Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende afamelanotid til behandling af erytropoietisk protoporfyri

Vers. 1.0

Bilagsoversigt

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Medicinrådet

Medicinrådets sundheds-økonomiske afrapportering

Afamelanotid

Erytropoietisk protoporfyri

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
SAIP	Sygehusapotekernes indkøbspriser
SmPC	*Summary of product characteristics*

2. Konklusion

Inkrementelle omkostninger og budgetkonsekvenser
I det scenarie, Medicinrådet mener, er mest sandsynligt, er de inkrementelle omkostninger for afamelanotid ca. [redacted] DKK pr. patient sammenlignet med ingen aktiv behandling. Når analysen er udført med apotekets indkøbspriser (AIP), er de inkrementelle omkostninger til sammenligning ca. 3,8 mio. DKK pr. patient.

Da erytropoietisk protoporfyri er en kronisk sygdom, kan behandlingen med afamelanotid potentielt være livsvarig. I analysen antages patienterne at modtage afamelanotid i 15 år, men hvor længe, patienterne faktisk vil være i behandling, er meget usikkert. Hvis der er tale om en livslang behandling, vil omkostningerne til behandlingen være voldsomt underestimeret.

Hvis behandlingslængden for afamelanotid ændres til 52 år, stiger de inkrementelle omkostninger fra [redacted] DKK til [redacted] DKK.

Det forventes, at hver patient i gennemsnit får tre implantater pr. år, men der kan være patienter, der vil have gavn af fire. Antallet af implantater årligt har stor betydning for de gennemsnitlige inkrementelle omkostninger pr. patient, da prisen for et enkelt implantat er meget høj.

Medicinrådet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af afamelanotid som mulig standardbehandling vil være ca. [redacted] DKK i år 5. Når analysen er udført med AIP, er budgetkonsekvenserne ca. 16,3 mio. DKK i år 5.

Der er usikkerhed om, hvor længe patienter vil være i behandling med afamelanotid. Hvis behandlingsvarigheden antages at være 15 år, da vil de gennemsnitlige inkrementelle omkostninger pr. år være ca. [redacted] DKK pr. patient.

Når analysen er udført med apotekets indkøbspriser (AIP), er de inkrementelle omkostninger pr. år til sammenligning ca. 256.000 DKK pr. patient.

3. Introduktion

Formålet med analysen er at estimere de gennemsnitlige inkrementelle omkostninger pr. patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af afamelanotid som mulig standardbehandling på danske hospitaler til erytropoetisk protoporfyri, som er en svær form for lysintolerance.

Analysen er udarbejdet, fordi Medicinrådet af egen drift har besluttet at vurdere lægemidlet. Beslutningen blev truffet den 28. august 2019. Virksomheden, som har markedsføringstilladelsen til afamelanotid, er blevet tilbudt at indsende en ansøgning med kliniske data samt en sundhedsøkonomisk analyse, hvilket de har gjort. Vi modtog ansøgningen den 19. november 2020.

3.1 Patientpopulation

Erytropoietisk protoporfyri (EPP) er en metabolisk sygdom, der gør patienterne ekstremt intolerante overfor lys og forårsager fototoksicitet i huden (smerter, hævelse og rødme). Patienterne er intolerante for både UV-lys og synligt lys – også gennem vinduesglas. Yderligere kan kunstigt lys fra f.eks. lamper og billygter også være generende, men graden af intolerance varierer mellem patienterne og kan forværres, hvis patienten har været udsat for lys i længere tid.

Forekomsten af EPP i Danmark anslås at være 13 pr. 1.000.000 indbyggere [1]. Fordelingen af patienter over og under 18 år er ukendt. Der skønnes at være 1-2 nye tilfælde pr. år.

Fagudvalget vurderer, at ca. 40-50 patienter vil have et behandlingsbehov og dermed vil kunne tilbydes behandling med afamelanotid, såfremt det bliver godkendt som standardbehandling.

Yderligere information om sygdomsområdet kan findes i Medicinrådets vurderingsrapport.

3.1.1 Komparator

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

Klinisk spørgsmål 1:

Hvilken værdi har afamelanotid sammenlignet med placebo til patienter med erytropoietisk protoporfyri?

