adjudicated VTE's was similar to that reported at week 24 in the SELECT PsA 1 trial (20). The incidence of malignancies at week 56 was also low, with malignancies reported being consistent with those most commonly seen in the PsA population (20).
Overall safety data up to week 56, in terms of events/100 patient years are presented in Table 17.

TABLE 17. OVERALL SAFETY UP TO WEEK 56 IN SELECT-PSA 2 (≥EVENTS/100 PATIENT YEARS).

	Upadacitinib 15 MG QD (N=290)
Any Adverse Event (AE)	269.6
Any Serious AE	14.3
Any Serious Infection	2.6
Cellulitis	0.5
AEs leading to treatment discontinuation	10
Nasopharyngitis	11.7
Upper respiratory tract infection	11.0
CPK increased	5.2
Urinary tract infection	9.8
Bronchitis	8.8
Herpes zoster	3.6
Diarrhea	3.1
Influenza	5.2
ALT increased	1.2
Hypertension	5.7
Sinusitis	5.5
Nausea	2.6
Psoriatic arthropathy	6.7
AST increased	0.2
Headache	1.4
Arthralgia	2.6
Cough	1.9
Pharyngitis	1.4
Anemia	1.0
Pneumonia	1.9
Back pain	4.3
Malignancies	2.4
Hepatic disorders	4.8
Adjudicated VTE	0.2

Source: Mease et al 2021 (20); ALT: alanine transaminase; AST: aspartate transaminase; CPK: creatine phosphokinase; VTE: venous thromboembolism.

For a description of the integrated safety analysis from the whole SELECT PsA program, see chapter 6.1.3.

6.2.4 Overview of results from SPIRIT-P2

TABLE 18: SPIRIT-P2 RESULTS ON KEY RANKED ENDPOINTS

Ranked endpoints		Endpoint	Placebo (N=118)	IXE Q4w (n=122)	IXE Q2w (n=123)
Primary		ACR20 Week 24	19%	53%	48%
Ranked Key Secondary	1	HAQ-DI Week 24	-0.2	-0.6	-0.4
	2	ACR20 Week 12	22%	50%	48%
	3	ACR50 Week 24	5%	35%	33%
	4	ACR70 Week 24	0%	22%	12%
	5	PASI-75 Week 12	10.4%	57.4%	61.8%
	6	MDA Week 24	3%	28%	24%
	7	LEI=0 Week 24	22%	35%	31%

Source: (15)

TABLE 19: SPIRIT-P2 RESULTS ON ALL OUTCOMES

Endpoint	Placebo (n=118)	IXE Q4w (n=122)	IXE Q2w (n=123)
ACR20 week 24	19%	53%	48%
ACR20 week 12	22%	50%	48%
ACR50 week 24	5%	35%	33%
ACR70 week 24	0%	22%	12%
HAQ-DI MCID week 24	17%	43%	40%
MDA week 24	3%	28%	24%
LDI-B=0 week 24	21%	75%	50%
LEI=0 week 24	22%	35%	31%
PASI-75 week 24	15%	56%	60%
PASI-90 week 24	12%	44%	50%
PASI-100 week 24	4%	35%	28%
sPGA (0) week 24	2%	37%	39%
NAPSI week 24	7%	20%	30%
Least squares mean change from baseline			
DAS28-CRP	-0.8	–2·1	–1·8
HAQ-DI	–0·2	–0·6	–0·4
SF-36 PCS	3·3	8·9	8·2
SF-36 MCS	0·9	3·6	4·0
LDI-B	–36·2	–34·7	–32·1
LEI	–1·0	–1·1	–1·4
NAPSI	1·0	–10·5	–12·5

Source: (15)

6.2.5 Results from the indirect treatment comparison of upadacitinib vs. ixekizumab.

An indirect treatment comparison was conducted using the Bucher's method.

See results in the Table 21, Table 23 and Table 25 were OR, RR and RD are presented for the different outcomes.

TABLE 20: EFFICACY ACR50 TREATMENT VS PBO

Study	Treatment	n	N	%		Results
SPIRIT-P2	IXE Q4W	43	122	35.2%	OR (95% CI)	[redacted]
SPIRIT-P2	PBO	6	118	5.1%	RR (95% CI)	
					RD (95% CI)	
SELECT-PSA 2	UPA 15 mg	81	211	38.4%	OR (95% CI)	
SELECT-PSA 2	PBO	20	212	9.4%	RR (95% CI)	
					RD (95% CI)	

TABLE 21: EFFICACY ACR50 ITC UPA VS IXE

UPA vs IXE (95 % CI)	
OR (95% CI)	[redacted]
RR (95 % CI)	
RD (95% CI)	

TABLE 22: ITC RESULTS FOR EFFICACY OUTCOME SF36 UPA VS IXE

Study	Treatment		Difference (SE)
SF36-Vitality			
SELECT-PSA 2	UPA vs PBO		[redacted]
SPIRIT-P2	IXE vs PBO		
SF36-MCS			
SELECT-PSA 2	UPA vs PBO		[redacted]
SPIRIT-P2	IXE vs PBO		
SF36-PCS			
SELECT-PSA 2	UPA vs PBO		[redacted]
SPIRIT-P2	IXE vs PBO		

TABLE 23: EFFICACY SF36 ITC UPA VS IXE

UPA vs IXE (95% CI)	
SF36-Vitality	[redacted]
SF36-MCS	
SF36-PCS	

TABLE 24: EFFICACY OUTCOME SAE TREATMENT VS PBO

Study	Treatment	n	N	%		Results
SPIRIT-P1/2	IXE Q4W	9	229	[redacted]	OR (95% CI)	[redacted]
SPIRIT-P1/2	PBO	6	224		RR (95% CI)	
					RD (95% CI)	
SELECT-PSA 1/2	UPA 15 mg	26	640	[redacted]	OR (95% CI)	
SELECT-PSA 1/2	PBO	17	635		RR (95% CI)	
					RD (95% CI)	

TABLE 25: EFFICACY OUTCOME SAE ITC UPA VS IXE

	UPA vs IXE (95% CI)
OR (95% CI)	[redacted]
RR (95 % CI)	
RD (95% CI)	

[redacted]

[redacted]

6.2.6 Comparative results by outcomes defined in the protocol.

Due to a lack of direct comparative data between upadacitinib and ixekixumab in the bio-experienced population, AbbVie have performed an indirect comparison on the outcomes specified in the DMC protocol. The result of this indirect comparison is presented in Table 27 below.

The indirect comparison for efficacy and PRO outcomes (ACR50, SF-36 physical function, SF-36 vitality and SF-36 mental component summary) are based on results at week 24 from Select PsA-2 and SPIRIT-P2. Unfortunately, mTSS was not an outcome assessed in any of the trials, so extracting data on this outcome was not possible.

While it is reasonable to assume that efficacy and PRO outcomes may differ between bio-naïve and bio-experienced populations, making an indirect comparison only on the bio-experienced population appropriate, AbbVie strongly believe that there is no medical reason why safety should differ between the bio-naïve and bio-experienced population. Therefore, AbbVie believes that utilizing a mixed population (bio-naïve and bio-experienced) for the safety outcome is the most robust approach.

Given the many methodological challenges in conducting a robust indirect treatment comparison (ITC) of safety outcomes between available treatment options in active PsA, AbbVie believes caution should be expressed when interpreting safety ITCs to compare AE rates, especially categories of AEs with relatively low frequency such as SAEs, among studies with different patient populations and sizes, different trial designs, occurring in different time periods, and in different regions. The rationale outlining AbbVie's overall position on safety ITCs and strong preference to utilize a mixed population (i.e. biologic-naïve & biologic-IR patients) for a safety ITC are detailed below.

The proportions of patients experiencing serious adverse events (SAE) are quite low during the placebo- or active-controlled period (24 weeks), this is notable given that there is a lack of sufficient statistical power to detect the differences in these rarely occurring safety events between treatments using the RCT data through 24 weeks.

Eligible placebo or active-controlled RCTs for active PsA typically report safety event rates by the end of the placebo- or active-controlled period, but not by other landmark time points prior to the end of the controlled period. The time period for the reporting varies across trials, depending on the length of the placebo- or active-controlled period of each trial. Thus, ITCs of safety event rates would have to rely on the assumption that the contrasts in safety event rates between active treatment and placebo remain similar across different time points, which is a strong but untestable assumption due to the lack of reported safety data at other time points.

Additionally, given that each of the clinical trials across treatments were completed in different time periods, there are legitimate temporal challenges when comparing safety results between SPIRIT-P2 which enrolled patients in Q1 2015 and had study results in Q4 2016 with SELECT-PsA-2 which enrolled patients in Q1 2017 and had study results in Q4 2019. This is especially relevant for trials completed during the COVID-19 pandemic, where trial sites and participants have been impacted by a multitude of issues ranging from potential inability to travel to their usual trial site, to a shift in behavior with a lower willingness to seek care for non-COVID-19 related illnesses, decreased incidence of certain communicable diseases (e.g. influenza) due to mask-wearing and physical distancing and an increased rate of mental health disorder diagnoses, hospitalizations and deaths related to COVID-19. All of these factors can contribute to variability in both the event rates as well as the timing of when these events are reported across trials to a magnitude that may not be adjusted for within an ITC.

Also, different treatment criteria in the studies are reflected; 16.1% of RINVOQ 15mg treated patients in SELECT-PsA-2 failed at least 3 prior biologics as compared to 0% in SPIRIT-P2. It is also notable that SPIRIT-P2 had a more homogenous study population which included enrollment from 10 countries with limited geographic spread; SELECT-PsA-2 recruited more globally with patients from 17 countries and greater spread. With greater heterogeneity comes greater variances in standard of care which may lead to differences in observed AEs and SAEs. Another difference is the sample size where a sample size that is greater than 4x the size in the bio-naïve population and nearly 2x the size for the bio-experienced population in the studies of RINVOQ compared to the studies of Ixekizumab, highlighting the more robust data-set within studies of RINVOQ.

Making a comparison in bio-experience patients only implies that a treatment's underlying risk of an SAE is systematically different based on past biologic use and therefore driven by whether a patient is biologic-naïve or biologic-experienced but there is no evidence to suggest that this is an accurate assumption. Abbvie believe that if a safety ITC needs to be performed between RINVOQ and Ixekizumab, the comparison should be done across a larger, mixed population which includes both bio-naïve and bio-experienced patients. This would allow for a more robust and meaningful analysis by increasing the ability to detect a difference if a difference truly exists between treatments. Evaluating safety across a mixed-population is also consistent with real-world clinical practice, where physicians seek to understand what is the safety risk with treatments when combined with csDMARDS. This rationale is further supported by a recently published PsA network meta-analysis by Ruyssen-Witrand et al (2020)(32), which evaluated efficacy outcomes in the bio-naive population only but assessed safety in a mixed population (i.e., including both bio-naive and bio-IR trials in the same network).

Therefore, the indirect analysis on the outcome "Serious Adverse Events" is done on the combined bio-naïve and bio-experienced population utilizing data from Select PsA-1, Select PsA-2, SPIRIT-P1 and SPIRIT-P2. AbbVie believe that this is the most appropriate approach that will provide a more robust analysis with higher patient numbers and more representative results on the safety outcome. Same as for clinical question 1, data on Serious Adverse Reactions did unfortunately not exist so the safety analysis has been done on Serious Adverse Events (SAE).

TABLE 27: UPADACITINIB AND IXEKIZUMAB ITC RESULTS BY OUTCOME DEFINED IN THE PROTOCOL, WEEK 24.

	Upadacitinib 15mg		ixekizumab Q4W		Absolute difference (UPA vs. IXE)	Relative difference (UPA vs. IXE)
Binary outcomes (proportion of patients)						
Outcome	N n	Response rate (95% CI)	N n	Response rate (95% CI)	AD (CI_low, CI_high)	RR (CI_low, CI_high)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]						
[redacted]						
Continuous outcomes (change from baseline, CFB)						
Outcome	**N**	**CFB (SE)**	**N**	**CFB (SE)**		
mTSS	NA	NA	NA	NA	NA	NA
[redacted]						NA
[redacted]						NA
[redacted]						NA

[redacted]

Serious AE's shows 0.0 difference with no significant statistical difference. The MCID for this outcome is 5 % (adjusted 2,5 %). This result suggests that there is no clinically relevant difference between upadacitinib and Ixekizumab for the binary outcomes.

The absolute difference between upadacitinib and adalimumab for the patient reported outcomes SF-36 PCS, SF-36 Vitality and SF-36 MCS, [redacted] respectively. The MCID defined in the protocol for these outcomes are 7.2, 7.8 and 3.1 points, respectively. In summary, the results are not larger than the MCID threshold. Upadacitinib has therefore shown to have similar clinical value as Ixekizumab for the bio-experienced population.

Serious infections

In the protocol from April 26th 2021, the Danish Medicine Council specified to summarize serious adverse events explicitly related to serious infections for upadacitinib and comparator. Below is a description of serious infections described in the SmPC of both upadacitinib and Ixekizumab.

Overall, the most common serious adverse reactions reported in patients treated with upadacitinib are serious infections such as pneumonia and cellulitis. (9)

In placebo-controlled clinical studies with background DMARDs in rheumatoid arthritis (RA), the frequency of serious infection over 12/14 weeks in the upadacitinib 15 mg group was 1.2% compared to 0.6% in the placebo group. In MTX-controlled studies, the frequency of serious infection over 12/14 weeks in the upadacitinib 15 mg monotherapy group was 0.6% compared to 0.4% in the MTX group. The overall long-term rate of serious infections for the upadacitinib 15 mg group across all five Phase 3 clinical studies was 3.8 events per 100 patient-years. The most common serious infection was pneumonia. The rate of serious infections remained stable with long-term exposure.(9)

Overall, the safety profile observed in patients with active psoriatic arthritis (PsA) treated with upadacitinib 15 mg was consistent with the safety profile observed in patients with rheumatoid arthritis. A higher incidence of acne and bronchitis was observed in patients treated with upadacitinib 15 mg (1.3% and 3.9%, respectively) compared to placebo (0.3% and 2.7%, respectively). A higher rate of serious infections (2.6 events per 100 patient-years and 1.3 events per 100 patient-years, respectively) and hepatic transaminase elevations (ALT elevations Grade 3 and higher rates 1.4% and

0.4%, respectively) was observed in patients treated with upadacitinib in combination with MTX therapy compared to patients treated with monotherapy. There was a higher rate of serious infections in patients ≥ 65 years of age, although data are limited.(9)

Treatment with ixekizumab is associated with an increased rate of infections such as upper respiratory tract infection, oral candidiasis, conjunctivitis, and tinea infections. (24)

In the placebo-controlled period of the phase III clinical studies in plaque psoriasis in adults, infections were reported in 27.2 % of patients treated with Taltz for up to 12 weeks compared with 22.9 % of patients treated with placebo. The majority of infections were non-serious and mild to moderate in severity, most of which did not necessitate treatment discontinuation. Serious infections occurred in 13 (0.6 %) of patients treated with Taltz and in 3 (0.4 %) of patients treated with placebo (see section 4.4). Over the entire treatment period infections were reported in 52.8 % of patients treated with Taltz (46.9 per 100 patient years). Serious infections were reported in 1.6 % of patients treated with Taltz (1.5 per 100 patient years). (24)

Infection rates observed in psoriatic arthritis and axial spondyloarthritis clinical studies were similar to those observed in the plaque psoriasis studies with the exception of the frequencies of the adverse reactions of influenza and conjunctivitis which were common in patients with psoriatic arthritis. (24)

6.3 Safety of upadacitinib related to specific considerations defined by DMC

The Danish Medicine Council (DMC) have asked AbbVie to specifically describe any additional data on upadacitinib related to risk of VTE and serious infections in patients above 65 years, as well as toxicity regarding reproduction and malignancy.

Upadacitinib has been investigated in an extensive clinical trial program for several indications (RA, PsA and AS) with more than 5000 patients and the safety signals reported in the clinical trials for PsA are consistent with safety signals reported across the clinical trial program for upadacitinib. The safety profile of upadacitinib is therefore well-defined. Below follows a description of the latest safety data of upadacitinib related to the specific consideration defined by DMC.

Serious infections in patients above >65 years:

Serious infections have been reported in patients receiving upadacitinib, and upadacitinib should not be initiated in patients with an active, serious infection, including localized infections. There was a higher rate of serious infections in patients ≥ 65 years of, but data on this population is limited. As there is a higher incidence of infections in the elderly ≥ 65 years of age, caution should be used when treating this population. (9) This is in line with what is stated in the SmPC for Humira as well, that frequency of serious infections were higher in subjects over 65 years of age, and that particular attention regarding the risk of infections should be paid when treating the elderly(25).

As mentioned in chapter 5.1.4, the integrated safety analysis of the SELECT PsA program shows that the safety profile of upadacitinib is consistent with adalimumab, with comparable rates of serious infections through week 24 and also long-term (up to three years) (17), (18). The most common serious infections reported was pneumonia.

This is also in line with a review assessing the risk-benefit profile of upadacitinib across the SELECT phase III program for RA. Results from this review shows that in the long-term integrated safety analysis the exposure adjusted event rate of serious infections among any patient receiving upadacitinib 15mg across all five phase III studies was 3.2 E/100PY (95% CI 2.7–3.7).(26) This was consistent with that observed in patients treated with adalimumab (3.9 E/100PY [95% CI 2.6–5.6])(26). Also here pneumonia was the most commonly reported serious infection in patients treated with upadacitinib, consistent with that reported in PsA. Patients aged ≥ 75 years and smokers had an increased risk of serious infections. (26)f

Venous thromboembolism (VTE):

Events of deep venous thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients receiving JAK inhibitors including upadacitinib. Upadacitinib should be used with caution in patients at high risk for DVT/PE. As opposed to tofacitinib, no evidence of a dose relationship in VTE rate with upadacitinib was identified in a long-term integrated safety analysis of the extensive SELECT phase 3 clinical program for RA (27).