4. Vurdering af den sundhedsøkonomiske analyse

Virksomheden har indsendt en sundhedsøkonomisk analyse, der består af en omkostningsanalyse og en budgetkonsekvensanalyse. I omkostningsanalysen estimeres de inkrementelle omkostninger pr. patient for afamelanotid sammenlignet med ingen aktiv behandling. Medicinrådet vurderer nedenfor den sundhedsøkonomiske analyse, som virksomheden har indsendt.

4.1 Antagelser og forudsætninger for model

Sammenligningen med ingen aktiv behandling er lavet på baggrund af data fra et fase III-studie fra 2015 og afamelanotids produktresumé (SmPC) [2,3].

Virksomheden har forsøgt at opnå viden om den nuværende standardbehandling til patienter, der er kandidater til behandling med afamelanotid. Det har ikke været muligt

for dem at få information fra kliniske eksperter i Danmark, og de vælger derfor at antage, at den eneste forskel i omkostninger mellem afamelanotid og nuværende standardbehandling er omkostningerne til implantatet med afamelanotid samt omkostninger til administration af dette. Derudover er patientomkostninger og transportomkostninger også inkluderet i analysen.

4.1.1 Modelbeskrivelse

Virksomheden har indsendt en simpel omkostningsanalyse, hvor kun omkostninger til selve behandlingen med afamelanotid indgår. Effektforskelle indgår ikke i modellen.

Da der ikke er nogen data for, hvor lang den gennemsnitlige behandlingsvarighed er for afamelanotid, vælger virksomheden en behandlingslængde på 1 år, men med mulighed for at ændre denne i op til 100 år. I modellen svarer tidshorisonten og behandlingslængden til hinanden.

Medicinrådets vurdering af virksomhedens modelantagelser
Virksomheden har valgt, at behandlingslængden for afamelanotid i analysen er ét år. Da behandlingen ifølge både virksomhed og fagudvalget potentielt kan være livslang, vurderes dette at være en underestimering af behandlingslængden. I Medicinrådets hovedanalyse sættes behandlingslængden til 15 år, mens der laves følsomhedsanalyser med tidshorisonter på henholdsvis 5 år og 52 år. Forøgelsen af behandlingslængden for afamelanotid vurderes at have stor betydning for analysens resultat.

Medicinrådet accepterer ikke virksomhedens tilgang vedr. modelantagelser, men vælger i stedet at øge behandlingslængden for afamelanotid til 15 år.

4.1.2 Analyseperspektiv

Virksomheden har valgt et begrænset samfundsperspektiv til sin analyse. Analysen har en tidshorisont på ét år.

Virksomheden har indsendt scenarieanalyser, hvor det er muligt at vælge tidshorisonter på længere end ét år. I disse scenarier diskonterer virksomheden med 4 % fra år 2-35 og 3 % fra år 36.

Medicinrådets vurdering af virksomhedens analyseperspektiv
Pr. 1. januar 2021 anbefaler Finansministeriet en diskonteringsrente på 3,5 % i år 2-35 og på 2,5 % fra år 36-70. Medicinrådet ændrer diskonteringsrenten til at følge Finansministeriets anbefaling.

Som tidligere beskrevet vurderes behandlingslængden på ét år potentielt at underestimere omkostningerne ved behandling med afamelanotid. Medicinrådet ændrer tidshorisonten i analysen til 15 år. Derudover udføres følsomhedsanalyser, der undersøger omkostningerne ved både længere og kortere tidshorisonter.

Medicinrådet accepterer virksomhedens valg vedr. analyseperspektiv, men ændrer tidshorisonten til 15 år og opdaterer diskonteringsrenterne, så de er tilsvarende gældende anbefalinger fra Finansministeriet.

4.2 Omkostninger

I det følgende præsenteres virksomhedens antagelser for omkostningerne i den sundhedsøkonomiske analyse af afamelanotid sammenlignet med ingen aktiv behandling.

Som nævnt tidligere antager virksomheden, at den eneste forskel i omkostninger mellem afamelanotid og nuværende standardbehandling er omkostninger til implantatet med afamelanotid samt omkostninger til administreringen af dette. Derudover er også patientomkostninger og transportomkostninger inkluderet i analysen.