A long term integrated safety analysis of the SELECT phase III program for PsA shows that the rates of VTE were similar between patients treated with upadacitinib 15 mg and adalimumab (E/100PY [95% CI]: 0.3 [0.0, 0.6] for UPA15mg and 0.4 [-0.1, 0.9] for ADA).(18)

These results are also consistent with a benefit-risk assessment of the SELECT phase III program for RA, where rates of VTE were comparable between upadacitinib 15mg and adalimumab (E/100PY [95%]: 0.5 [0.3, 0.7] for UPA15mg and 0.5 [0.3, 0.7] for ADA). (26) This was also similar to that observed in the general RA population (0.6 n/100PY) (28). In total, 21 VTEs were observed in 20 patients receiving upadacitinib 15 mg, of which 11 events were PE only, five events were DVT only, and four events were PE + DVT (26). There was no pattern in the timing of VTEs in patients receiving upadacitinib 15 mg, and the accumulative probability of VTE in this treatment group over 3 years was ≤ 1% (26). All patients who experienced a VTE had at least one known risk factor. Subsequent analysis suggested prior VTE, age ≥ 65 years, non-steroidal anti-inflammatory drug or statin use, and—to a lesser extent—higher body mass index (BMI), were risk factors for the development of VTE in patients receiving upadacitinib 15 mg (26). These factors are known to increase the risk of VTE in the general population (29).

Toxicity regarding reproduction and malignancy

In the SELECT-PsA phase III program long term integrated safety analysis, malignancy rates were reported to be similar between upadacitinib 15 mg and adalimumab (E/100PY [95%]: 0.7 [0.3, 1.2] for UPA15mg and 0.7 [0.0, 1.4] for ADA)(18). No event of lymphoma were reported and age-gender-adjusted standardized incidence ratios for malignancies excluding NMSC indicated no increased risk with UPA compared to the general population (18).

There is limited data or no data on the toxicity of upadacitinib regarding reproduction, especially in pregnant women. The limited human data on use of upadacitinib in pregnant women are not sufficient to evaluate a drug-associated risk for major birth defects or miscarriage. Studies in animals have shown reproductive toxicity and that upadacitinib has the potential to adversely affect a developing fetus. Upadacitinib was teratogenic in rats and rabbits with effects in bones in rat foetuses and in the heart in rabbit foetuses when exposed in utero. Upadacitinib is therefore contraindicated during pregnancy.(9)

With regards to impairment of fertility, upadacitinib had no effect on fertility in male or female rats at oral doses up to 50 mg/kg/day in males and 75 mg/kg/day in females in a fertility and early embryonic development study (approximately 42 and 84 times the MRHD in males and females, respectively, on an AUC basis).(9), (30)

To the best of our knowledge, no studies has indicated that upadacitinib may reduce fertility or cause infertility in males and no authority has requested further investigation into this matter.

Summary:

To summarize, the safety profile of upadacitinib has been investigated in a comprehensive clinical trial program across RA, PsA and AS. The safety profile is therefore well-defined. The most commonly reported adverse events in patients treated with upadacitinib are infections and the most commonly reported serious infection is pneumonia. A higher incidence of serious infections has been shown in patients above 65 years, although data for this population is limited. Anyway, particular consideration regarding the risk of serious infections should be taken when treated elderly patients above 65 years. The same considerations should be taken when treating elderly patients above 65 years with adalimumab.

Based on long-term safety analysis of the SELECT PsA program, the risk of VTE in subjects treated with upadacitinib are consistent with patients treated with adalimumab and no dose relationship on the risks of VTE's were identified with upadacitinib, as opposed to what have been seen with another JAKi, with a different selectivity profile. Regarding malignancies age-gender-adjusted standardized incidence ratios for malignancies excluding NMSC indicated no increased risk with UPA compared to the general population. Upadacitinib is contraindicated during pregnancy, however studies have not indicated that upadacitinib has any negative effect on male fertility.

Therefore, the safety profile of upadacitinib in PsA is generally consistent with what has been observed across indications, and there are no new safety signals identified. Safety data will continuously be collected in the long-term follow-up study programs of upadacitinib.

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20. Mease PJ, Lertratanakul A, Papp KA, van den Bosch FE, Tsuji S, Dokoupilova E, et al. Upadacitinib in Patients with Psoriatic Arthritis and Inadequate Response to Biologics: 56-Week Data from the Randomized Controlled Phase 3 SELECT-PsA 2 Study. Rheumatol Ther. 2021.
21. AbbVie. Data on file NMA PsA. 2020.
22. NICE. Technology appraisal guidance: Ixekizumab for treating active psoriatic arthritis after inadequate response to DMARDs. 2018.
23. AbbVie. Data-on-file Select PsA-2. 2020.
24. EMA. TALTZ Summary of product characteristics. 2021.
25. EMA. Humira SUMMARY OF PRODUCT CHARACTERISTICS. 2021.
26. Philip G. Conaghan EM, Yoshiya Tanaka, Barbara Da Silva-Tillmann, Tim Shaw, John Liu, Ryan Ferguson, Jeffrey V. Enejosa, Stanley Cohen, Peter Nash, William Rigby, Gerd Burmester. Upadacitinib in Rheumatoid Arthritis: A Benefit–Risk Assessment Across a Phase III Program. Drug Safety. 2021;44:515–30.
27. Cohen SB, van Vollenhoven RF, Winthrop KL, Zerbini CAF, Tanaka Y, Bessette L, et al. Safety profile of upadacitinib in rheumatoid arthritis: integrated analysis from the SELECT phase III clinical programme. Ann Rheum Dis. 2020.
28. Kim SC, Schneeweiss S, Liu J, Solomon DH. Risk of venous thromboembolism in patients with rheumatoid arthritis. Arthritis Care Res (Hoboken). 2013;65(10):1600-7.
29. Kroegel C, Reissig A. Principle mechanisms underlying venous thromboembolism: epidemiology, risk factors, pathophysiology and pathogenesis. Respiration. 2003;70(1):7-30.
30. AbbVie. Data on file, use in pregnancy. 2019.
31. AbbVie. Data on File. 2020.

32. Ruyssen-Witrand A, Perry R, Watkins C, et al. Efficacy and safety of biologics in psoriatic arthritis: a systematic literature review and network meta-analysis. *RMD Open*. 2020;6(1):e001117. doi:10.1136/rmdopen-2019-001117

7 Appendices

7.1 Literature search

Table A1: Inclusion and exclusion criteria

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.

Note: From the Medicines council protocol regarding in- and exclusion

Search strategy: MEDLINE (Pubmed) and CENTRAL (Cochrane Library) Date: May 17th, 2021

MEDLINE (via PubMed)

#	Søgetermer	Hits	Kommentar
1	"Arthritis, Psoriatic"[mh]	6,530	Søgetermer for populationen
2	PsA[tiab] OR (psoria*[tiab] AND (arthriti*[tiab] OR arthropath*[tiab] OR polyarthriti*[tiab] OR poly-arthriti*[tiab] OR oligoarthr*[tiab] OR oligo-arthr*[tiab] OR rheumato*[tiab]))	46,978	
3	#1 OR #2	47,905	
4	upadacitinib [nm]	63	Søgetermer for intervention og komparatorer
5	upadacitinib [tiab] OR ABT-494 [tiab] OR Rinvoq*[tiab]	160	
6	ixekizumab[nm]	292	
7	ixekizumab[tiab] OR taltz*[tiab] OR LY-2439821[tiab] OR LY2439821[tiab]	630	
8	#4 OR #5 OR #6 OR #7	843	
9	randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti] NOT (animals[mh] NOT humans [mh])	1,304,326	Filter til identifikation af RCT'er
10	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Letter[pt] OR Guideline[pt] OR Review[pt] OR case report[ti]	6,609,460	Søgetermer for ikke relevante publikationstyper (der ekskluderes)
11	animal*[ti] OR murine[ti] OR mouse[ti] OR mice[ti] OR rat[ti] OR rats[ti] OR rodent[ti]	1,564,458	
12	#10 OR #11	8,121,018	
13	#3 AND #8 AND #9 NOT #12	41	Endelig søgning

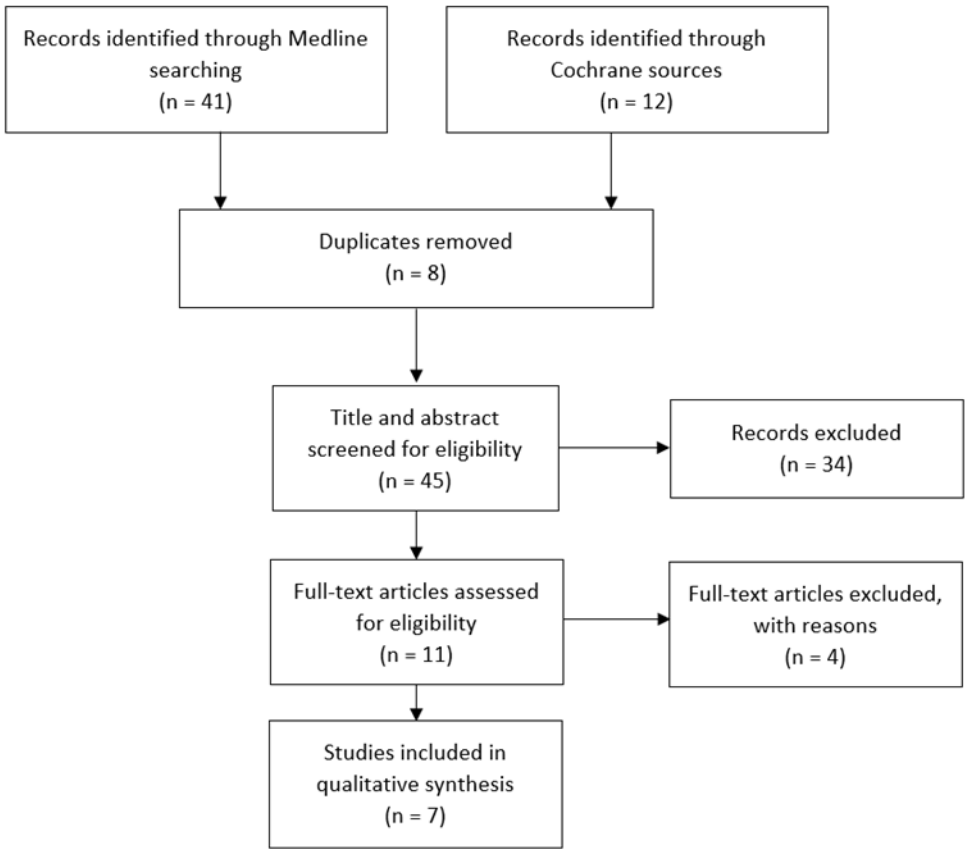
Feltkoder: mh = MeSH Term nm = Supplementary Concept/Substance tiab = title/abstract, inkl. forfatterkeywords pt = publication type

CENTRAL (via Cochrane Library)

#ID	Søgetermer	Hits	Kommentar
1	[mh "Arthritis, Psoriatic"]	461	Søgetermer for populationen
2	(psoria* near (arthriti* or arthropath* or polyarthriti* or poly-arthriti* or oligoarthr* or oligo-arthr* or rheumato*)):ti,ab,kw	2,365	
3	(PsA):ti,ab	7,012	
4	#1 or #2 or #3	7,877	
5	(upadacitinib or ABT-494 or Rinvoq*):ti,ab,kw	318	Søgetermer for intervention og komparatorer
6	(ixekizumab or taltz* or LY-2439821 or LY2439821):ti,ab,kw	506	
7	#5 or #6	824	
8	#4 and #7	186	
9	("conference abstract" or review):pt	191,629	Søgetermer for ikke relevante publikationstyper (der ekskluderes)
10	(clinicaltrials.gov or trialsearch):so	362,707	
11	NCT*:au	205,912	
12	#9 or #10 or #11	554,502	
13	#8 not #12	30	
14	#13 not pubmed:an	12	Endelig søgning

Feltkoder: ti: title ab: abstract kw: keywords, her kontrollerede/indekserede termer fra databaserne Medline og/eller Embase. pt = publication type

7.1.1 PRISMA Flow Diagram



7.1.2 List of excluded articles

Title	Publication	Reason for exclusion
Efficacy and Safety of Ixekizumab in Patients with Active Psoriatic Arthritis: 52-week Results from a Phase III Study (SPIRIT-P1)	van der Heijde D., Gladman D.D., Kishimoto M. et al. J Rheumatol. 2018 Mar;45(3):367-377.	Wrong population. Not bio-IR. Safety and efficacy of Ixekizumab in bio-naïve patients.
Ixekizumab treatment of biologic-naïve patients with active psoriatic arthritis: 3-year results from a phase III clinical trial (SPIRIT-P1)	Chandran V., van der Heijde D., Fleischmann R. M., et al. Rheumatology (Oxford). 2020 Oct 1;59(10):2774-2784.	Wrong population. Not bio-IR. Safety and efficacy of Ixekizumab in bio-naïve patients.
Multicentre, randomised, open-label, parallell-group study evaluating the efficacy and safety of ixekizumab versus adalimumab in patients with psoriatic arthritis naïve to biological disease-modifying antirheumatic drug: final results by week 52	Smolen J. S., Mease P., Tahir H., et al. Ann Rheum Dis. 2020 Oct;79(10):1310-1319.	Wrong population and intervention. Not bio-IR. Head-to-head comparison of ixekizumab with adalimumab.
Ixekizumab, with or without concomitant methotrexate, improves signs and symptoms of PsA: week 52 results from Spirit-P1 and Spirit-P2 studies	Combe B., Tsai T. F., Huffstutter J. E., et al. Arthritis Res Ther. 2021 Jan 27;23(1):41.	Wrong intervention. Ixekizumab with or without concomitant MTX.

7.1.3 List of included articles

Studies relevant for clinical question, comparison and outcomes	
Title	**Clinical question**
McInnes IB, Anderson JK, Magrey M, et al. Trial of Upadacitinib and Adalimumab for Psoriatic Arthritis. N Engl J Med 2021;384(13):1227-39.	Q1, direct comparison, all outcomes
Mease PJ, Lertratanakul A, Anderson JK, et al. Upadacitinib for psoriatic arthritis refractory to biologics: SELECT-PsA 2. *Ann Rheum Dis* 2020;80(3):312-20.	Q2, Indirect comparison, all outcomes
Nash P, Kirkham B, Okada M, et al. Ixekizumab for the treatment of patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors: results from the 24-week randomised, double-blind, placebo-controlled period of the SPIRIT-P2 phase 3 trial. *Lancet* 2017;389(10086):2317-27.	Q2, Indirect comparison, all outcomes
Not relevant for assessment of clinically added value (long term extensions).	
Title	**Clinical question**
Orbai AM, Gratacós J, Turkiewicz A, et al. Efficacy and Safety of Ixekizumab in Patients with Psoriatic Arthritis and Inadequate Response to TNF Inhibitors: 3-Year Follow-Up (SPIRIT-P2). Rheumatol Ther 2021;8(1):199-217.	N/A
Mease PJ, Lertratanakul A, Papp KA, et al. Upadacitinib in Patients with Psoriatic Arthritis and Inadequate Response to Biologics: 56-Week Data from the Randomized Controlled Phase 3 SELECT-PsA 2 Study. Rheumatol Ther 2021	N/A
Kavanaugh A, Marzo-Ortega H, Vender R, et al. Ixekizumab improves patient-reported outcomes in patients with active psoriatic arthritis and inadequate response to tumour necrosis factor inhibitors: SPIRIT-P2 results to 52 weeks. *Clin Exp Rheumatol* 2019;37(4):566-74.	N/A
Genovese MC, Combe B, Kremer JM, et al. Safety and efficacy of ixekizumab in patients with PsA and previous inadequate response to TNF inhibitors: week 52 results from SPIRIT-P2. *Rheumatology (Oxford)* 2018;57(11):2001-11.	N/A

7.1.4 Main characteristics of studies included to assess the comparative efficacy and safety

SELECT PsA-1

Trial name	Select-PSA 1
NCT number	NCT03104400
Objective	The study was designed to compare efficacy, safety and tolerability between patients receiving upadacitinib (15 mg and 30 mg) and those receiving placebo and adalimumab for patients with moderate to severe PsA and with inadequate response on biological DMARDs.
Publications – title, author, journal, year	Trial of Upadacitinib and Adalimumab for Psoriatic Arthritis, McInnes et al, N Engl J Med 2021.
Study type and design	SELECT PsA-1 is a phase III, randomized, double-blind, study in patients with PsA that previously failed ≥1 non-biologic DMARD The study was divided into two periods. Period 1 is 56 weeks and includes a 24-week randomized, double-blind, parallel-group, placebo-controlled and active comparator-controlled period followed by an additional 32 weeks of blinded, active comparator-controlled treatment (Weeks 24 – 56). Period 1 is designed to compare the safety, tolerability, and efficacy of upadacitinib 15 mg QD and 30 mg QD versus placebo and adalimumab 40 mg every other week (eow) for the treatment of signs and symptoms of subjects with moderately to severely active PsA who have an inadequate response or DMARD-IR. Period 1 is also designed to compare the efficacy of upadacitinib 15 mg and 30 mg versus placebo for the prevention of structural progression. Period 2 is an open label (blinded until the last subject completes the last visit of Period 1), long-term extension of up to a total treatment duration of approximately 3 years to evaluate the safety, tolerability and efficacy of upadacitinib 15 mg QD and 30 mg QD in subjects with PsA who have completed Period 1. At the baseline, all eligible subjects were randomized in a 2:2:2:1:1 ratio to one of the following five treatment groups (Figure 1): • Group 1: Upadacitinib 15 mg QD, N = 429 • Group 2: Upadacitinib 30 mg QD, N = 423 • Group 3: Adalimumab (40 mg eow), N = 429 • Group 4: Placebo followed by upadacitinib 15 mg QD, N= 211 • Group 5: Placebo followed by upadacitinib 30 mg QD, N= 212 Based on the benefit:risk assessment of 15 mg and 30 mg for PsA patients only the 15 mg upadacitinib dose was submitted in PsA. Hence, the results of the PsA clinical trials focus on the 15 mg QD dose.
Follow-up time	24 weeks: randomized, double-blind, parallel-group, placebo-controlled and active comparator-controlled 24-56 week: blinded, active comparator-controlled treatment period 56-156 week: Open-label long term extension

Population (inclusion and exclusion criteria)	**Study population:** Adults with active PsA. Fullfilled CASPAR criteria; ≥3 swollen joints and ≥3 tender joints at screening and baseline visits. Presence at screening of either ≥1 erosion on x-ray as determined by central imaging review or high sensitivity-CRP >ULN. Diagnosis or history of plaque psoriasis; DMARD-IR (lack of efficacy after a minimum 12-week duration of therapy to at least one non-biologic DMARD) or intolerant or contraindicated to DMARDs, ie. bDMARD-naive **Key inclusion Criteria:** • Adult male or female, ≥ 18 years old at Screening. • Clinical diagnosis of PsA with symptom onset at least 6 months prior to the Screening Visit and fulfilment of the Classification Criteria for PsA (CASPAR) criteria. • Subject has active disease at Baseline defined as ≥ 3 tender joints (based on 68 joint counts) and ≥ 3 swollen joints (based on 66 joint counts) at Screening and Baseline Visits. • Presence of either at Screening: - ≥ 1 erosion on x-ray as determined by central imaging review or; - hs-CRP > laboratory defined upper limit of normal (ULN). • Diagnosis of active plaque psoriasis or documented history of plaque psoriasis. • Subject has had an inadequate response (lack of efficacy after a minimum 12 week duration of therapy) to previous or current treatment with at least 1 non-biologic DMARD at maximally tolerated dose or up to dose defined in Inclusion Criterion 7 [(inadequate response to MTX is defined as ≥ 15 to ≤ 25 mg/week; or ≥ 10 mg/week in subjects who are intolerant of MTX at doses ≥ 12.5 mg/week after complete titration; for subjects in China, Taiwan, and Japan inadequate response to MTX is defined as ≥ 7.5 mg/week), SSZ, LEF, apremilast, bucillamine or iguratimod)], or subject has an intolerance to or contraindication for DMARDs as defined by the investigator. • Subject who is on current treatment with concomitant non-biologic DMARDs at study entry must be on ≤ 2 non-biologic DMARDs (except the combination of MTX and leflunomide) at the following doses: MTX (≤ 25 mg/week), SSZ (≤ 3000 mg/day), leflunomide (LEF) (≤ 20 mg/day), apremilast (≤ 60 mg/day), HCQ (≤ 400 mg/day), bucillamine (≤ 300 mg/day) or iguratimod (≤ 50 mg/day) for ≥ 12 weeks and at stable dose for ≥ 4 weeks prior to the Baseline Visit. No other DMARDs are permitted during the study. • Subjects who need to discontinue DMARDs prior to the Baseline Visit to comply with this inclusion criterion must follow the procedure specified below or at least five times the mean terminal elimination half-life of a drug: ○ ≥ 8 weeks for LEF if no elimination procedure was followed, or adhere to an elimination procedure (i.e., 11 days with cholestyramine, or 30 days washout with activated charcoal or as per local label); ○ ≥ 4 weeks for all others. **Key exclusion Criteria:** • Prior exposure to any Janus Kinase (JAK) inhibitor (including but not limited to ruxolitinib, tofacitinib, baricitinib, and filgotinib)

<table>
<tr><td></td><td>

Current treatment with > 2 non-biologic DMARDs or use of DMARDs other than MTX, SSZ, LEF, apremilast, HCQ, bucillamine or iguratimod or use of MTX in combination with LEF at Baseline
History of fibromyalgia, any arthritis with onset prior to age 17 years, or current diagnosis of inflammatory joint disease other than PsA (including, but not limited to rheumatoid arthritis, gout, overlap connective tissue diseases, scleroderma, polymyositis, dermatomyositis, systemic lupus erythematosus). Prior history of reactive arthritis or axial SpA including ankylosing spondylitis and non-radiographic axial SpA is permitted if documentation of change in diagnosis to PsA or additional diagnosis of PsA is made. Prior history of fibromyalgia is permitted if documentation of change in diagnosis to PsA or documentation that the diagnosis of fibromyalgia was made incorrectly.

</td></tr>
<tr><td>Intervention</td><td>

Oral upadacitinib 15 mg or 30 mg once daily
Active control: adalimumab 40 mg every other week
Placebo

</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th>Key Demographic and Baseline Characteristics Mean (SD) or n (%)</th><th>PLACEBO (N=423)</th><th>ADALIMUMAB 40 MG EOW (N=429)</th><th>UPADACITINIB 15 mg QD (N=429)</th></tr>
<tr><td>Female</td><td>211 (49.9%)</td><td>222 (51.7%)</td><td>238 (55.5%)</td></tr>
<tr><td>Age (years)</td><td>50.4 (12.2)</td><td>51.4 (12.0)</td><td>51.6 (12.2)</td></tr>
<tr><td>Duration of PsA diagnosis, years</td><td>6.2 (7.0)</td><td>5.9 (7.1)</td><td>6.2 (7.4)</td></tr>
<tr><td>TJC68</td><td>20.0 (14.3)</td><td>20.1 (13.8)</td><td>20.4 (14.7)</td></tr>
<tr><td>SJC66</td><td>11.0 (8.6)</td><td>11.6 (8.8)</td><td>11.6 (9.3)</td></tr>
<tr><td>HAQ-DI</td><td>1.12 (0.6)</td><td>1.12 (0.6)</td><td>1.15 (0.7)</td></tr>
<tr><td>≥3% BSA-Ps</td><td>211 (49.9%)</td><td>211 (49.2%)</td><td>214 (49.9%)</td></tr>
<tr><td>LEI > 0</td><td>241 (57.0%)</td><td>265 (61.8%)</td><td>270 (62.9%)</td></tr>
<tr><td>LEI[a]</td><td>2.7 (1.5)</td><td>2.5 (1.4)</td><td>2.6 (1.6)</td></tr>
<tr><td>LDI>0</td><td>126 (29.8%)</td><td>127 (29.6%)</td><td>136 (31.7%)</td></tr>
<tr><td>LDI[b]</td><td>87.7 (114.8)</td><td>99.0 (163.1)</td><td>89.0(106.5)</td></tr>
<tr><td colspan="4">Number of prior DMARDs used</td></tr>
<tr><td>0</td><td>0</td><td>2 (0.5)</td><td>1 (0.2)</td></tr>
<tr><td>1</td><td>274 (64.8%)</td><td>286 (66.7%)</td><td>274 (63.9%)</td></tr>
<tr><td>2</td><td>105 (24.8%)</td><td>112 (26.1%)</td><td>112 (26.1%)</td></tr>
<tr><td>≥3</td><td>44 (10.4%)</td><td>29 (6.8%)</td><td>42 (9.8%)</td></tr>
</table>
[a]Leeds Enthesitis Index (LEI)>0; [b]Leeds Dactylitis Index (LDI)>0.
</td></tr>
<tr><td>Primary and secondary endpoints</td><td>Primary: proportion of patients achieving ACR20 response at week 12.

Key ranked secondary endpoints:</td></tr>
</table>

	• Change from baseline in HAQ-DI at Week 12; • Proportion of subjects achieving a static Investigator Global Assessment (sIGA) of Psoriasis of 0 or 1 and at least a 2-point improvement from baseline at Week 16; • Psoriasis Area Severity Index (PASI) 75 response at Week 16 (for subjects with ≥ 3% BSA psoriasis at baseline); • Change from baseline in SHS at Week 24; • Proportion of subjects achieving MDA at Week 24; • Change from baseline in LEI at Week 24; • ACR20 response rate at Week 12 (non-inferiority of upadacitinib versus adalimumab); • Change from baseline in SF-36 PCS at Week 12; • Change from baseline in FACIT-Fatigue Questionnaire at Week 12 • ACR20 response rate at Week 12 (superiority of upadacitinib versus adalimumab). • Change from baseline in LDI at Week 24; • Change from baseline in Patient's Assessment of Pain NRS at Week 12 (superiority of upadacitinib versus adalimumab). • Change from baseline in HAQ-DI at Week 12 (superiority of upadacitinib versus adalimumab). • Change from baseline in Self-Assessment of Psoriasis Symptoms (SAPS) Questionnaire at Week 16. **Additional key secondary endpoints:** • ACR50/70 response at Week 12. • ACR20 response at Week 2. **Additional secondary variables:** • Proportion of subjects with no radiographic progression (defined as change from baseline in SHS ≤ 0); • Change from baseline in individual components of ACR response; o Change from baseline in Tender Joint Count (TJC) (0 – 68); o Change from baseline in Swollen Joint Count (SJC) (0 – 66); o Change from baseline in Physician Global Assessment (PGA) – Disease Activity Numerical Rating Scale (NRS); o Change from baseline in Patient's Global Assessment (PtGA)-Disease Activity NRS; o Change from baseline in Patient's Assessment of Pain NRS; o Change from baseline in Health Assessment Questionnaire – Disability Index (HAQ-DI); o Change from baseline in High-Sensitivity C Reactive Protein (hs-CRP); • ACR 20/50/70 response rates; • Change from baseline in Leeds Dactylitis Index (LDI); • Change from baseline in dactylitis count; • Proportion of subjects with resolution of dactylitis; • Change from baseline in Leeds Enthesitis Index (LEI); • Proportion of subjects with resolution of enthesitis sites included in the LEI; • Change from baseline in SPARCC Enthesitis Index; • Proportion of subjects with resolution of enthesitis sites included in the SPARCC Enthesitis Index; • Change from baseline in total enthesitis count; • Proportion of subjects with resolution of enthesitis;

	• PASI 75/90/100 response rates (for subjects with ≥ 3% Body Surface Area (BSA) psoriasis at baseline); • Proportion of subjects achieving a static Investigator Global Assessment of Psoriasis (sIGA) score of 0 or 1 and at least a 2-point improvement from baseline; • BSA-Ps; • Change from baseline in Modified Psoriatic Arthritis Response Criteria (PsARC); • Change from baseline in Disease Activity Score 28 (DAS28) (CRP); • Change from baseline in DAS28 (ESR); • Change from baseline in PsA Disease Activity Score (PASDAS); • Change from baseline in Disease Activity in Psoriatic Arthritis (DAPSA) score; • Change from baseline in Short Form 36 (SF-36) Health Questionnaire; • Change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Questionnaire; • Change from baseline in EuroQol-5-Dimensions-5-Levels (EQ-5D-5L) Questionnaire; • Change from baseline in Work Productivity and Activity Impairment (WPAI) Questionnaire; • Change from baseline in Health Resource Utilization (HRU) Questionnaire; • Change from baseline in SAPS Questionnaire; • Change from baseline in BASDAI; • BASDAI 50 response rates: • Change from baseline in Morning stiffness (mean of BASDAI Questions 5 and 6); • Change from baseline in Ankylosing Spondylitis Disease Activity Score (ASDAS); • Proportion of subjects with ASDAS Inactive Disease; • Proportion of subjects with ASDAS Major Improvement; • Proportion of subjects with ASDAS Clinically Important Improvement; • Proportion of subjects achieving a clinically meaningful improvement in HAQ-DI (≥ 0.35).
Method of analysis	All efficacy analyses were carried out using the Full Analysis Set population, which includes all randomized subjects who receive at least one dose of study drug. For binary endpoints, frequencies and percentages are reported for each treatment group. Pairwise comparisons between each upadacitinib treatment group and the combined placebo groups were conducted using the Cochran-Mantel-Haenszel test adjusting for main stratification factors. For continuous endpoints, the mean, standard deviation, median, and range was reported for each treatment group. Pairwise comparisons between each upadacitinib dose group and the combined placebo groups was carried out using the Mixed-Effects Model Repeated Measures with treatment group, visit, treatment-by-visit interaction as the fixed factor, and the corresponding baseline value and the main stratification factors as the covariates. The overall type I error rate of the primary and key secondary endpoints for the two doses was strongly controlled using a graphical multiple testing procedure. All efficacy results are presented according to the NRI analysis unless stated otherwise.
Subgroup analyses	None pubished

SELECT PsA-2

Trial name	Select-PSA 2
NCT number	NCT03104374
Objective	To assess the safety and efficacy of upadacitinib in patients with a history of inadequate response to bDMARDs.
Publications – title, author, journal, year	Upadacitinib for psoriatic arthritis refractory to biologics: SELECT-PsA 2, Mease PJ, Lertratanakul A, Anderson JK, et al. Annals of the Rheumatic Diseases, 03 December 2020. doi: 10.1136/annrheumdis-2020-218870
Study type and design	The study was divided into two periods. Period 1 was 56-weeks in duration and includes a 24-week randomized, double-blind, parallel-group, placebo-controlled period followed by an additional 32 weeks of blinded treatment (Weeks 24–56). Period 1 was designed to compare the safety, tolerability, and efficacy of upadacitinib 15 mg QD and 30 mg QD versus placebo in subjects with moderately to severely active PsA who have bDMARD-IR. Period 2 is an open label (blinded until the last subject completes the last visit of Period 1) long-term extension of up to a total treatment duration of approximately 3 years to evaluate the safety, tolerability and efficacy of upadacitinib 15 mg QD and 30 mg QD in subjects with PsA who have completed Period 1. Patients were enrolled in sites in North America, eastern and western Europe, Asia, and Oceania in accordance with the inclusion and exclusion criteria described below. At the baseline visit, all eligible patients were randomized in a 2:2:1:1 ratio. • Group 1: Upadacitinib 15 mg QD (N = 210) (Period 1) → Upadacitinib 15 mg QD (Period 2) • Group 2: Upadacitinib 30 mg QD (N = 210) (Period 1) → Upadacitinib 15 mg QD (Period 2) • Group 3: Placebo (N = 105) (Period 1) → Upadacitinib 15 mg QD (Period 2) • Group 4: Placebo (N = 105) (Period 1) → Upadacitinib 30 mg QD (Period 2) Based on the benefit:risk assessment of 15 mg and 30 mg for PsA patients only the 15 mg upadacitinib dose was submitted in PsA. Hence, the results of the PsA clinical trials focus on the 15 mg QD dose.
Follow-up time	Up to week 24: randomized, double-blind, parallel-group, placebo-controlled period Week 24-56: blinded treatment Week 56-156: open label long term extension
Population (inclusion and exclusion criteria)	**Study population:** Adults with active PsA. Fullfilled CASPAR criteria; ≥3 swollen joints and ≥3 tender joints at screening and baseline visits. Diagnosis or history of plaque psoriasis; bDMARD-IR (lack of efficacy after a minimum 12-week duration of therapy to at least one non-biologic DMARD) or intolerance to at least 1 bDMARD.

Key inclusion criteria:

- Clinical diagnosis of PsA with symptom onset at least 6 months prior to the Screening Visit and fulfilment of the Classification Criteria for PsA (CASPAR) criteria
- Participant has active disease at Baseline defined as >= 3 tender joints (based on 68 joint counts) and >= 3 swollen joints (based on 66 joint counts) at Screening and Baseline Visits
- Diagnosis of active plaque psoriasis or documented history of plaque psoriasis
- Participant has had an inadequate response (lack of efficacy after a minimum 12-week duration of therapy) or intolerance to treatment with at least 1 bDMARD.

Subject who is on current treatment with concomitant non-biologic DMARDs at study entry must be on ≤ 2 non-biologic DMARDs (except the combination of MTX and leflunomide) at the following doses: MTX (≤ 25 mg/week), SSZ (≤ 3000 mg/day), leflunomide (LEF) (≤ 20 mg/day), apremilast (≤ 60 mg/day), HCQ (≤ 400 mg/day), bucillamine (≤ 300 mg/day) or iguratimod (≤ 50 mg/day) for ≥ 12 weeks and at stable dose for ≥ 4 weeks prior to the Baseline Visit. No other DMARDs are permitted during the study.

Key exclusion criteria:

- Prior exposure to any Janus Kinase (JAK) inhibitor (including but not limited to ruxolitinib, tofacitinib, baricitinib, and filgotinib)
- Current treatment with > 2 non-biologic DMARDs or use of DMARDs other than Methotrexate (MTX), Sulfasalazine (SSZ), Leflunomide (LEF), apremilast, Hydroxychloroquine (HCQ), bucillamine or iguratimod or use of MTX in combination with LEF at Baseline.
- History of fibromyalgia, any arthritis with onset prior to age 17 years, or current diagnosis of inflammatory joint disease other than PsA (including, but not limited to rheumatoid arthritis, gout, overlap connective tissue diseases, scleroderma, polymyositis, dermatomyositis, systemic lupus erythematosus). Prior history of reactive arthritis or axial spondyloarthritis including ankylosing spondylitis and non-radiographic axial spondyloarthritis is permitted if documentation of change in diagnosis to PsA or additional diagnosis of PsA is made. Prior history of fibromyalgia is permitted if documentation of change in diagnosis to PsA or documentation that the diagnosis of fibromyalgia was made incorrectly.

Intervention

1. Oral upadacitinib 15 mg or 30 mg once daily
2. Placebo

Baseline characteristics

Key Demographic and Baseline Characteristics Mean (SD) or n (%)	Placebo (N=212)	Upadacitinib 15 MG QD (N=211)
Female	120 (57)	113 (54)
Age (years)	54.1 (11.5.)	53.0 (12.0)
Duration of PsA Symptoms, years	14.6 (11.7)	12.2 (8.8)
TJC68	25.3 (17.6)	24.9 (17.3)
SJC66	12.0 (8.9)	11.3 (8.2)
HAQ-DI	1.23 (0.7)	1.10 (0.6)
≥3% BSA-Ps	131 (62)	130 62)
PASI (for baseline BSA-Ps ≥3%)	11.7 11.4)	10.1 (9.2)
Presence of enthesitis[a]	173 (82)	173 (82)
Enthesitis count[b] (out of those with presence of enthesitis)	7.7 (82)	173 (82)
Presence of dactylitis[c]	64 (30)	55 (26)
Dactylitis count[d] (out of those with presence of dactylitis)	4.2 (4.3)	3.8 (4.1)
Number of prior bDMARDs failed		
0[e]	18 (8.5)	16 (7.6)

	1	135 (63.7)	126 (59.7)
	2	35 (16.5)	35 (16.6)
	≥3	24 (11.3)	34 (16.1)
	Current use of ≥1 non-biologic DMARD	100 (47.2)	98 (46.4)

[a]Leeds Enthesitis Index (LEI)>0, [b]Of 18 sites, [c]Leeds Dactylitis Index (LDI)>0, [d]Of 20 digits, [e]Indicates subjects enrolled due to intolerance to bDMARD therapy

Primary and secondary endpoints

Primary: Proportion of subjects achieving ACR20 response at Week 12.