4.2.1 Lægemiddelomkostninger

Virksomheden har jf. *Metodevejledning for omkostningsanalyser af nye lægemidler og indikationer i hospitalssektoren* estimeret lægemiddelomkostninger på baggrund af apotekets indkøbspris (AIP). Doser anvendt i virksomhedens analyse er i overenstemmelse med SmPC'et. Det angives både i SmPC'et og i Medicinrådets protokol, at patienter kan modtage tre implantater årligt og maks. fire. Da der kan være en andel af patienterne, der modtager fire implantater årligt, undersøger virksomheden omkostningerne ved fire implanter årligt i en følsomhedsanalyse.

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

Tabel 1. Anvendte lægemiddelpriser, SAIP, (november 2021)

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Afamelanotid	16 mg	1 stk.	[redacted]	Amgros

Medicinrådet accepterer virksomhedens valg vedr. lægemiddelomkostninger.

4.2.2 Hospitalsomkostninger

Virksomheden har inkluderet lægemiddelomkostninger, administrationsomkostninger, patientomkostninger og transportomkostninger i sin analyse. Omkostninger til bivirkninger har virksomheden ikke inkluderet, da der argumenteres for, at der ses lignende bivirkningsprofiler for afamelanotid sammenlignet med ingen aktiv behandling. Omkostninger til monitorering er ligeledes ikke inkluderet, da virksomheden argumenterer, at monitoreringen vil finde sted under samme besøg, som når patienten får et nyt implantat.

Administrationsomkostninger

Virksomheden har inkluderet administrationsomkostninger for afamelanotid i form af DRG-takster. Virksomheden har anvendt taksten DRG-2020 10MA98, 1-dagsgruppe, pat. mindst 7 år.

Medicinrådets vurdering af virksomhedens antagelser vedr. administrationsomkostninger

Medicinrådet accepterer virksomhedens tilgang til estimering af administrationsomkostninger. Dog udskiftets virksomhedens anvendte takst, som baserer sig på DRG-2020, med en takst fra DRG-2021. Anvendte enhedsomkostninger kan ses i Tabel 2.

Tabel 2. Omkostninger til lægemiddeladministration

	Enhedsomkostning [DKK]	Kode	Kilde
Administration af afamelanotidimplantat	1.518	10MA98	DRG-2021

Medicinrådet accepterer virksomhedens tilgang vedr. administrationsomkostninger. En enkelt DRG-takst ændres fra 2020-takst til 2021-takst.

Monitoreringsomkostning

Virksomheden har ikke inkluderet monitoreringsomkostninger i sin analyse, da der argumenteres for, at al monitorering af patienterne vil ske, mens de alligevel er på hospitalet for at få afamelanotidimplantatet.

Medicinrådets vurdering af virksomhedens antagelser vedr. monitoreringsomkostninger

Fagudvalget mener, at der vil være ét opstartsbesøg i forbindelse med første behandling med afamelanotid, hvor patientens hud fotograferes, så ændringer kan følges. Derfor tilføjes et ambulant opstartsbesøg. Yderligere forventer fagudvalget, at der vil være yderligere tre monitoreringsbesøg om året. Både opstartsbesøg samt monitoreringsbesøg vil blive takseret med 10MA98 DRG-2021 på 1518 DKK.

Virksomheden har ikke antaget nogen omkostninger ved ingen aktiv behandling. Fagudvalget mener, at disse patienter vil have én årlig kontrol på hospitalet. Dette besøg takseres også med taksten DRG-2021 10MA98.

Disse ændringer vurderes at have minimal betydning for analysens resultat.

Medicinrådet accepterer ikke virksomhedens tilgang til estimering af monitoreringsomkostninger og tilføjer i egen hovedanalyse omkostninger til yderligere monitoreringsbesøg.

4.2.3 Patientomkostninger

Patientomkostninger er estimeret på baggrund af administrationsbesøg på hospitalet, og inkluderer patientens effektive tid på hospitalet og transporttid.

Virksomheden anvender en enhedsomkostning for patienttid på 179 DKK pr. time og transportomkostninger på 3,52 DKK pr. km, jf. *Medicinrådets værdisætning af enhedsomkostninger*.

Medicinrådets vurdering af virksomhedens antagelser vedr. patientomkostninger
Fagudvalget estimerer, at der udover de konsultationer, hvor implantaterne indsættes, vil være tre monitoreringsbesøg hvert år samt et opstartsbesøg i det første år for patienter, der modtager afamelanotid. For patienter, der ikke er i aktiv behandling, vil der være ét kontrolbesøg årligt.

Fagudvalget estimerer, at et besøg, hvor afamelanotid administreres, vil have en varighed på 90 minutter, da patienten skal observeres efter administrationen. Den estimerede tid ved hospitalsbesøg er opgjort i Tabel 3.

Tabel 3. Estimerede patientomkostninger pr. år

	Afamelanotid	Ingen aktiv behandling
Patienttid, monitoreringsbesøg	30 minutter	30 minutter
Opstartsbesøg	30 minutter	N/A
Patienttid, administration af lægemiddel	90 minutter	N/A
Patienttid, transport	60 minutter	60 minutter

Medicinrådet accepterer virksomhedens tilgang til at estimere patienttid, men ændrer antal hospitalsbesøg for både afamelanotid og patienter, som ikke er i aktiv behandling. Derudover ændres varigheden af administrationsbesøget til at være 90 minutter.

4.3 Følsomhedsanalyser

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

Virksomheden har udarbejdet en række følsomhedsanalyser, hvor effekten af variation i forskellige parametre undersøges. Følgende følsomhedsanalyser er udført af virksomheden:

Tabel 4. Følsomhedsanalyse indsendt af virksomheden og beskrivelse

Følsomhedsanalyse	Beskrivelse
Fire implantater med afamelanotid årligt	Det antages, at en gennemsnitlig patient vil modtage fire implantater med afamelanotid årligt

Medicinrådets vurdering af virksomhedens valg af følsomhedsanalyser
Da Medicinrådet har ændret på tidshorisonten i virksomhedens indsendte analyse og inkluderet yderligere omkostningselementer, vil virksomhedens følsomhedsanalyse ikke blive præsenteret.

Medicinrådet vælger at lave tre følsomhedsanalyser, hvor én enkelt parameter i hver af følsomhedsanalyserne ændres. I én følsomhedsanalyse øges antallet af afamelanotidimplantater fra tre til fire pr. år. I de to andre følsomhedsanalyser sættes tidshorisonten og dermed også behandlingslængden for afamelanotid til henholdsvis 5 år og 52 år.

Medicinrådet vælger ikke at præsentere virksomhedens følsomhedsanalyser. Medicinrådet præsenterer egne følsomhedsanalyser, der undersøger alternative behandlingslængder for afamelanotid og antal afamelanotidimplantater årligt.

4.4 Opsummering af basisantagelser

I Tabel 5 opsummeres basisantagelserne i henholdsvis virksomhedens og Medicinrådets hovedanalyse.

Tabel 5. Basisantagelser for virksomhedens og Medicinrådets hovedanalyse

Basisantagelser	Viksomheden	Medicinrådet
Tidshorisont	1 år	15 år
Diskonteringsrate	4 % i år 2-35 3,5 % fra år 36	3,5 % i år 2-35 2,5 % fra år 36
Inkluderede omkostninger	Lægemiddelomkostninger Administrationsomkostninger Patient- og transportomkostninger	Lægemiddelomkostninger Administrationsomkostninger Monitoreringsomkostninger Patient- og transportomkostninger
Dosering	16 mg tre gange årligt	16 mg tre gange årligt
Hospitalskontakter		
Afamelanotid:	Tre årlige kontakter	Seks årlige kontakter + en ekstra kontakt første behandlingsår
Ingen aktiv behandling:	Ingen kontakter	En årlig kontakt

5. Resultater

5.1 Resultatet af Medicinrådets hovedanalyse

Medicinrådets hovedanalyse bygger på samme antagelser som virksomhedens hovedanalyse med undtagelse af de ændringer, der fremgår af Tabel 5.

Den gennemsnitlige inkrementelle omkostning pr. patient bliver [redacted] DKK i Medicinrådets hovedanalyse. Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient 3,8 mio. DKK. Hvis behandlingsvarigheden antages at være 15 år, da vil de gennemsnitlige inkrementelle omkostninger pr. år være ca. [redacted] DKK pr. patient. Er analysen udført med AIP, bliver den årlige inkrementelle omkostning pr. patient ca. 256.000 DKK.

Resultaterne fra Medicinrådets hovedanalyse er præsenteret i Tabel 6.