Key multiplicity adjusted secondary efficacy endpoints:

- Change from baseline in HAQ-DI at Week 12
- Static Investigator Global Assessment (sIGA) of Psoriasis of 0 or 1 and at least a 2-point improvement from baseline at Week 16
- Psoriasis Area Severity Index (PASI) 75 response at Week 16 (for subjects with ≥ 3% BSA psoriasis at baseline)
- Change from baseline in SF-36 PCS at Week 12
- Proportion of subjects achieving Minimal Disease Activity (MDA) at Week 24
- Change from baseline in FACIT-Fatigue Questionnaire at Week 12; and change from baseline in Self-Assessment of Psoriasis Symptoms (SAPS) Questionnaire at Week 16.

Additional secondary variables:

- Change from baseline in individual components of ACR response;
    - Change from baseline in Tender Joint Count (TJC) (0 – 68);
    - Change from baseline in Swollen Joint Count (SJC) (0 – 66);
    - Change from baseline in Physician Global Assessment (PGA) – Disease Activity (NRS);
    - Change from baseline in Patient's Global Assessment (PtGA) – Disease Activity (NRS);
    - Change from baseline in Patient's Assessment of Pain Numerical Rating Scale (NRS)
    - Change from baseline in Health Assessment Questionnaire – Disability Index (HAQ-DI)
    - Change from baseline in High-Sensitivity C Reactive Protein (hs-CRP);
- ACR 20/50/70 response rates
- Change from baseline in Leeds Dactylitis Index (LDI)
- Change from baseline in dactylitis count
- Proportion of subjects with resolution of dactylitis
- Change from baseline in LEI
- Proportion of subjects with resolution of enthesitis sites included in the LEI
- Change from baseline in SPARCC Enthesitis Index
- Proportion of subjects with resolution of enthesitis sites included in the SPARCC Enthesitis Index;
- Change from baseline in total enthesitis count
- Proportion of subjects with resolution of enthesitis
- PASI 75/90/100 response rates (for subjects with ≥ 3% Body Surface Area (BSA) psoriasis at baseline)
- Proportion of subjects achieving a sIGA score of 0 or 1 and at least a 2-point improvement from baseline;
- BSA-Ps;
- Change from baseline in Modified PsARC
- Change from baseline in Disease Activity Score 28 (DAS28) (CRP)
- Change from baseline in DAS28 (ESR);
- Change from baseline in PsA Disease Activity Score (PASDAS);

	• Change from baseline in Disease Activity in Psoriatic Arthritis (DAPSA) score • Change from baseline in SF-36 Health Questionnaire • Change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Questionnaire • Change from baseline in EuroQol-5D-5L (EQ-5D-5L) Questionnaire; • Change from baseline in Work Productivity and Activity Impairment (WPAI) Questionnaire • Change from baseline in Health Resource Utilization (HRU) Questionnaire • Change from baseline in Self-Assessment of Psoriasis Symptoms (SAPS) Questionnaire • Change from baseline in BASDAI • BASDAI 50 response rates • Change from baseline in Morning stiffness (mean of BASDAI Questions 5 and,6) • Change from baseline in ASDAS • Proportion of subjects with ASDAS Inactive Disease • Proportion of subjects with ASDAS Major Improvement • Proportion of subjects with ASDAS Clinically Important Improvement.
Method of analysis	Analysis was conducted on the FAS based on randomized treatment groups. For binary endpoints, frequencies and percentages were reported for each treatment group. Missing data handling included As Observed) data analysis and NRI based on As Observed data. Point estimate and 95% CI using normal approximation were provided for the response rate for each randomized treatment group. For continuous endpoints, the statistical analysis was conducted using the Mixed-Model Repeated Measures model, with fixed effects of treatment, visit, treatment-by-visit interaction, the stratification factor of current DMARD use (yes/no), and the continuous fixed covariate of baseline measurement. The least square (LS) mean and 95% CI for each randomized treatment group were provided.(31) All efficacy results are presented according to the NRI analysis unless stated otherwise.
Subgroup analyses	None published

SPIRIT-P2

Trial name	SPIRIT-2
NCT number	NCT03104374
Objective	To evaluate the safety and efficacy of ixekizumab in biologic disease-modifying antirheumatic drug-experienced patients with active psoriatic arthritis.
Publications – title, author, journal, year	Ixekizumab for the treatment of patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors: results from the 24-week randomised, double-blind, placebo-controlled period of the SPIRIT-P2 phase 3 trial. Nash P et al: Lancet, 2017.
Study type and design	The study was double-blind, multicentre, randomised, placebo-controlled, phase 3 study.

	Patients were randomly assigned (1:1:1) by a computer-generated random sequence to receive a subcutaneous injection of 80 mg ixekizumab every 4 weeks or every 2 weeks after a 160 mg starting dose or placebo. Patients in all treatment groups with an inadequate response at week 16, distinguished by predefined tender and swollen joint count criteria (ie, inadequate responders), were required to add or modify concomitant drugs. The investigators, study site personnel, and patients were blinded to the inadequate response criteria. Inadequate responders continued taking their originally assigned dose of ixekizumab or, if receiving placebo, were re-randomized to ixekizumab every 2 weeks or every 4 weeks in a 1:1 ratio. Arms: - IXE Q2W: Ixekizumab 80 mg every 2 weeks (n=123) - IXE Q4W: Ixekizumab 80 mg every 4 weeks (n=122) - PBO: Placebo (n=118)
Follow-up time	24 week randomized, double-Blind, placebo controlled period followed by a long term extension.
Population (inclusion and exclusion criteria)	**Study population:** Biologic disease-modifying antirheumatic drug-experienced-patients with active psoriatic arthritis. **Key inclusion criteria:** • Presents with established diagnosis of active psoriatic arthritis (PsA) for at least 6 months, and currently meets Classification for Psoriatic Arthritis (CASPAR) criteria • Active PsA defined as the presence of at least 3 tender and at least 3 swollen joints • Presence of active psoriatic skin lesion or a history of plaque psoriasis (Ps) • Men must agree to use a reliable method of birth control or remain abstinent during the study • Women must agree to use reliable birth control or remain abstinent during the study and for at least 12 weeks after stopping treatment • Have been treated with 1 or more conventional disease-modifying antirheumatic drugs (cDMARDs) • Have had prior treatment with at least 1 and not more than 2 tumor necrosis factor (TNF) inhibitors. The participant must have discontinued at least 1 TNF inhibitor due to either an inadequate response (based on a minimum of 12 weeks on therapy) or documented intolerance. **Key exclusion criteria:** • Current use of biologic agents for treatment of Ps or PsA • Inadequate response to greater than 2 biologic DMARDs • Current use of more than one cDMARDs • Diagnosis of active inflammatory arthritic syndromes or spondyloarthropathies other than PsA • Have received treatment with interleukin (IL) -17 or IL12/23 targeted monoclonal antibody (MAb) therapy • Serious disorder or illness other than psoriatic arthritis

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- Serious infection within the last 3 months
- Breastfeeding or nursing (lactating) women

</td></tr>
<tr><td>Intervention</td><td>

- Ixekizumab 80 mg every 2 Weeks (Q2W)
- Ixekizumab 80 mg Q4W
- Placebo

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<tr><td>Baseline characteristics</td><td>

Key Demographic and Baseline Characteristics Mean (SD) or n (%)	Placebo n=118	Ixekizumab n=122 (every 4 weeks)	Ixekizumab n=123 (every 2 weeks)
Age	51.5 (10.4)	52.6 (13.6)	51.7 (11.9)
Sex			
Male	56 (47%)	63 (52%)	50 (41%)
Female	62 (53%)	59 (48%)	73 (59%)
Weight (kg)	91.0 (22.1)	89.9 (22.0)	85.2 (20.7)
BMI (kg/m2)	31.6 (7.6)	30.9 (7.1)	30.1 (6.8)
Race			
White	108 (92%)	111 (91%)	113 (93%)
Asian	7 (6%)	7 (6%)	7 (6%)
Other	3 (3%)	4 (3%)	2 (2%)
Time since psoriatic arthritis diagnosis (years)	9.2 (7.3)	11.0 (9.6)	9.9 (7.4)
Time since psoriasis diagnosis (years)	15.3 (12.6)	15.7 (12.3)	16.5 (13.0)
Present use of cDMARD	52 (44%)	60 (49%)	73 (59%)
Present use of methotrexate	40 (34%)	48 (39%)	61 (50%)
Previous TNFi treatment			
Inadequate response to one TNFi	68 (58%)	71 (58%)	65 (53%)
Inadequate response to two TNFi	41 (35%)	41 (34%)	46 (37%)
Intolerance to a TNFi*	9 (8%)	10 (8%)	12 (10%)
Patients with specific disease characteristics			
Present psoriasis†	108 (92%)	118 (97%)	113 (92%)
Psoriasis ≥3% of body surface area†	67 (57%)	68 (56%)	68 (55%)
Fingernail psoriasis†	73 (62%)	89 (73%)	74 (60%)
Dactylitis‡	14 (12%)	28 (23%)	20 (16%)
Enthesitis§	69 (58%)	68 (56%)	84 (68%)
Baseline disease and quality of life scores			
Tender joint count (68 joints)	23.0 (16.2)	22.0 (14.1)	25.0 (17.3)
Swollen joint count (66 joints)	10.3 (7.4)	13.1 (11.2)	13.5 (11.5)
HAQ-DI	1.2 (0.7)	1.2 (0.6)	1.2 (0.6)
Patient-reported pain¶	63.9 (20.1)	63.9 (21.4)	62.7 (20.9)
Patient-assessed global disease¶	64.1 (21.5)	66.4 (20.5)	66.0 (20.5)
Physician-assessed global disease¶	58.9 (20.7)	60.3 (20.9)	64.6 (16.8)
C-reactive protein (mg/L)	12.1 (19.6)	17.0 (27.5)	13.5 (26.1)
28-joint Disease Activity Score with C-reactive protein	5.0 (1.1)	5.1 (1.1)	5.1 (1.1)
LEI§	2.9 (1.7)	2.9 (1.4)	3.0 (1.7)
LDI Basic‡	37.3 (25.2)	31.5 (33.8)	53.9 (37.6)

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	Psoriasis body surface area involved (%)||	9.0 (13%)	12.5 (17%)	11.6 (19%)
	PASI total score||	5.2 (6.3)	6.4 (7.9)	6.2 (8.7)
	NAPSI**	18.7 (18.8)	20.5 (20.0)	21.0 (22.0)
	SF-36 physical component summary score	33.9 (9.0)	34.8 (8.8)	34.3 (9.1)
	SF-36 mental component summary score	48.0 (13.1)	49.6 (11.3)	49.1 (11.5)
	Data are mean (SD) or n (%). BMI=body-mass index. cDMARD=conventional disease-modifying antirheumatic drug. TNFi=tumour necrosis factor inhibitor. HAQ-DI=Health Assessment Questionnaire-Disability Index. LDI=Leeds Dactylitis Index. LEI=Leeds Enthesitis Index. PASI=Psoriasis Area and Severity Index Improvement. NAPSI=Nail Psoriasis Severity Index. SF-36=Short Form (36 Items) Health Survey. *Patients had previously received a TNFi and had discontinued. †Qualitatively assessed by the investigator at baseline. ‡Defined as LDI>0. §Defined as LEI>0. ¶Visual analogue scale 0–100. ||Assessed only in patients with psoriasis. **Assessed only in patients with fingernail psoriasis.			

Primary and secondary endpoints	**Primary:** Percentage of Participants Achieving American College of Rheumatology 20 Index (ACR20) [Time Frame: Week 24] **Secondary endpoints:** • Change From Baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) Score [Time Frame: Baseline, Week 24] • Percentage of Participants Achieving ACR20 [Time Frame: Week 12] • Percentage of Participants Achieving American College of Rheumatology 50 Index (ACR50) [Time Frame: Week 24] • Percentage of Participants Achieving American College of Rheumatology 70 Index (ACR70) [Time Frame: Week 24] • Percentage of Participants With Psoriasis Area and Severity Index (PASI) 75 [Time Frame: Week 12] • Percentage of Patients Achieving Minimal Disease Activity (MDA) [Time Frame: Week 24] • Percentage of Patients Achieving Complete Resolution in Enthesitis as Assessed by the Leeds Enthesitis Index (LEI) [Time Frame: Week 24] • Change From Baseline in Itch Numeric Rating Scale (NRS) [Time Frame: Baseline, Week 12] • Change From Baseline in Tender Joint Count (TJC) [Time Frame: Baseline, Week 24] • Change From Baseline in Swollen Joint Count (SJC) [Time Frame: Baseline, Week 24] • Change From Baseline in Participants Assessment of Pain Visual Analog Scale (VAS) [Time Frame: Baseline, Week 24] • Change From Baseline in Patients Global Assessment of Disease Activity VAS [Time Frame: Baseline, Week 24] • Change From Baseline in Physicians Global Assessment of Disease Activity VAS [Time Frame: Baseline, Week 24] • Change From Baseline in C-Reactive Protein (CRP) [Time Frame: Baseline, Week 24] • Change From Baseline in Disease Activity Score-CRP (DAS28-CRP) [Time Frame: Baseline, Week 24]

	• Change From Baseline in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) Score [Time Frame: Baseline, Week 24] • Change From Baseline in Fatigue Severity Numeric Rating Scale (NRS) Score [Time Frame: Baseline, Week 24] • Change From Baseline in 36-Item Short-Form Health Survey (SF-36) Scores: Physical Component Summary (PCS) [Time Frame: Baseline, Week 24] • Change From Baseline in 36-Item Short-Form Health Survey (SF-36) Scores: Mental Component Summary (MCS) [Time Frame: Baseline, Week 24] • Number of Participants With Treatment Emergent Anti-Drug Antibodies (TE-ADA) [Time Frame: Week 24] • Pharmacokinetics (PK):Minimum Observed Serum Concentration at Steady State (Ctrough,ss) of Ixekizumab [Time Frame: All immunogenicity samples post the first Ixekizumab dose (Week 4, 12, 24, 36, and 52) and PK samples collected per dedicated sparse sampling plan (4-5 samples per patient) across Weeks 1 through 24 and Early termination visit (ETV)] • Pharmacokinetics: Area Under the Concentration-Time Curve for Dosing Interval (Tau) at Steady State [AUC(Tau,Steady State)] of Ixekizumab [Time Frame: All immunogenicity samples post the first Ixekizumab dose (Week 4, 12, 24, 36, and 52) and PK samples collected per dedicated sparse sampling plan (4-5 samples per patient) across Weeks 1 through 24 and Early termination visit (ETV)]
Method of analysis	Efficacy and health outcomes were analysed with the intention-to-treat population defined as all patients who were randomly assigned. For categorical data, a logistic regression model (with Wald's test with treatment, geographical region, and previous TNF inhibitor use incorporated into the model) was used for comparisons unless otherwise noted. Patients who had missing data, who were deemed inadequate responders at week 16, or who discontinued treatment early were imputed as nonresponders. For continuous data, a mixed-effect model repeated measurement was used for comparisons. This model used treatment, visit, geographical region, previous TNF inhibitor use, treatment-by-visit interaction, geographical region-by-visit interaction, and TNF inhibitor use by visit as factors and with baseline and baseline value by visit interactions as continuous, fixed covariates.
Subgroup analyses	None published

7.2 EPAR upadacitinib, ixekizumab and adalimumab

Upadacitinib: https://www.ema.europa.eu/en/documents/variation-report/rinvoq-h-c-004760-ii-0004-epar-assessment-report-variation_en.pdf

Ixekizumab: https://www.ema.europa.eu/en/documents/variation-report/taltz-h-c-3943-ii-0009-epar-assessment-report-variation_en.pdf

Adalimumab: https://www.ema.europa.eu/en/documents/scientific-discussion-variation/humira-h-c-481-ii-22-epar-scientific-discussion-variation_en.pdf

7.3 Statistical methodology

As answering the clinical questions involved two comparators, and head-to-head data for only one comparator (adalimumab) existed, indirect therapy comparison was undertaken for the other comparator (ixekizumab). Upadacitinib was studied head-to-head vs. adalimumab in the SELECT PSA 1 trial.

Direct comparison; upadacitinib vs. adalimumab

For the outcomes efficacy analyses were conducted in the modified intention-to-treat population and at least 85% power for evaluating the noninferiority and superiority of each upadacitinib dose as compared with adalimumab.

For outcomes ACR50, serious adverse events, serious infections, modified total Sharp/van der Heijde score (CFB≤0.5) and relative effects were estimated using Mantel-Haenszel risk ratio with 95% confidence interval.

Risk ratio was estimated using the formula.

$$RR = \frac{rate(UPA)}{rate(ADA)}.$$

Confidence interval for RR was estimated using the formula

$$CI95\% = EXP\left(LN(RR) \pm 1.96 * \sqrt{\frac{(N_{UPA} - n_{UPA})/n_{UPA}}{N_{UPA}} + \frac{(N_{ADA} - n_{ADA})/n_{ADA}}{N_{ADA}}}\right).$$

Absolute effects, defined as risk-difference assuming comparator event rate were calculated using the estimated risk ratio from the analysis in the following formula:

$RD = ACR * (RR - 1)$, *where RD is risk difference, ACR is the event rate for the relevant outcome for adalimumab patients and RR is the risk ratio estimated as described above.*

where RD is risk difference, ACR is the event rate for the relevant outcome for adalimumab patients and RR is the risk ratio estimated as described above.

The estimated 95% confidence interval for RD was computed by inserting the low and high confidence limit estimated using the Mantel-Haenszel risk ratio 95% confidence intervals in the formula for RD.

Results for modified total Sharp/van der Heijde score (CFB≤0.5) are based on ANCOVA with linear extrapolation for missing data. The 95% CI for response rate are calculated based on normal approximation to binomial distribution. The 95 % CI for response rate difference are calculated based on normal approximation.

The relative risk is calculated based on formula described above.