Tabel 6. Resultatet af Medicinrådets hovedanalyse ved sammenligning med ingen aktiv behandling, DKK, diskonterede tal

	Afamelanotid	Ingen aktiv behandling	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	110.090	22.770	87.320
Patientomkostninger	33.022	5505.9	27.516
Totale omkostninger	[redacted]	[redacted]	[redacted]

5.1.1 Resultatet af Medicinrådets følsomhedsanalyser

Ved samme antagelser som i Medicinrådets hovedanalyse for meromkostninger har Medicinrådet udført en følsomhedsanalyse på parametrene listet i Tabel 7.

Tabel 7. Resultatet af Medicinrådets følsomhedsanalyse sammenlignet med hovedanalysen, DKK

Scenarie	Inkrementelle omkostninger
Resultatet af hovedanalysen	[redacted]
Fire implantater om året	[redacted]
Behandlingslængde på 5 år	[redacted]
Behandlingslængde på 52 år	[redacted]

6. Budgetkonsekvenser

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

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

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

6.1 Virksomhedens estimat af patientantal og markedsandel

Baseret på fagudvalgets estimat af patienter, der vil være kandidater til afamelanotid, antager virksomheden, at behandlingen vil være relevant for 45 patienter. Virksomheden estimerer, at der årligt vil være 0,75 nye patienter, som kandiderer til behandlingen.

Virksomheden forventer et langsomt markedsoptag, hvor kun 20 % af patienterne vil modtage afamelanotid i det første år efter en anbefaling. De efterfølgende år vil der årligt være 20 % yderligere, der vil modtage implantatet årligt, indtil det i år 5 vil være 100 % af patienterne, der modtager afamelanotid.

Medicinrådets vurdering af virksomhedens budgetkonsekvensanalyse
Fagudvalget er blevet konsulteret i forhold til patientantal, hvis afamelanotid anbefales som mulig standardbehandling, og hvis afamelanotid ikke anbefales. Fagudvalget estimerer, at 40-50 patienter vil forventes at være kandidater til behandling med afamelanotid til den pågældende indikation, og at der årligt vil være 1-2 nye patienter. Fagudvalget mener, at ved en potentiel anbefaling af afamelanotid da vil alle patienter blive tilbudt behandlingen fra første år, se Tabel 8.

Tabel 8. Medicinrådets estimat af antal patienter pr. år

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Afamelanotid	45	47	48	50	51
Ingen aktiv behandling	0	0	0	0	0
			Anbefales ikke		
Afamelanotid	0	0	0	0	0
Ingen aktiv behandling	45	47	48	50	51

Medicinrådet har udført sin egen budgetkonsekvensanalyse, hvor antallet af nye patienter er ændret til 1,5 om året.

6.2 Medicinrådets budgetkonsekvensanalyse

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

- Antal nye patienter om året sættes til 1,5.

Medicinrådet estimerer, at anvendelse af afamelanotid vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Resultatet er præsenteret i Tabel 9.

Er analysen udført med AIP, bliver budgetkonsekvenserne ca. 16,3 mio. DKK i år 5.

Tabel 9. Medicinrådets analyse af totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal

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

7. Diskussion

Behandling med afamelanotid er forbundet med inkrementelle omkostninger på [redacted] DKK sammenlignet med ingen aktiv behandling. De inkrementelle omkostninger er næsten udelukkende drevet af lægemiddelomkostningerne for afamelanotid.

Da erytropoietisk protoporfyri er en kronisk sygdom, vil behandlingen med afamelanotid potentielt være livsvarig. I analysen antages patienterne at modtage afamelanotid i 15 år, men hvor længe, patienterne faktisk vil være i behandling, er meget usikkert. Hvis der er tale om en livslang behandling, vil omkostningerne til behandlingen være voldsomt underestimeret.

Hvis behandlingslængden for afamelanotid ændres til 52 år, stiger de inkrementelle omkostninger fra [redacted] DKK til [redacted] DKK.

Antallet af implantater med afamelanotid forventes at være tre årligt, men der kan være patienter, hvor fire implantater vil være mere passende. Det årlige forbrug af implantater har stor betydning for den gennemsnitlige omkostning pr. patient, da prisen for et enkelt implantat er meget høj.

8. Referencer

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9. Bilag

9.1 Resultatet af virksomhedens hovedanalyse

I virksomhedens hovedanalyse bliver den inkrementelle omkostning pr. patient ca. [redacted] DKK over en tidshorisont på 1 år. Resultaterne fra virksomhedens hovedanalyse er præsenteret i Tabel 10.

Tabel 10. Resultatet af virksomhedens hovedanalyse, DKK

	Afamelanotid	Ingen aktiv behandling	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	4.620	0	4.620
Patientomkostninger	1.370	0	1.370
Totale omkostninger	[redacted]	[redacted]	[redacted]

9.2 Resultatet af virksomhedens budgetkonsekvensanalyse

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

Med virksomhedens antagelser om patientantal og markedsandel estimerer de, at anvendelse af afamelanotid vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Virksomhedens estimat af budgetkonsekvenserne fremgår af Tabel 11.

Tabel 11. Virkomhedens hovedanalyse for totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal

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

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Prisnotat

Dato for behandling i Medicinrådet	28.04.2021
Leverandør	Clinuvel
Lægemiddel	Afamelanotid (Scenesse)
Indikation	Medicinrådet – egen drift. Afamelanotid til patienter med diagnosen erytropoetisk protoporfyri

Aftalestatus:

Afamelanotid er et lægemiddel, der ikke er markedsført i Danmark og som indtil nu er blevet indkøbt af regionerne direkte fra leverandøren.

Firmaet har ikke været villig til at indgå aftale med Amgros og sygehusapotekerne. Derfor gælder den samme pris som i resten af Europa.

Lægemiddel	Pakning	Pakningsstørrelse	Europas indkøbspris	AIP pris (DKK)
Afamelanotid (scenesse)	Ét implantat	16 mg	[redacted]	[redacted]

Konklusion

[redacted]

Status fra andre lande:

Norge: Afamelanotid blev ikke godkendt. Januar 2019[1].

[1] Afamelanotide (Scenesse) (nyemetoder.no)

PRIVILEGED & CONFIDENTIAL

CLINUVEL

Danish Medicines Council
Secretariat
[redacted]
Dampfærgevej 27-29, 3. th.
2100 Copenhagen Denmark
Sent to [redacted]

Cc: [redacted]

31 March 2021

Re: Response to the Danish Medicines Council's draft evaluation of afamelanotide in the treatment of erythropoietic protoporphyria

Dear [redacted]

CLINUVEL has reviewed the Danish Medicines Council's (DMC's) draft report dated 24 March 2021. The Company is at loss as to how fundamental errors and inconsistencies could have been made. These shortcomings are affecting the procedure and decision making and require rectification, since these impact the considerations and preliminary decision on the introduction of SCENESSE® (afamelanotide 16mg) for erythropoietic protoporphyria (EPP) patients in Denmark.

Attached is comprehensive feedback from our teams on issues that must be addressed. We note that this is not exhaustive but illustrates the failings of the DMC to accurately present clinical results, understand the unique nature of EPP in its review, and follow its own processes.

Our team can be contacted to clarify any of the matters outlined in the attached documentation. We look forward to your further correspondence.

Yours sincerely,

[redacted]

Lachlan Hay
Director of Global Operations,
CLINUVEL Group

CLINUVEL has reviewed the Danish Medicines Council's (DMC's) draft report dated 24 March 2021 (hereafter "the Report") and provides the following response.

I. Errors and inconsistencies

I.I Interpretation and presentation of clinical results

I.I (i) Exceptional circumstances approval

The Report concludes in Section 5.1.4 that the quality of the evidence presented is "low, which means that new studies are fairly likely to change the conclusion"[1]. This finding, which underpins the Report, is contrary to the findings of the European Medicines Agency (EMA), including the Danish representative who voted in favour of marketing authorisation for SCENESSE®.