Results for SF-36 outcomes are based on MMRM model. Within group LS mean and 95% CI, and between group LS mean difference and 95% CI are based on ANCOVA model including treatment and the stratification factor current DMARD use (yes/no) as fixed factors and baseline value as covariate.

Indirect comparison; upadacitinib vs. ixekizumab

The indirect treatment comparisons were conducted using the methodology described by Bucher et al. (1). This approach is widely used; it describes how to indirectly compare the odds ratios (OR) from randomised trials that share a common reference arm. Although Bucher et al. present their approach by using OR as the

measure of treatment effect, it may also be used when the relative efficacy is measured by risk ratio (RR) or by risk difference (RD) (2).

Indirect treatment comparisons were conducted in R (R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/).

7.4 Results per study

SELECT PsA-1

Trial name:	SELECT PsA-1									
NCT number:	NCT03104400									
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of method used for estimation**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**	
ACR50	UPA 15mg	429	52.4% (47.7, 57.2)	8.16%	1.49%, 14.8%	0.0164	1.18	1.03, 1.36	0.0173	Relative difference was estimated using Mantel-Haenszel risk ratio with 95% confidence interval. Absolute difference, defined as risk-difference assuming comparator event rate were calculated using the observed rates in each outcome.
	ADA 40mg EOW	429	44.3% (39.6, 49.0)							
Serious AE's	UPA 15mg	429	3.3% (1.7, 5.4)	-0.47%	-2.12%, 2.87%	0.7101	0.875	0.43, 1.77	0.7103	
	ADA 40mg EOW	429	3.7% (2.1, 6.0)							
mTSS (CFB≤0,5)	UPA 15mg	387	95.9% (93.9, 97.8)	0.98%	(-1.94%, 3.99%)	0.5147	1.01	0.98, 1.04	0.5149	
	ADA 40mg EOW	391	94.9% (92.7, 97.1)							
SF-36 physical component summary	UPA 15mg	398	9.66 (8.82, 10.50)	1.82	0.64, 2.99	NA	NA	NA	NA	Results for SF-36 outcomes are based on MMRM model. Within group LS mean and 95% CI, and between group LS mean difference and 95% CI are based on ANCOVA model including treatment and the stratification factor current DMARD use (yes/no) as fixed factors and baseline value as covariate.
	ADA 40mg EOW	403	7.84 (7.01, 8.66)							
SF-36 vitality	UPA 15mg	398	8.13 (7.23, 9.03)	1.93	0.64, 3.19	NA	NA	NA	NA	
	ADA 40mg EOW	305	6.20 (5.31, 7.09)							
SF-36 mental component summary	UPA 15mg	398	4.80 (3.89, 5.70)	0.55	-0.72, 1.82	NA	NA	NA	NA	
	ADA 40mg EOW	403	4.25 (3.36, 5.14)							

SELECT PsA-2

Trial name:	SELECT PsA-2									
NCT number:	NCT03104374									
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of method used for estimation**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**	
ACR50	UPA 15mg	211	38.4%	29%	21.3%, 36.61%	0.000	4.07	2.59, 6.39	0.0000	Relative difference was estimated using Mantel-Haenszel risk ratio with 95% confidence interval. Absolute difference, defined as risk-difference assuming comparator event rate were calculated using the observed rates in each outcome.
	Placebo	212	9.4%							
Serious AE's	UPA 15mg	211	5.7%	3.8%	1.8%, 7.42%	0.0397	3.01	0.99, 9.2	0.0525	
	Placebo	212	1.9%							
mTSS (CFB≤0,5)	UPA 15mg	NA	NA	NA	NA	NA	NA	NA	NA	
	Placebo	NA	NA							
SF-36 physical component summary	UPA 15mg	183	6.38 (5.28, 7.48)	5.04	3.45, 6.63	NA	NA	NA	NA	NA
	Placebo	168	1.34 (0.19, 2.49)							
SF-36 vitality	UPA 15mg	183	10.7 (8.1, 13.2)	7.7	4.0, 11.4	NA	NA	NA	NA	
	Placebo	168	3.0 (0.3, 5.7)							
SF-36 mental component summary	UPA 15mg	183	2.25 (0.98, 3.52)	1.88	0.05, 3.71	NA	NA	NA	NA	
	Placebo	168	0.37 (-0.95, 1.70)							

SPIRIT-P2

Trial name:	SPIRIT-P2									
NCT number:	NCT02349295									
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of method used for estimation**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**	
ACR50	IXE Q4W	122	35.2%	30.2%	20.8%, 39.52%	0.0000	6.93	3.07, 15.67	0.0000	Relative difference was estimated using Mantel-Haenszel risk ratio with 95% confidence interval. Absolute difference, defined as risk-difference assuming comparator event rate were calculated using the observed rates in each outcome.
	Placebo	118	5%							
Serious AE's	IXE Q4W	122	2.46%	-0.9%	-5.2%, 3.34%	0.669	0.73	0.17, 3.17	0.6698	
	Placebo	118	3.39%							
mTSS (CFB≤0,5)	IXE Q4W	122	NA	NA	NA	NA	NA	NA	NA	
	Placebo	118	NA							
SF-36 physical component summary	IXE Q4W	122	8.9 (6.35, 11.45)	5.6	3.2, 8.0	<0.0001	NA	NA	NA	For continuous data, analyses using last observation carried forward and modified baseline observation carried forward were performed.
	Placebo	118	3.3 (0.56, 6.04)							
SF-36 vitality	IXE Q4W	122	14.4	8.9	0.27, 17.52	NA	NA	NA	NA	
	Placebo	118	5.5							
SF-36 mental component summary	IXE Q4W	122	3.6	2.7	0.4, 5.0	0.02	NA	NA	NA	
	Placebo	118	0.9							

7.5 Results per PICO

TABLE 28 RESULTS REFERRING TO CLINICAL QUESTION 1

Results per outcome	Studies included in the	Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
		Difference	CI	*P* value	Difference	CI	*P* value	
ACR50	SELECT PsA-1	8.16%	1.49%, 14.8%	0.0164	1.18	1.03, 1.36	0.0173	Relative difference was estimated using Mantel-Haenszel risk ratio with 95% confidence interval. Absolute difference, defined as risk-difference assuming comparator event rate were calculated using the observed rates in each outcome. For continuous data, analyses using last observation carried forward and modified baseline observation carried forward were performed.
Serious AE's	SELECT PsA-1	-0.47%	-2.12%, 2.87%	0.7101	0.875	0.43, 1.77	0.7103	
mTSS (CFB≤0,5)	SELECT PsA-1	0.98%	-1.94%, 3.99%	0.5147	1.01	0.98, 1.04	0.5149	
SF-36 physical component summary	SELECT PsA-1	1.83	0.75, 2.91	NA	NA	NA	NA	
SF-36 vitality	SELECT PsA-1	1.93	0.76, 3.09	NA	NA	NA	NA	
SF-36 mental component summary	SELECT PsA-1	0.55	-0.62, 1.71	NA	NA	NA	NA	

TABLE 29 RESULTS REFERRING TO CLINICAL QUESTION 2

Results per outcome	Studies included in the	Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
		Difference	CI	*P* value	Difference	CI	*P* value	
ACR50	SELECT PsA-2 SPIRIT-P2	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	Bucher's Method
Serious AE's	SELECT PsA-1 SELECT PsA-2 SPIRIT-P1 SPIRIT-P2	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	Bucher's Method
mTSS (CFB≤0,5)	SELECT PsA- 2 SPIRIT-P2	NA	NA	NA	NA	NA	NA	NA
SF-36 physical component summary	SELECT PsA-2 SPIRIT-P2	[redacted]	[redacted]	NA	NA	NA	NA	Bucher's Method
SF-36 vitality	SELECT PsA-2 SPIRIT-P2	[redacted]	[redacted]	NA	NA	NA	NA	Bucher's Method
SF-36 mental component summary	SELECT PsA-2 SPIRIT-P2	[redacted]	[redacted]	NA	NA	NA	NA	Bucher's Method

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Economic application for the assessment of Rinvoq™ (upadacitinib) for psoriatic arthritis

Contents

1 Basic information

Table 1 Contact information

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Table 2 Overview of the pharmaceutical

Proprietary name	Rinvoq
Generic name	Upadacitinib
Marketing authorization holder in Denmark	AbbVie Deutschland GmbH & Co. KG
ATC code	L04AA44
Pharmacotherapeutic group	Janus kinase inhibitor (JAK)
Active substance(s)	Upadacitinib
Pharmaceutical form(s)	Prolonged-release tablet
Mechanism of action	Upadacitinib is a selective and reversible JAK inhibitor. In human cellular assays, upadacitinib preferentially inhibits signaling by JAK1 or JAK1/3 with functional selectivity over cytokine receptors that signal via pairs of JAK2
Dosage regimen	The recommended dose of upadacitinib is 15 mg once daily.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	RINVOQ is indicated to treatment of psoriatic arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs). RINVOQ may be used as monotherapy or in combination with methotrexate.
Other approved therapeutic indications	RA
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	Monotherapy or in combination with methotrexate
Packaging – types, sizes/number of units, and concentrations	Each pack contains 28, 15mg prolonged-release tablets
Orphan drug designation	No

2 Abbreviations

ACR: American college of rheumatology

ADA: Adalimumab

AE: Adverse Event

AIP: Pharmaceutical paying price

bDMARDS: Biologic disease-modifying antirheumatic drugs

csDMARDS: conventional synthetic disease-modifying antirheumatic drugs

DMARDs: Disease-modifying antirheumatic drugs

EBC: Extended basis of comparison

EMA: European Medicines Agency

EOW: every other week

IBD: inflammatory bowel disease

IR: Inadequate responder

IXE: Ixekizumab

IV: Intravenously

JAK: Januse kinase

JAKi: Januse kinase inhibitor

MDA: Minimal disease activity

MR: Medicinraadet

MTX: Methotrexate

NSAID: Non-steroidal anti-inflammatory drug

PsA: Psoriasis arthritis

PsARC: PsA Response Criteria

QoL: Quality of Life

RA: Rheumatoid arthrit

SC: Subcutaneously

SF-36: Short Form 36

SmPC: Summary of product Characteristics

TNF: Tumor Necrosis Factor

UPA: upadacitinib

VTE: venous thrombosis event

3 Summary

On January 25th 2021, upadacitinib received an approval from EMA for an extension of indication for the treatment of active psoriatic arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs). RINVOQ may be used as monotherapy or in combination with methotrexate.

There remains an unmet need for patients with PsA in the treatment landscape today. During the 21st annual international Advances in Targeted Therapies meeting, more than 100 scientists and clinical researchers were brought together to discuss the unmet need over several rheumatologic diseases, including PsA. [1] The group identified a range of unmet needs in PsA where the most pressing unmet needs are related to the need for improved efficacy, especially related to joint outcomes, higher achievement of MDA, a favorable safety profile and formulations that can offer greater patient convenience. Upadacitinib has shown through an extensive clinical trial program to meet these needs. Currently, no other JAKis are present in the Danish treatment recommendations for PsA and upadacitinib therefore represents a different and valuable treatment option to the existing TNF-inhibitors, IL-17 inhibitors and IL12/23 inhibitors. Upadacitinib is also the only novel therapy that offers oral administration once a day without the need for methotrexate. This simplifies the treatment routine for patients and can require fewer healthcare resources, compared with treatment administered via infusions or injections. The oral administration of upadacitinib also provides another treatment option for patients who are ineligible/do not want to use infusion and/or injection treatment. Considering the current COVID-19 pandemic, a simple oral treatment can provide an additional benefit with the reduced health care contacts, and thus reduction of risk of infection via close contact, compared to injection/infusion treatments.

The Medicines Council have stated in their protocol for evaluating upadacitinib that adalimumab is the relevant comparator for the bio-naïve population, and that Ixekizumab is the relevant comparator for the bio-experienced population.

A simple cost-analysis was adapted to evaluate the cost for upadacitinib as standard treatment of active psoriatic arthritis. The time horizon for the analysis is 18 months. Costs included in the analysis are drug costs, hospital costs and patient costs. The assumptions for the time horizon, hospital and patient costs as based on the extended base of comparison report (EBC) by the Medicines council, looking in the differences in costs between oral and subcutaneous therapies in the treatment of Rheumatoid Arthritis (RA).

The cost analysis for the bio-naïve population resulted in total costs for upadacitinib being approximately 35.000 DKK (AIP) per patient higher compared to adalimumab. For the bio-experienced population the cost analysis resulted in upadacitinib being cost saving, with total costs being approximately 30.000 DKK per patient lower compared to Ixekizumab.

The overall budget impact for a recommendation will not lead to any additional costs, but rather be cost saving. The analysis shows that the budget impact is approximately +111.000 DKK in year five for the bio-naïve population and approximately -7,9 million DKK for the bio experienced population in year 5. Overall, this leads to a cost saving of 7,77 million DKK (AIP). However, the analysis and budget impact calculations are based on list prices and upadacitinib is included in the tender with a discount resulting in even lower costs. In general, a recommendation of upadacitinib will lead to lower cost as the drug will be included and ranked in the clinical guidelines/recommendation for PsA and will therefore only be used instead of drugs that are more expensive. Overall, a recommendation of upadacitinib will contribute to more competition and cost savings for society.

On November 18th 2020 the Medicines Council decided to update the treatment guidelines and recommendation for PsA. A recommendation for upadacitinib will results in a new and valuable clinical option for a patient population with unmet needs, and lead to more competition in the market for biologic treatment of PsA.

4 Background

4.1 Disease description/pathophysiology

Psoriatic arthritis (PsA) is a common inflammatory arthritis of the peripheral and axial skeleton.(1) PsA can be distinguished from other spondyloarthropathies by the presence of peripheral arthritis, asymmetrical distribution of axial involvement, with lower levels of pain, and movement limitation.(2) Almost one-third of patients with psoriasis will also develop PsA approximately 10 years after initial psoriasis diagnosis. However, in 15% of cases, arthritis and psoriasis occur at the same time, or even precedes psoriasis.(3) PsA is associated with many comorbidities and extra-articular manifestation and besides psoriasis (69-98%) is also cardiovascular disease, inflammatory bowel disease (2%-4%), uveitis (1%-25%), diabetes, osteoporosis, depression, and anxiety common. This disease heterogeneity has a major negatively impact on both the patient and the health care resources needed by the patient group.

The pathophysiology of PsA is complex and not fully understood, with pathogenic variation across the different involved sites. PsA occurrence is immune-mediated and possibly shares pathogenic mechanisms with psoriasis.(4) It affects the skin, nail, bone, and enthesis in peripheral joints, and PsA may also affect axial joints. Around 30–50% of the patients have mono-/oligoarticular disease, 30–50% have symmetrical polyarthritis, and 5% have mainly axial disease.(5, 6) PsA manifestation is linked to the interaction between genetic, environmental, and immune mechanisms.

The hallmark of PsA consists of the coexisting progression of joint disease and skin inflammation, where joint pain is the most important parameter hampering daily activities. The clinical characteristics of PsA, particularly joint deformity, cause an increase in daily life impairment and work productivity impairment, causing a sharp decline in QoL. The severe physical effect of PsA is associated with higher frequency of healthcare visits and hospitalizations than patients suffering from psoriasis alone.(7) Joint deformity results in loss of function and limited movement of axial and peripheral joints such as the phalanges, which are essential for mediating movements involved in carrying out daily activities and working.

PsA also has a high economic burden, with high direct cost related to an increased health care resource utilization (8), and indirect costs due to work impairment and/or unemployment (9). This is mainly driven by disease severity and increased physical function impairment, as higher costs are associated with higher scores on measures of physical function, HAQ-DI(10).

4.2 Current Treatment

At the moment there is no cure for PsA. Current treatment is to target the patient's pain and symptoms. Treatment goals for patients is to achieve as low disease activity as possible and remission for optimizing patient's life quality and social life.

PsA is diagnosed using the CASPAR-criteria, but due to the heterogeneity of the disease a plethora of specific and composite measurements are used to assess the severity of the disease. The most used disease tool is Minimal Disease Activity (MDA), PsA Response Criteria (PsARC), and the ACR Response Criteria. Furthermore, measurements of axial involvements, enthesis, dactylitis, psoriasis, and different patient reported outcomes are the most important indicators of disease severity.

In the national treatment guidelines for PsA from the Danish Rheuma association it appears that validated clinical diagnose criteria's for PsA are missing, but classifications criteria's can be used as support. The diagnose is made by an objective exam of the musculoskeletal system and skin together with serology and biochemistry (11).

Over half of patients with PsA have reported that their primary goals for therapy including reducing symptoms are not met by current treatments.(12) Patients with PsA usually receive NSAIDs as first-line therapy, with the addition of csDMARDs in patients with low risk of progressive disease (under 5 joints affected) with methotrexate as a first choice.(3, 13) However, less than a quarter of patients treated with MTX achieve MDA.(14)

Following failure or intolerance to NSAIDs and csDMARDs, the current treatment guideline in Denmark is to treat patients according to the Danish national treatment recommendations for PsA. The treatment recommendation for PsA differentiate between patients with or without moderate to severe plaque psoriasis and former or existing uveitis or former or existing inflammatory bowel disease (IBD). Currently the TNF-inhibitor adalimumab is recommended as first choice for all patient groups.(15) The next options for patients are another TNF-inhibitor, IL-17 inhibitor and IL-12/23 inhibitor. Ixekizumab is the first choice after TNF-inhibitors for bio-experienced patients. For patients with former or existing comorbidities, uveitis or IBD, options are rather limited as the only 2nd choice options in the guidelines is another TNF-inhibitor or IL12/23 inhibitor (Crohns disease only).

Currently there exist no JAK inhibitors in the Danish treatment guidelines or recommendations for PsA as tofacitinib was removed due to safety concerns regarding VTE(15). Therefore, there is a need for a new JAK-inhibitor with a proven efficacy and a well-defined safety profile.

4.3 Patient population

The prevalence is difficult to estimate due to unclear diagnostic criteria, however it is estimated to be between 6.000 - 25.000 of the danish population (16),(17). PsA normally develops in early 40s and 50s, with no difference between genders.

In the protocol for assessing the clinical added value of upadacitinib published by the Medicines Council on April 26th it is stated that at the end of 2019, 2560 patients with PsA were currently on biologic treatment, of which 330 patients were bio- naïve and approx. 860 patients were bio-experienced (switch patients). The population includes patients with moderate to severe plaque psoriasis uveitis, Chron's disease and colitis ulcerosa.(11)

The analysis includes following populations as requested in the protocol by the Medicines Council:

- Bio-naive patients with PsA
- Bio-experienced patients with PsA

4.4 Upadacitinib

Upadacitinib is an oral JAK-inhibitor, with a greater selectivity for JAK1 over the three other tyrosine kinases in the JAK family, that is administered as a tablet once daily regardless of food intake. The inhibition of JAK1 mediated signaling pathway inhibits several of the key inflammatory mediators in patients with spondylarthritis and was in 2019 approved for the treatment of RA. Upadacitinib may be used as a monotherapy or in combination with methotrexate.

The efficacy and safety of upadacitinib 15 mg has been assessed in two dedicated phase III studies in both patients previously failing non-biological DMARDs (SELECT PsA-1) and biological DMARD failures (SELECT PsA-2).

In SELECT PsA 1, Upadacitinib 15 mg demonstrated a significantly higher proportion of patients who achieved the primary endpoint of ACR20 at Week 12 compared to placebo. Importantly upadacitinib also achieved the secondary endpoint of non-inferiority compared with adalimumab for ACR20 at week 12 and was numerically better on the other assessed outcomes. At week 24 upadacitinib 15mg also demonstrated significant improvements on PsARC, ACR20/50/70, enthesitis, axial improvement, physical function, and pain compared with adalimumab. At week 12 upadacitinib also demonstrated significant improvements compared with both placebo and adalimumab ($p<0.05$) for SF-36. Patients treated with upadacitinib showed substantial improvements in QoL with upadacitinib demonstrating

significant improvements compared to both placebo ($p<0.001$) and adalimumab ($p<0.05$) at week 12. Upadacitinib showed significantly greater MDA response compared with placebo at week 24, and a numerical higher, although non-significant, MDA response compared with adalimumab.

In SELECT PsA-2 the study met its primary endpoint with a significantly higher proportion of patients achieving ACR20 compared with placebo. Upadacitinib 15 mg was significantly greater compared with placebo for all other measurements, including the highly important measures PsARC, MDA, and HAQ-DI, with similar response rates regardless of the number of previous biological DMARDS used.

Both studies showed the risk profile to be in line with the clinical program for upadacitinib across indications, with no new safety signals detected.

Upadacitinib has the potential to meet the needs of patients with PsA that offers significant improvement of the most burdensome symptoms related to PsA such as joint pain, enthesitis, dactylitis, and pain in both DMARD-IR and bDMARD-IR patients. Upadacitinib has also demonstrated significant improvement on radiographic involvement, skin involvement, back pain, patient reported outcomes (including improvements in fatigue, disability as well as physical QoL) with significantly more patients achieving MDA and PsARC compared with placebo. Importantly, significantly higher response rates were observed over time compared with adalimumab in patients treated with upadacitinib for ACR20/50/70, enthesitis, BASDAI, ASDAS, HAQ-DI, pain, PsARC, and SF-36 PCS, which in turn can help patients improve their work participation and reduce societal costs. The safety profile of upadacitinib is well-characterized and is consistent in PsA compared to previous trials across indications. There were no new safety signals identified in patients with PsA.(18)

Additionally, upadacitinib is the only novel therapy for PsA that offers a simple once daily oral administration without the need for methotrexate. This simplifies the treatment routine for patients compared to treatments administered via infusions and injections. Compared to infusion treatments where patients need to go to the hospital or treatments where patients need to be trained by health professionals to administer the treatment, an oral administered therapy can require fewer healthcare resources.

The oral administration of upadacitinib also provides another treatment option for patients who are ineligible/do not want to use infusion and/or injection treatment. Considering the current COVID-19 pandemic, a simple oral treatment can provide an additional benefit with the reduced health care contacts, and thus reduction of risk of infection via close contact, compared to injection/infusion treatments.

4.5 Comparators

Relevant comparators to upadacitinib in PsA is according to the Medicine council's protocol adalimumab for the bio-naive patient population and ixekizumab for the bio-experienced patient population.

The approved dosing for adalimumab in PsA is 40 mg every two weeks, administered subcutaneously.

The approved dosing for ixekizumab is 160 mg at week zero, then 80 mg every fourth week, administered subcutaneously.

4.6 Model description

In the application for the assessment of clinical added value of upadacitinib in PsA, the results showed that upadacitinib is at least as effective as the comparators adalimumab and Ixekizumab for the treatment of bio-naïve and bio-experienced patients with active PsA. Furthermore, adalimumab and Ixekizumab are both assessed to be clinically equal to the rest of the drugs mentioned in the Medicines Council recommendation for the treatment of PsA. Therefore, a simple cost analysis of upadacitinib and the relevant comparators (adalimumab and Ixekizumab) in the clinical assessment has been performed. The costs included in the analysis are drug cost, hospital costs (monitoring and administration), patient time- and transportation costs.

Costs for adverse events and monitoring of the disease is assumed to be the same between treatments. See 4.7 for argumentation of equal efficacy and safety between upadacitinib and the comparators.

The hospital costs (monitoring and administration) and patient time and transportation costs are based on Medicine Council's EBC from the treatment area RA.

4.7 Efficacy and safety between the comparators

The efficacy and safety of upadacitinib vs. adalimumab for the bio-naïve population (clinical question 1) and vs. Ixekizumab (clinical question 2) for the bio-experienced population is assumed to be clinically equal in this cost analysis.

The assumption for the bio-naïve population is based on the Select PsA-1 study, which investigated the efficacy and safety of upadacitinib vs. placebo and adalimumab in patients with active PsA who have had an inadequate response to at least one non-biologic DMARD (DMARD-IR). Results from the comparative analysis in the clinical part on efficacy and safety outcomes defined in the protocol demonstrated that upadacitinib is at least clinically equal to adalimumab. The safety analysis from Select PsA-1 also demonstrated the overall safety profile of upadacitinib to be comparable to adalimumab, see Table 1 for the safety between adalimumab and upadacitinib. See Table 9 for the difference in costs related to side effects for both treatments. Cost for AE's are included if more than 5% of the patients experience it. Not to include AE's in the cost analysis is a conservative estimate, however the difference is small.

Therefore, AbbVie find it reasonable to assume similar efficacy and safety for upadacitinib and adalimumab in the cost analysis.

TABLE 1: OVERVIEW OF SAFETY IN SELECT PSA-1 THROUGH TO WEEK 24

	Placebo (N=423)		Adalimumab 40mg EOW (N=429)		Upadacitinib 15 mg QD (N=429)	
Subjects with:	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Any Adverse Event (AE)	252	(59.6)	278	(64.8)	287	(66.9)
Any Serious AE	13	(3.1)	16	(3.7)	14	(3.3)
Any AE Leading to Discontinuation of Study Drug	13	(3.1)	22	(5.1)	13	(3.0)
Any Severe AE	16	(3.8)	27	(6.3)	21	(4.9)
Any AE With Reasonable Possibility of Being Related to Study Drug	120	(28.4)	167	(38.9)	157	(36.6)
Deaths	1	(0.2)	0		0	
Occurring ≤30 days (for ADA 70 days) after last dose)	1	(0.2)	0		0	
Occurring >30 days (for ADA 70 days) after last dose)	0		0		0	

Subjects with:	Placebo (N=423)		Adalimumab 40mg EOW (N=429)		Upadacitinib 15 mg QD (N=429)	
	n	(%)	n	(%)	n	(%)
Any Infection	140	(31.1)	146	(34.0)	169	(39.4)
Any Serious Infection	4	(0.9)	3	(0.7)	5	(1.2)
Any Opportunistic Infection excluding TB and herpes zoster	0		0		1	(0.2)
Any possible malignancy	1	(0.2)	4	(0.9)	3	(0.7)
Any Malignancy	1	(0.2)	3	(0.7)	1	(0.2)
Any Non-Melanoma Skin Cancer (NMSC)	1	(0.2)	0		0	
Any malignancy other than NMSC	0		3	(0.7)	1	(0.2)
Any Lymphoma	0		0		0	
Any Hepatic Disorder	16	(3.8)	67	(15.6)	39	(9.1))
Any Gastrointestinal Perforation	0		0		0	
Any Anemia	4	(0.9)	1	(0.2)	3	(0.7)
Any Neutropenia	1	(0.2)	10	(2.3)	4	(0.9)
Any Lymphopenia	5	(1.2)	1	(0.2)	6	(1.4)
Any herpes zoster	3	(0.7)	0		4	(0.9)
Any Creatine Phosphokinase (CPK) Elevation	6	(1.4)	24	(5.6)	38	(8.9)
Any Renal Dysfunction	1	(0.2)	0		0	
Any active tuberculosis	0		0		0	
Any Adjudicated MACE*	1	(0.2)	2	(0.5)	0	
Any Adjudicated VTE **	1	(0.2)	2	(0.5)	0	

Source: McInnes et al 2021 (19)

The assumption for the bio-experienced population is based on an indirect analysis of efficacy data from Select PsA-2 and Spirit P2 and an indirect analysis of safety data from Select PsA-1, Select PsA-2 and Spirit-P1 and Spirit-P2. Results from the comparative analysis on efficacy and safety outcomes defined in the protocol demonstrated no clinically relevant difference between upadacitinib and Ixekizumab.

A narrative description of safety results from both Select PsA-2 and Spirit P2 suggest comparable safety profiles and that difference in costs related to side effects for both treatments is negligible. See Table 2 and Table 3 for all safety results of SPIRIT-P2 and Select PSA-P2. See Table 10 for the cost difference, where only AE's experienced by more than 5 % of the patients are included. The results for the included AE's indicate higher cost for Ixekizumab than upadacitinib. Not including AE's in the cost analysis is a conservative estimate.

Table 4 compares key adverse events results from the upadacitinib arm in Select PsA-2 and the ixekizumab arm in Spirit-P2. This comparison shows that upadacitinib had a lower rate of "any infection" of 5,4 percentage points compared to Ixekizumab. For any of the other outcomes, the difference was not bigger than 5 percentage points.

All in all, when considering the indirect analysis as well as the narrative description of the safety profile and the difference in cost, AbbVie finds it conservative but reasonable to assume similar efficacy and safety for upadacitinib and Ixekizumab in the cost analysis.

TABLE 2: OVERVIEW OF SAFETY IN SELECT PSA-2 THROUGH WEEK 24

Subjects with:	Placebo (N=212)		Upadacitinib 15 mg (N=211)	
	n	(%)	n	(%)
Any Adverse Event (AE)	139	(65.6)	135	(64.0)
Any Serious AE	4	(1.9)	12	(5.7)
Any AE Leading to Discontinuation of Study Drug	11	(5.2)	15	(7.1)

Any Severe AE	8	(3.8)	13	(6.2)
Any AE With Reasonable Possibility of Being Related to Study Drug	17	(18.1)	27	(29.0)
Deaths	1	(0.5)	0	
Any Infection	76	(34.4)	71	(33.6)
Any Serious Infection	1	(0.5)	1	(0.5)
Any Opportunistic Infection	0		1	(0.5)
Herpes Zoster	2	(0.9)	3	(1.4)
Tuberculosis	0		0	
Any Malignancy	0		3	(1.4)
Any Non-Melanoma Skin Cancer (NMSC)	0		1	(0.5)
Any Lymphoma	0		1[a]	(0.5)
Any Hepatic Disorder	3	(1.4)	4	(1.9)
Any Gastrointestinal Perforation	0		0	
Any Anemia	2	(0.9)	4	(1.9)
Any Neutropenia	1	(0.5)	2	(0.9)
Any Lymphopenia	0		2	(0.9)
Any Creatine Phosphokinase (CPK) Elevation	4	(1.9)	4	(1.9)
Any Renal Dysfunction	1	(0.5)	0	
Any Adjudicated MACE	0		1	(0.5)
Any Adjudicated VTE	0		1	(0.5)

Source: Mease et al 2020 (20)

TABLE 3: OVERVIEW OF SAFETY IN SPIRIT-P2 THROUGH WEEK 24

	Placebo (N=118)		Ixekizumab every 4 weeks (N=122)	
Subjects with:	**n**	**(%)**	**n**	**(%)**
Treatment-emergent adverse event				
Any Adverse Event (AE)	76	(64)	83	(68)
Mild	32	(27)	48	(39)
Moderate	42	(36)	31	(25)
Severe	2	(2)	4	(3)
Most frequent treatment-emergent adverse events				
Injection site reaction	1	(1)	8	(7)
Upper respiratory tract infection	9	(8)	11	(9)
Nasopharyngitis	4	(3)	8	(7)
Sinusitis	2	(2)	7	(6)
Diarrhoea	3	(3)	5	(4)
Urinary tract infection	3	(3)	6	(5)
Cough	3	(3)	4	(3)
Oropharyngeal pain	0	-	7	(6)
Headache	3	(3)	5	(4)
Hypertension	3	(3)	2	(2)
Injection-site erythema	0	-	2	(2)
Injections site hypersensitivity	0	-	1	(1)

Back pain	2	(2)	5	(4)
Bronchitis	4	(3)	1	(1)
Psoriatic arthropathy	8	(7)	2	(2)
Adverse events				
Serious AE	4	(3)	3	(2)
Any Serious Infection	0	(0)	0	(0)
Discontinuation due to adverse event	6	(5)	5	(4)
Adverse events of special interest				
Any Infection	35	(30)	47	(39)
Any candida infection	0	-	2	(2)
Active or reactivated tuberculosis	0	-	0	-
Hepatic events	2	(2)	2	(2)
Allergic reactions or hypersensitivities	1	(1)	8	(7)
Injections-site reactions	5	(4)	14	(11)
Cerebrocardiovascular events	2	(2)	0	-
Malignancies	0	-	2	(2)
Depression	3	(3)	2	(2)

Source: Nash et al 2017 (21)

TABLE 4: COMPARISON ON KEY SAFETY OUTCOMES BETWEEN UPADACITINIB 15MG AND IXEKIZUMAB Q4W AT WEEK 24

	Upadacitinib 15 mg QD (N=211)		Ixekizumab every 4 weeks (N=122)		Difference between UPA and IXE
Subjects with:	**n**	**(%)**	**n**	**(%)**	**%**
Any Adverse Event (AE)	135	(64.0)	83	(68)	-4
Any Serious AE	12	(5.7)	3	(2)	3,7
Any Severe AE	13	(6.2)	4	(3)	3.2
Any Infection	71	(33.6)	47	(39)	-5.4
Any Serious Infection	1	(0.5)	0	-	0,5
Any Malignancy	3	(1.4)	2	(2)	-0.6

Source: Mease et al 2020, Nash et al 2017 (20, 21)

For more information regarding the comparative clinical analyses, see “Application for the assessment of clinically added value of Rinvoq (upadacitinib) for psoriatic arthritis”.

The pharmaceutical recommendation for the treatment of PsA in Denmark is ranked according to clinical equality and price. As shown above, upadacitinib have shown to be at least clinically equal to adalimumab and Ixekizumab in the bio-naïve and bio-experienced population without moderate to severe plaque psoriasis. Due to this and that The Medicines Council recommendations considers the other treatment alternatives in the recommendations (with the exception of ustekinumab) to be clinically equal, AbbVie finds it reasonable to assume clinical equality between upadacitinib and the other comparators in the cost analysis.

4.8 Time horizon and perspective

The cost analysis is considered to have a limited societal cost perspective, and a time horizon of 18 month.

18 months is used as the basis for calculating treatment length for RA in the Medicines Council's treatment guidelines as well as by RADS in developing pharmaceutical recommendations for PsA (22). Furthermore, treatments for RA and PsA are primarily the same type of treatments with the same dosing schedule regardless of indication. Therefore, AbbVie have also based the cost calculations on an 18-month time horizon.

Also, this timeline will capture all relevant differences in the treatments. Cost after year 1 is discounted with 3,5% in line with suggested methodology in the MR methods.

5 Cost

5.1 Drug cost

All drug costs in the cost analysis and budget impact analysis are based on the PPP (AIP) from medicinpriser.dk.

Doses are estimated based on the approved dosing regimen in SmPC. See Table 5 for strength, pack size, units and cost. Treatment with methotrexate is excluded in the analysis as it is expected to be the same between treatments.

Drug wastage is not included as it is unknown how often it occurs in clinical practice for these drugs.

TABLE 5: STRENGTH, PACK SIZE AND COST PER PACK FOR UPA, ADA AND IXE

Drug	Strength	Pack size	AIP (DKK)
Upadacitinib	15 mg	28 pc.	6.641,45
Adalimumab	40 mg	2 pc.	4.712,25
Ixekizumab	80 mg	1 pc.	7.565,49
Secukinumab	150 mg	2 pc.	7.908,00
	300 mg	1 pc.	
Certolizumab	200 mg	2 pc.	7.305,00

5.2 Monitoring and administration costs

For the monitoring and administrations cost an overall cost based on Medicine Council's EBC from treatment area RA was used.(23) AbbVie considers that these costs are relevant since they are based on input from all five danish regions regarding costs and resource use associated with treatment of biologic treatments given subcutaneous and orally.

Costs for hospital monitoring for tofacitinib is considered to be representable for upadacitinib, as both drugs are JAK-inhibitors with the same administration method.

Adalimumab is represented in the EBC in RA from the Medicine council, and the same costs are therefore used for adalimumab in PsA.

Ixekizumab is not represented in the EBC for RA, but we assume that the costs for ixekizumab will be comparable with certolizumab as that is also a subcutaneous regime. Certolizumab is dosed 21 times during an 18-month period which is the same dosing frequency as for ixekizumab. Therefore, we think using the costs related to Certolizumab is a relevant estimation of patient time and costs for ixekizumab.

TABLE 6: HOSPITAL- AND ADMINISTRATIONS COST OVER 18 MONTHS FROM THE EBC, UNDISCOUNTED

(DKK)		Upadacitinib	Adalimumab	Ixekizumab
Worktime	Doctor	2.753	2.550	2.550
	Nurse	1.852	2.114	2.114
Diagnostics test	Utenciles	-	78	78
Diagnostics test	Bloodtest	1.437	1.421	1.421
Others	Rooms	65	72	72
Sum hospital and administration cost		6.107	6.235	6.235

Reference: (23)

In the EBC costs for doctor time and blood tests are calculated to be higher for tofacitinib than for subcutaneous treatment. Tofacitinib is currently the only oral treatment included in the EBC and it is stated that there is limited experience with oral treatments (tofacitinib), so that the costs are based on assumptions(23). Compared to tofacitinib, upadacitinib is given orally only once a day without the need for methotrexate which can impact the doctor time and blood test to be lower than estimated in the EBC. However, this is the best estimate of the monitoring and administration costs that we currently have and is a conservative estimate for hospital costs related to upadacitinib.

5.3 Patient- and transport costs

Patient time and transport costs are also estimated based on the Medicines Council EBC.

TABLE 7: PATIENT TIME AND TRANSPORT OVER 18 MONTHS, UNDISCOUNTED

(DKK)		Upadacitinib	Adalimumab	Ixekizumab
Patient cost	Patient time	1.284	2.256	1.813
	Transport	1.651	1.642	1.642

Reference: (23)

5.4 Cost for AE's

The cost difference between AE's were estimated for the argumentation of exclusion. AE's experienced by more than 5 % of the patients in the studies are included.

See Table 8 for the cost resources used per AE.

TABLE 8: AE'S UNIT COST AND DRG TARIFF

AE	Unit cost (DKK)	SOURCE
Hepatic Disorder	2.610	DRG 2021: 07MA98: MDC07 1-dagsgruppe, pat. mindst 7 år
Creatine Phosphokinase (CPK) Elevation	1.617	DRG 2021: 08MA98: MDC08 1-dagsgruppe, pat. mindst 7 år
Injection site reaction	1.617	DRG 2021: 08MA98: MDC08 1-dagsgruppe, pat. mindst 7 år
Upper respiratory tract infection	1.862	DRG 2021: 03MA98: MDC03 - 1-dagsgruppe, pat. Mindst 7 år
Nasopharyngitis	147,09	GP visit (2021 value): https://www.laeger.dk/sites/default/files/honorartabel_01.10.20.pdf
Sinusitis	147,09	GP visit (2021 value): https://www.laeger.dk/sites/defa

		ult/files/honorartabel_01.10.20.pdf
Allergic reactions or hypersensitivities	4.888	DRG2021: 21MA01: Allergiske og allergi lignende reaktioner

See Table 9 for cost difference in AE's between upadacitinib and adalimumab

TABLE 9: AE COST DIFFERENCE UPA VS. ADA

AE	ADA	UPA
Hepatic Disorder	40.716	23.751
Creatine Phosphokinase (CPK) Elevation	9.055,2	14.391,3
Total cost	49.771,2	38.142,3
Cost difference		**-11.628,9**

See Table 10 for the cost difference in AE's between upadacitinib and ixekizumab.

TABLE 10: AE COST DIFFERENCE UPA VS. IXE

AE	IXE	UPA
Injection site reaction	11.319	-
Upper respiratory tract infection	16.758	-
Nasopharyngitis	1.029,63	-
Sinusitis	882,54	-
Allergic reactions or hypersensitivities	11.319	-
Total cost	41.308,17	-
Cost difference		**-41.308,17**

The results for the included AE's indicate higher cost for adalimumab and ixekizumab than upadacitinib. Not including AE's in the cost analysis is a conservative estimate. However, it is difficult to compare the cost of adverse events between the treatment as the adverse events differs between the studies SELECT-PsA-2 and SPIRIT-P2 as more information about unit cost exist for AE's in SPIRIT-P2. Therefore, Abbvie find it reasonable to assume similar cost regarding safety although it looks to be conservative to not include.

5.5 Sensitivity analysis

The primary cost driver of this analysis are drug costs and therefore no sensitivity analysis is needed.

6 Results

6.1 Base case

Table 11 shows the result for the cost difference between upadacitinib compared to adalimumab and ixekizumab.

TABLE 11: PER PATIENT COST OVER 18 MONTHS, DISCOUNTED, DKK, AIP

	Upadacitinib	Adalimumab	Ixekizumab
Drug cost	128.772	91.367	157.972
Monitoring cost	6.241	6.241	6.113
Patient cost	3.458	3.902	2.938
Total cost	138.471	101.509	167.023
Incremental cost		**36.962**	**-28.551**

Results of the analysis show that the incremental cost per patient at list price (AIP) is 36.754 DKK per patient for upadacitinib vs adalimumab.

For upadacitinib compared to Ixekizumab the incremental cost per patients at list price (AIP) is –28.391 DKK per patient.

7 Budget impact

For the recommendation of upadacitinib the cost consequences for the regions needs to be assessed. Therefore, budget impact is estimated in two scenarios.

- Upadacitinib is recommended by the Medicine Council as a standard treatment for patients with PsA.
- Upadacitinib is not recommended by the Medicine Council as a standard treatment for patients with PsA.

The budget impact is the difference between the two scenarios.

7.1 Estimating patient population

In 2019, 2560 patients were registered with being treated with csDMARDs for PsA in the DANBIO registry, of which 330 patients started the treatment that year (bio naïve) and approximately 860 patients switched treatment (bio experienced). The patient population includes patients with moderate to severe plaque psoriasis, uveitis, Chron's disease and ulcerative colitis. (11)

In the current treatment recommendations, TNF-inhibitors (adalimumab, infliximab and etanercept) are ranked highest and we assume that it will be used by at least 90% of bio-naïve patients. We assume that the other 10% will need a different treatment due to contraindications, patient preference etc., most likely secukinumab 150mg or ixekizumab as they are the next alternatives in the recommendations for bio-naïve patients. Since upadacitinib potentially will be the only JAK-inhibitor and orally administered treatment in the recommendation we assume a small proportion of patients eligible for secukinumab and ixekizumab will instead be treated with upadacitinib. See Table 12 and Table 13 for assumed market shares.

TABLE 12: MARKET UPTAKE BIO NAIVE, NOT RECOMMENDED

	Year 1	Year 2	Year 3	Year 4	Year 5
Adalimumab	90 %	90 %	90 %	90 %	90 %
Upadacitinib	0 %	0 %	0 %	0 %	0 %
Secukinumab 150 mg	5 %	5 %	5 %	5 %	5 %
Ixekizumab	5 %	5 %	5 %	5 %	5 %

TABLE 13: MARKET UPTAKE BIO NAIVE, RECOMMENDED

	Year 1	Year 2	Year 3	Year 4	Year 5
Adalimumab	90 %	90 %	90 %	90 %	90 %
Upadacitinib	2 %	3 %	4 %	4 %	4 %
Secukinumab 150 mg	4 %	3,5 %	3 %	3 %	3 %
Ixekizumab	4 %	3,5 %	3 %	3 %	3 %

For the bio experienced population, we assume that 10 % will be treated with a TNF-inhibitor (most likely adalimumab) and that most patients (70 %) will get ixekizumab since that is the cheapest alternative for biologic treatments after TNF's today. We assume that upadacitinib will take market shares from secukinumab 300mg and

certolizumab pegol since they are preferred after Ixekizumab in the recommendation for PsA. See Table 14 and Table 15 for market shares.

TABLE 14: MARKET UPTAKE BIO EXPERIENCED, NOT RECOMMENDED

	Year 1	Year 2	Year 3	Year 4	Year 5
Adalimumab	10 %	10 %	10 %	10 %	10 %
Upadacitinib	0 %	0 %	0 %	0 %	0 %
Secukinumab 300 mg	15 %	15 %	15 %	15 %	15 %
Ixekizumab	70 %	70 %	70 %	70 %	70 %
Certolizumab Pegol	5 %	5 %	5 %	5 %	5 %

TABLE 15: MARKET UPTAKE BIO EXPERIENCED, RECOMMENDED

	Year 1	Year 2	Year 3	Year 4	Year 5
Adalimumab	10 %	10 %	10 %	10 %	10 %
Upadacitinib	7,5 %	14 %	14 %	14 %	14 %
Secukinumab 300 mg	10 %	5 %	5 %	5 %	5 %
Ixekizumab	70 %	70 %	70 %	70 %	70 %
Certolizumab Pegol	2,5 %	1 %	1 %	1 %	1 %

7.2 Result base case

The budget impact analysis does not include patient costs and discounting. Time on treatment for bio-naïve patients are based on the EBC that states that patients are on average on treatment for 1,5 years. After this period patients in the bio-naïve budget impact calculation are assumed to discontinue and not followed further as they are not bio-naïve anymore.

For the bio-experienced population we assume that the starting population is 860 patients (See section 4.3) each year and that time on treatment is on average the same as for the bio-naïve population, ie. 1,5 years. This is a simplification since in clinical practice bio-experienced patients will start on another treatment (3th and 4th treatment lines) when they stop responding or become intolerant to treatment. However, this scenario would complicate the model without contributing with a more realistic outcome as it is uncertain how the treatment pattern and market share is between all the drugs included in the recommendation.

The results of the budget impact analysis for the bio-naïve and bio-experienced population are presented below in Table 16 and Table 17.

TABLE 16: BUDGET IMPACT RESULTS, BIO NAÏVE, DKK, AIP

	Year 1	Year 2	Year 3	Year 4	Year 5
If recommended	22.325.132	33.421.419	33.449.221	33.465.012	33.465.012
if not recommended	22.301.111	33.353.805	33.353.805	33.353.805	33.353.805
Total	**24.021**	**67.613**	**95.415**	**111.207**	**111.207**

TABLE 17: BUDGET IMPACT RESULTS, BIO EXPERIENCED, DKK, AIP

	Year 1	Year 2	Year 3	Year 4	Year 5
If recommended	90.670.847	137.123.421	134.931.105	134.931.105	134.931.105
if not recommended	92.485.526	142.813.399	142.813.399	142.813.399	142.813.399
Total	**-1.814.679**	**-5.689.978**	**-7.882.294**	**-7.882.294**	**-7.882.294**

Results shows that if upadacitinib is recommended for the bio-naïve population the budget impact is 111.207 DKK in year 5. If upadacitinib is recommended for the bio-experienced population, the budget impact is -7.882.294 DKK in year 5.

Overall, the budget impact analysis shows that recommending upadacitinib for the treatment of PsA is cost saving.

8 Discussion

A recommendation to include upadacitinib in the recommendations as standard care for patients with PsA leads to an incremental cost of 36.962 DKK per patient compared to adalimumab and incremental cost saving of –28.551 DKK per patient compared to Ixekizumab per patient over 18 months.

The overall budget impact for a recommendation will not lead to any additional costs, but rather be cost saving. The analysis shows that the budget impact is approximately +111.000 DKK in year five for the bio-naïve population and approximately -7,9 million DKK for the bio experienced population in year 5. Overall, this leads to a cost saving of 7,77 million DKK (AIP). However, the analysis and budget impact calculations are based on list prices and upadacitinib is included in the tender with a discount resulting in even lower costs. In general, a recommendation of upadacitinib will lead to lower cost as the drug will be included and ranked in the clinical guidelines/recommendation for PsA and will therefore only be used instead of drugs that are more expensive. Overall, a recommendation of upadacitinib will contribute to more competition and cost savings for society.

Furthermore, it is possible that the estimated hospital- and patient cost for upadacitinib is conservative due to the calculation of resource use (doctor time, blood test) is based on tofacitinib with limited experience with the drug. Compared to tofacitinib, upadacitinib is given orally only once a day without the need for methotrexate which can impact the doctor time and blood test. Additionally, upadacitinib has not reported the same safety concerns as tofacitinib, a factor that could also impact resource use calculations. Due to the limited experienced with an oral treatment regime in the EBC, upadacitinib could potentially lead to lower monitoring- and patient cost than estimated in this analysis, possibly making the calculations used in this analysis for upadacitinib conservative.

There are no other JAKis present in the Danish treatment recommendations for PsA and upadacitinib therefore represent a new mode of action and is a valuable treatment option to the existing TNF-inhibitors, IL-17 inhibitors, and IL12/23 inhibitors. Upadacitinib is also the only novel therapy that offers oral administration once a day without the need for methotrexate. This simplifies the treatment routine for patients and can require fewer healthcare resources, compared with treatment administered via infusions or injections, such as the comparators adalimumab and ixekizumab. The oral administration of upadacitinib also provides another treatment option for patients who are ineligible/do not want to use infusion and/or injection treatment. Considering the current COVID-19 pandemic, a simple oral treatment can provide an additional benefit with the reduced health care contacts, and thus reduction of risk of infection via close contact, compared to injection/infusion treatments.

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Medicinrådet

Medicinrådets protokol for vurdering vedrørende upadacitinib til behandling af psoriasisartrit

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.

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1. Begreber og forkortelser

ACR50: *American College of Rheumatology 50 % response*

bDMARD: Biologisk *Disease Modifying Anti-Rheumatic Drug*

CRP: C-Reaktivt Protein

csDMARD: Konventionel *Disease Modifying Anti-Rheumatic Drug*

DANBIO Dansk Reumatologisk Database

DMARD: Sygdomsmodificerende antireumatisk lægemiddel (*Disease Modifying Anti-Rheumatic Drug)*

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)*

IL-17: Interleukin 17

IL-23: Interleukin 23

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

ITT: *Intention-to-treat*

MKRF: Mindste klinisk relevante forskel

mTSS: *Modified Total Sharp Score*

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

PASI: *Psoriasis Area Severity Index*

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

PsA: Psoriasisartrit

SF-36: Short Form 36

SMD: *Standardized Mean Difference*

tsDMARD: Targeteret syntetisk *Disease Modifying Anti-Rheumatic Drug*

VAS: *Visual Assessment Scale*

VTE: Venøs tromboemboli

2. Introduktion

Protokollen er udarbejdet, fordi Medicinrådet har modtaget en foreløbig ansøgning fra Abbvie, som ønsker, at Medicinrådet vurderer upadacitinib (Rinvoq®) til psoriasisartrit. Medicinrådet modtog den foreløbige ansøgning den 30. december 2020. Abbvie fik forhåndsgodkendelse (positive opinion) i EMA den 10. december 2020.

2.1 Psoriasisartrit

Psoriasisartrit (PsA) er en kronisk inflammatorisk ledsygdom, der ofte (men ikke nødvendigvis) optræder sammen med den kroniske hudsygdom psoriasis [1,2]. Patogenesen er en T-celle-medieret inflammation og involverer en kompleks række interaktioner mellem immunceller og proinflammatoriske cytokiner, hvor T-celler og makrofager rekrutteres til led- og hudvæv [3]. Disse immunceller fremmer derefter inflammatoriske processer involveret i sygdommen, hvoraf inflammation medieret af det ekstracellulære interleukin 17 og 23 (IL-17 og IL-23) ser ud til at spille en nøglerolle [3–6]. Sygdommen er multifaktoriel og betinget af både genetiske og miljømæssige faktorer [7].

PsA kan både manifestere sig ved inflammation i perifere led og i rygsøjlen, og der kan desuden optræde ekstraartikulære symptomer som inflammation i senetilhæftninger (entesit), hævede fingre eller tæer (daktylit) og negledystrofi [8]. Patienterne kan også have betændelse i øjets regnbue- og årehinde (uveitis) eller have kronisk inflammatorisk tarmsygdom. Det kan være vanskeligt at skelne diagnostisk mellem PsA med aksial involvering og rygsøjlegigt (spondylartrit) af anden art. De kliniske manifestationer varierer betydeligt mellem patienter [9–11] og har stor betydning for patienternes liv. PsA-patienter rapporterer ofte om smerter, nedsat fysisk funktion, træthed og vanskeligheder med daglige aktiviteter [12,13].

I den nationale behandlingsvejledning for PsA fra Dansk Reumatologisk Selskab fremgår det, at der mangler validerede kliniske diagnosekriterier for PsA, men at der er udviklet klassifikationskriterier, som kan benyttes som støtte. Diagnosen stilles på baggrund af en objektiv undersøgelse af bevægeapparat og hud sammen med serologi og biokemi [8].

Prævalensen er svær at estimere grundet manglen på klare diagnostiske kriterier. Baseret på estimater fra et studie fra 2008 og beregninger fra Gigtforeningen finder Medicinrådet, at prævalensen formentlig er mellem 6.000 og 25.000 personer [14,15]. Det skønnes desuden, at op til ca. 15 % af patienter med psoriasis udvikler PsA [8]. Sygdommen debuterer oftest i alderen 40-50 år, og prævalensen er ens for mænd og kvinder.

2.2 Upadacitinib

Upadacitinib er en selektiv Janus kinase (JAK) inhibitor, der primært hæmmer JAK1 og JAK1/3. JAK spiller en vigtig rolle i betændelsesprocessen og i den beskadigelse af leddene, som finder sted ved PsA.

Der er tale en indikationsudvidelse til PsA med følgende EMA-indikation:

RINVOQ er indiceret til aktiv psoriasisartrit hos voksne patienter, der har udvist utilstrækkeligt respons på eller er intolerante over for et eller flere sygdomsmodificerende anti-reumatiske lægemidler (DMARD'er). RINVOQ kan anvendes som monoterapi eller i kombination med methotrexat.

Den anbefalede daglige dosis af upadacitinib er 15 mg oralt. Lægemidlet er formuleret som en depottablet.

Upadacitinib er i forvejen indiceret til behandling af kronisk leddegigt, og Medicinrådet anbefalede det som mulig standardbehandling i september 2020 [16]. Sideløbende med denne vurdering er Medicinrådet ved at vurdere upadacitinib til patienter med ankyloserende spondylitis (AS).

2.3 Nuværende behandling

Der findes ingen behandling, som kan kurere PsA. Den nuværende behandling er i stedet målrettet patienternes smerter og symptomer som beskrevet i afsnit 2.1. Behandlingsmålet er, at patienterne opnår så lav sygdomsaktivitet som muligt og helst remission, så symptomer og inflammation er kontrollerede. Dette er bl.a. for at optimere patientens livskvalitet og sociale liv, forhindre progredierende strukturelle ledskader og bevare funktionsevne.

Sygdomsmodificerende behandling (*disease modifying antirheumatic drugs* (DMARDs)) gives ved betydelig affektion af led. Til patienter med lav sygdomsaktivitet og lav risiko for progressiv ledsygdom (ledaffektion i mindre end fem led) anvendes monoterapi med lægemidler af typen konventionelle DMARDs (csDMARDs), hvor methotrexat sædvanligvis er førstevalg i dansk klinisk praksis [8].

Hos patienter med betydelig ledaffektion (mere end fire led) eller ved utilstrækkelig effekt af csDMARDs, eventuelt i kombination med lokale steroidinjektioner [17], kan biologisk behandling med antistoffer (bDMARDs) eller targeteret syntetisk behandling med små molekyler (tsDMARDs) indledes. Kriterierne for at indlede b/tsDMARD-behandling omfatter sygdomsaktivitet, fravær af kontraindikationer, og at beslutningen træffes på konference med speciallæger i reumatologi [8]. Af b/tsDMARDs-behandling benyttes på nuværende tidspunkt forskellige TNF-alfa-hæmmere, monoklonale antistoffer rettet mod IL-12, -17 og -23 samt en JAK-hæmmer.

Medicinrådets nuværende lægemiddelrekommandation for biologisk behandling af PsA [18] er delt op i behandling til flere forskellige patientgrupper, afhængigt af om patienten har samtidig moderat til svær psoriasis, uveitis eller inflammatorisk tarmsygdom (Crohns sygdom eller colitis ulcerosa). Flere af lægemidlerne er godkendt til både PsA og en eller flere af de nævnte indikationer, hvilket har betydning for, hvilke lægemidler der anvendes til de relevante patientgrupper.

TNF-hæmmeren adalimumab er p.t. førstevalg for behandling af alle patientpopulationerne i Medicinrådets lægemiddelrekommandation for PsA [18]. Jf. RADS' baggrundsnotat for biologiske og syntetiske targeterede lægemidler til behandling af PsA udelukker behandlingssvigt ved anvendelse af en TNF-hæmmer ikke muligheden for effekt af en ny TNF-hæmmer eller lægemidler med anden virkningsprofil. Efter svigt af to effektfulde TNF-hæmmere (sekundært svigt) eller ved manglende respons fra start (primært svigt) kan et lægemiddel med anden virkningsprofil overvejes [19]. Ixekizumab er p.t. andet valg efter forudgående behandling med TNF-hæmmer [18].

I DANBIO (Dansk Reumatologisk Database) var der ved udgangen af 2019 registreret ca. 2.560 patienter i biologisk behandling for PsA, hvoraf ca. 330 patienter startede på biologisk behandling (behandlingsnaive), og ca. 860 patienter skiftede behandling (behandlingserfarne). Tallene dækker over alle PsA-patienter, inkl. dem, der har følgesygdommene uveitis og inflammatorisk tarmsygdom.

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.

De kliniske spørgsmål afspejler populationerne i lægemiddelrekommandationen. Da upadacitinib imidlertid ikke er godkendt til behandling af uveitis, Crohns sygdom, colitis ulcerosa eller moderat til svær plaque psoriasis, vil Medicinrådets vurdering af upadacitinib ikke omhandle patienter med PsA, der også har en af disse sygdomme. Derudover afspejler de kliniske spørgsmål, at der i dansk klinisk praksis skelnes mellem såkaldt behandlingsnaive patienter (der ikke tidligere har været behandlet med b/tsDMARDs og skal begynde behandling med en af disse) og behandlingserfarne patienter (der tidligere har været behandlet med b/tsDMARDs og skal skifte til en anden).

3.1 Klinisk spørgsmål 1

Hvilken værdi har upadacitinib sammenlignet med adalimumab for behandlingsnaive patienter med PsA?

Population
Patienter med PsA, som endnu ikke har modtaget behandling med b/tsDMARDs.

Intervention
Upadacitinib, oralt 15 mg pr. dag.

Komparator
Adalimumab, subkutan injektion à 40 mg hver 14. dag.

Effektmål
De valgte effektmål fremgår af tabel 1.

3.2 Klinisk spørgsmål 2

Hvilken værdi har upadacitinib sammenlignet med ixekizumab for behandlingserfarne patienter med PsA?

Population
Patienter med PsA, som tidligere har modtaget behandling med b/tsDMARDs.

Intervention
Upadacitinib, oralt 15 mg pr. dag.

Komparator
Ixekizumab, subkutan injektion à 160 mg i uge 0 og herefter 80 mg hver 4. uge.

Effektmål
De valgte effektmål fremgår af tabel 1.

3.3 Effektmål

Medicinrådet mener, at vurderingen af lægemidlets værdi bliver bedst understøttet af de effektmål, der er nævnt i tabel 1. 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 1. Oversigt over valgte effektmål

Effektmål*	Vigtighed	Effektmålsgruppe**	Måleenhed	Mindste klinisk relevante forskel
Sygdomsaktivitet - ledaffektion	Kritisk	Livskvalitet, alvorlige symptomer og bivirkninger	Andel patienter, der oplever respons på ACR50	15 %-point
			Andel patienter uden progression, jf. mTSS	10 %-point
Bivirkninger	Kritisk	Livskvalitet, alvorlige symptomer og bivirkninger	Andel patienter, der oplever alvorlige bivirkninger	5 %-point
			Kvalitativ gennemgang af bivirkningsprofil	
Livskvalitet	Kritisk	Livskvalitet, alvorlige symptomer og bivirkninger	Gennemsnitlig ændring fra baseline på SF-36, energi-subdomæne	7,8 point
			Gennemsnitlig ændring fra baseline på SF-36, den mentale komponent summary	3,1 point
			Gennemsnitlig ændring fra baseline på SF-36, den fysiske komponent summary	7,2 point

*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.
ACR50 = American College of Rheumatology 50 % forbedring, mTSS = Modified Total Sharp Score, SF36 = Short Form 36, PASI90 = Psoriasis Area Severity Index 90 % reduktion.

3.3.1 Kritiske effektmål

Sygdomsaktivitet – ledaffektion
Fagudvalget finder, at sygdomsaktivitet ift. ledaffektion er et kritisk effektmål, da patienter, der oplever nedsat sygdomsaktivitet, opnår forbedret funktionsniveau, livskvalitet og tilknytning til arbejdsmarkedet [20,21]. Medicinrådet betragter sygdomsaktivitet som et selvstændigt kritisk effektmål og ikke som et surrogat for livskvalitet. Sygdomsaktivitet kan bl.a. måles ved de kompositte værktøjer American College of Rheumatology (ACR) og modified Total Sharp Score (mTSS).

ACR50
Det primære mål for effekt på sygdomsaktivitet er ACR50. Dette er defineret som en 50 %'s forbedring i både ømme og hævede led samt 50 %'s forbedring inden for mindst tre ud af følgende fem domæner: patientens overordnede vurdering af, hvor meget gigten som helhed påvirker hverdagen (*Visual Assessment Scale* (VAS) global), patientens

vurdering af smerte, lægens overordnede vurdering af patientens samlede sygdomsaktivitet (VAS doctor), HAQ-DI score, som måler patientens funktionsniveau, og C-Reaktivt Protein (CRP). Medicinrådet vurderer, at en 50 %'s forbedring er et patientrelevant effektmål og betragtes her som tilstrækkeligt for at definere respons.

Medicinrådet vurderer, at en forskel på 15 %-point i andelen af patienter, der opnår ACR50, er klinisk relevant. Dette er i overensstemmelse med Medicinrådets tidligere vurderinger af lægemidler til PsA [22–24].

mTSS

Medicinrådet ønsker at benytte et radiografisk effektmål, der kan tolkes som udtryk for leddestruktion og dermed sygdomsprogression. Medicinrådet ønsker at benytte en modificeret udgave af *Total Sharp Score* (mTSS), som er udviklet til scoring af patienter med PsA [25].

Medicinrådet vurderer, at en forskel på 10 %-point i andelen af patienter uden progression, dvs. fravær af radiologiske ændringer, jf. mTSS, er klinisk relevant. Dette er i overensstemmelse med Medicinrådets tidligere vurderinger af lægemidler til PsA [22–24].

Bivirkninger

Medicinrådet vægter effektmålet bivirkninger som kritisk for vurderingen af lægemidlets værdi.

Alvorlige bivirkninger

Fagudvalget ønsker data på alvorlige bivirkninger (serious adverse reactions, SAR), da disse særligt frygtes af patienter og klinikere, fordi de kan forårsage pauser i behandlingen med risiko for forværring af symptomer og sygdomsprogression. Medicinrådet vurderer, at den mindste klinisk relevante forskel er 5 %-point. Dette er i overensstemmelse med Medicinrådets protokol vedr. guselkumab til PsA [24].

Kvalitativ gennemgang af bivirkningsprofil

Fagudvalget ønsker en kvalitativ gennemgang af upadacitinibs og komparatorernes bivirkningsprofiler for at vurdere bivirkningernes type, håndterbarhed og reversibilitet. Ansøger bedes derfor levere bivirkningsdata fra lægemidlernes produktresuméer og i den forbindelse forholde sig eksplicit til alvorlige infektioner (som defineret i de kliniske studier), da dette er af særlig betydning for patienterne.

Medicinrådet har tidligere udtrykt en bekymring for den øgede risiko for lungeemboli og venøs tromboemboli (VTE) hos patienter med risikofaktorer for VTE samt øget risiko for alvorlige infektioner hos patienter over 65 år ved behandling med JAK-hæmmeren tofacitinib [26]. Medicinrådet har i den forbindelse fundet, at det ikke kan udelukkes, at der er tale om en klasseeffekt for JAK-hæmmere. Derfor ønsker fagudvalget i gennemgangen af upadacitinibs bivirkningsprofil en redegørelse for, om der er fremkommet nye data, der kan belyse, om behandling med upadacitinib, ligesom tofacitinib, kan medføre risiko for lungeemboli og VTE samt alvorlige infektioner hos patienter over 65 år.

Sluttelig ønsker fagudvalget en redegørelse for lægemidlernes toksicitet ift. hhv. reproduktion og malignitet.

Livskvalitet
Livskvalitet er et patientrelevant effektmål, som udover at give indblik i sygdomsbyrden kan indikere, om bivirkningerne ved lægemidlet påvirker patienternes livskvalitet. Patienter med PsA er ofte mærket af deres sygdom både fysisk og mentalt, og det er derfor af stor betydning, om et nyt lægemiddel kan afhjælpe dette. På baggrund heraf betragter Medicinrådet livskvalitet som et kritisk effektmål.

Medicinrådet ønsker effektmålet opgjort med det generiske instrument SF-36 (Short Form 36). SF-36 er et spørgeskema, som bygger på 36 spørgsmål og måler helbredsrelateret livskvalitet og funktionsevne. Spørgeskemaet er inddelt i 8 helbredsrelaterede domæner (subdomæner): fysisk funktion, fysisk betingede begrænsninger, psykisk betingede begrænsninger, social funktion, fysisk smerte, psykisk helbred, energi og alment helbred. Derudover kan to sammenfattede scores også opgøres: fysisk komponent summary og mental komponent summary. Scoren måles på en skala fra 0 til 100, hvor høj score repræsenterer bedre livskvalitet.

I kliniske studier bliver livskvalitet ofte opgjort på de individuelle subdomæner eller de to sammenfattede scorer fremfor på en global score for SF-36. Fagudvalget ønsker data på subdomænet energi (*vitality*) og de to sammenfattede scorer for mental sundhed og fysiske komponenter, da disse betragtes som særligt vigtige parametre i patienternes livskvalitet. Inden for kronisk leddegigt er der for subdomænet energi og for den sammenfattede score for mental sundhed blevet rapporteret mindste klinisk relevante forskelle på hhv. 7,8 og 3,1 point [27]. Ligeledes inden for kronisk leddegigt er der for den sammenfattede score for fysiske komponenter blevet rapporteret en mindste klinisk relevant forskel på 7,2 point [28]. Fagudvalget finder, at disse mindste klinisk relevante forskelle rapporteret for kronisk leddegigt også kan anvendes inden for PsA.

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 (f.eks. NICE, EUnetHTA, FINOSE og IQWiG) indgå i vurderingen. Hvis disse data er tilstrækkelige til at kunne vurdere lægemidlet, vil Medicinrådet som hovedregel ikke anvende andre data[1]. Data skal derudover stemme overens med protokollens beskrivelser. Hvis ansøger har kendskab til upublicerede data,

[1] For yderligere detaljer se Princippapir for anvendelse af upublicerede data i vurderinger af nye lægemidler og indikationsudvidelser (medicinraadet.dk)

der kan belyse eventuelle angivne mangler, kan de indgå/indsendes, jf. Medicinrådets princippapir.

Klinisk spørgsmål 1
Medicinrådet er i den foreløbige ansøgning blevet orienteret om, at der findes et studie, hvor upadacitinib er sammenlignet direkte med adalimumab. Der er tale om følgende studie, som endnu ikke er publiceret:

- Select-PSA 1 (NCT03104400)

Det er tilstrækkeligt datagrundlag til at besvare det kliniske spørgsmål. Ansøger skal derfor ikke søge efter yderligere data, men skal konsultere EMAs EPAR for både det aktuelle lægemiddel og dets komparator(er).

Klinisk spørgsmål 2
Medicinrådet er i den foreløbige ansøgning blevet orienteret om, at der ikke findes studier, hvor upadacitinib er sammenlignet direkte med ixekizumab. 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, f.eks. 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 (f.eks. 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.

Særlige forhold i denne protokol

- Andre studiedesign end randomiserede kontrollerede forsøg (RCT) ekskluderes.
- Fase I- og IIa-studier, studier med andre populationer end de valgte og studier, som ikke rapporterer mindst et af de kritiske eller vigtige effektmål, ekskluderes.

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.

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, f.eks. 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

Medicinrådet er opmærksom på, at der for nogle af populationerne i de kliniske spørgsmål kan være problemer med at fremskaffe data. I disse tilfælde vil Medicinrådet forholde sig til, om det er muligt at ekstrapolere fra de populationer, hvor der er data.

8. Relation til behandlingsvejledning

Medicinrådet vil i forbindelse med vurderingen af upadacitinib tage stilling til, hvor lægemidlet foreløbigt kan placeres i RADS' *Behandlingsvejledning for biologisk behandling af Psoriasis Artritis (PsA).*

9. Referencer

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10. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende gigtsygdomme

Sammensætning af fagudvalg	
Formand	**Indstillet af**
Annemarie Lyng Svensson *Overlæge*	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
Salome Kristensen *Overlæge*	Region Nordjylland
Lars Erik Bartels *Afdelingslæge*	Region Midtjylland
Hanne M. Lindegaard *Overlæge, klinisk lektor*	Region Syddanmark
Thomas Adelsten *Uddannelsesansvarlig overlæge*	Region Sjælland
Maria Krogstrup *Afdelingslæge*	Region Hovedstaden
Per Damkier *Professor, overlæge*	Dansk Selskab for Klinisk Farmakologi
Thomas Loof Hedegård *Farmaceut*	Dansk Selskab for Sygehusapotekledelse
Dorte Vendelbo Jensen *Overlæge, sekretariatsleder*	DANBIO
Udpegning i gang	Dansk Reumatologisk Selskab
Connie Ziegler *Patient/patientrepræsentant*	Danske Patienter
Lene Mandrup Thomsen *Patient/patientrepræsentant*	Danske Patienter

Medicinrådets sekretariat
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Dampfærgevej 27-29, 3.th.
2100 København Ø
+45 70 10 36 00
medicinraadet@medicinraadet.dk

11. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	26. april 2021	Godkendt af Medicinrådet.

12. Bilag

Bilag 1: Søgestrenge

Klinisk spørgsmål 2, 3 og 4
Søgestreng til PubMed:

https://www.ncbi.nlm.nih.gov/pubmed/advanced

#	Søgetermer	Kommentar
1	"Arthritis, Psoriatic"[mh]	Søgetermer for populationen
2	PsA[tiab] OR (psoria*[tiab] AND (arthriti*[tiab] OR arthropath*[tiab] OR polyarthriti*[tiab] OR poly-arthriti*[tiab] OR oligoarthr*[tiab] OR oligo-arthr*[tiab] OR rheumato*[tiab]))	
3	#1 OR #2	
4	upadacitinib[nm]	Søgetermer for intervention og komparatorer
5	upadacitinib[tiab] OR ABT-494[tiab] OR rinvoq*[tiab]	
6	ixekizumab[nm]	
7	ixekizumab[tiab] OR taltz*[tiab] OR LY-2439821[tiab] OR LY2439821[tiab]	
8	#4 OR #5 OR #6 OR #7	
9	randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti] NOT (animals[mh] NOT humans [mh])	Filter til identifikation af RCT'er
10	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Letter[pt] OR Guideline[pt] OR Review[pt] OR case report[ti]	Søgetermer for ikke relevante publikationstyper (der ekskluderes)
11	animal*[ti] OR murine[ti] OR mouse[ti] OR mice[ti] OR rat[ti] OR rats[ti] OR rodent[ti]	
12	#10 OR #11	
15	#3 AND #8 AND #9 NOT #12	Endelig søgning

Feltkoder: mh = MeSH Term nm = Supplementary Concept/Substance tiab = title/abstract, inkl. forfatterkeywords pt = publication type

Søgestreng til CENTRAL:

https://www.cochranelibrary.com/advanced-search/search-manager

#	Søgetermer	Kommentar
1	[mh “Arthritis, Psoriatic”]	Søgetermer for populationen
2	(psoria* near (arthriti* or arthropath* or polyarthriti* or poly-arthriti* or oligoarthr* or oligo-arthr* or rheumato*)):ti,ab,kw	
3	PsA:ti,ab	
4	#1 or #2 or #3	
5	(upadacitinib or ABT-494 or rinvoq*):ti,ab,kw	Søgetermer for intervention og komparatorer
6	(ixekizumab or taltz* or LY-2439821 or LY2439821):ti,ab,kw	
7	#5 or #6	
8	#4 and #7	
9	("conference abstract" or review):pt	Søgetermer for ikke relevante publikationstyper (der ekskluderes)
10	(clinicaltrials.gov or trialsearch):so	
11	NCT*:au	
12	#9 or #10 or #11	
13	#8 not #12	
14	#13 not pubmed:an	Endelig søgning

Feltkoder: ti: title ab: abstract kw: keywords, her kontrollerede/indekserede termer fra databaserne Medline og/eller Embase. pt = publication type