SCENESSE® was approved by the EMA under exceptional circumstances, with the EMA's Committee of Medicinal Products for Human Use (CHMP) noting in the European Public Assessment Report:

> *In accordance with Article 14(8) of Regulation (EC) No 726/2004 and Annex I, part II of Directive 2001/83/EC the applicant applied for a marketing authorisation under exceptional circumstances based on the inability to provide comprehensive data on* ***the efficacy and safety under normal conditions of use because the indication for which afamelanotide is intended is encountered so rarely that the applicant cannot reasonably be expected to provide a comprehensive dossier…***
> [The EMA justified that the Sponsor is] *unable to provide comprehensive data on the efficacy and safety under normal conditions of use, due to the fact that:*
>
> 1. *EPP is an extremely rare condition and there are insufficient naïve patients available who are able and willing to join a clinical trial;*
> 2. *it would be medically unethical to collect such efficacy data owing to the fact that EPP patients are unwilling to expose themselves to light sources or sunlight based on past preconditioning from ingrained anxiety of burning;"*
> 3. *there is no existing satisfactory assessment tool to capture meaningful and comprehensive efficacy data for afamelanotide;*

The EPAR also outlines the views of the CHMP in detail (page 89-90):

> *"Given the rarity of the disease, the CHMP considered that the applicant cannot be reasonably expected to provide comprehensive non-clinical and clinical evidence. Patients are so rarely identified that conduct of a controlled clinical trial would be unachievable.*
> *…*
> *It would be contrary to medical ethics principles to collect evidence of clinical efficacy of afamelanotide in the intended indication in a controlled clinical study. A controlled study implies for an extended period of time oblige* (sic) *EPP patients to expose themselves to sunlight in order for the benefits of Scenesse to be detected, in particular in a placebo-controlled trial. Therefore, participation in a controlled clinical trial would expose patients to a risk of severe phototoxicity and pain that would not be ethically acceptable.*
> *…*
> *Under normal conditions of use, the status of current scientific knowledge, tools and instruments, does not allow for sufficient precise measurements of impact of disease and 'visible light' to exposed skin. It is also conceivable that the complexity of the EPP patients behaviour and the dependence of phototoxicity with environmental factors in real life differ to such an extent that the actual benefit cannot be captured in conventional clinical trial designs, for ex. randomised blinded clinical trial design and that no design could address this matter taking into account the current scientific and technical knowledge. It is therefore not foreseeable that the request of additional studies would allow to generate a comprehensive dossier in terms of safety and efficacy."*

The DMC's process guide for assessing new pharmaceuticals notes (Section 3.1.3) that the EPAR should be consulted by companies as part of their evidence submission. As the EPAR is referenced in the Report, it is

[1] Verbatim English translation of: *Lav: Nye studier vil med moderat sandsynlighed ændre konklusionen*.

assumed that the Committee has read this document as part of its review. The EMA Report is binding and it is irrational for the DMC to contradict or selectively use parts of the Report where fit.

I.I (ii) Selective approach to data

Throughout its discussion, the Report makes subjective claims as to the validity of data and the Committee's rationale for its inclusion and consideration. These approaches are inconsistent and reveal either a confirmation bias or failure of fundamental understanding by the Committee.

In its review of the reduction of phototoxic symptoms in CUV039, the Committee states in the report that the CUV039 study "does not demonstrate a clinically relevant effect on either symptoms or the duration of symptoms". It is presumed that this is due to the Committee setting the arbitrary measure of 20 minutes in its protocol for the minimum clinically important difference (MCID), although this assumption is not discussed in the report. To reach its conclusion the Committee dismisses an average variance between study groups due to the distribution of data (which meets the 20 minute threshold), yet select a post-hoc analysis figure of 8.4 minutes, an average figure over the same cohort. The Report provides a narrative on blinding (addressed below) and conditioned behaviour to justify its approach, but lacks transparency on the Committee's arbitrary dismissal of data. A similar approach is taken to dismiss duration of symptoms seen in the studies.

The conclusions of the Report on clinical benefit contradict those of the independent publications by Langendonk et al and fail to acknowledge the findings of the EMA. The DMC has given these conclusions without justification or transparency as to the rationale for their decision making.

I.I (iii) Unjustified omission of study CUV029

The Committee's decision to omit data from the CUV029 study is unjustified and based on an erroneous understanding of the CUV029 study and EPP.

Discussion of Study CUV029 in Section 5.1.2 suggests that the data generated in CUV029 "do not provide an accurate picture of afamelanotide in the summer months" as it was conducted between September and May. The Company notes that the study – as summarised in Table 1 of the report – was conducted between **September 2009 and May 2011**, with the first patients enrolled (in a nine-month study) during **January 2010**. Put differently, patients enrolled in CUV029 were indeed exposed to afamelanotide treatment during the Summer months.

CLINUVEL designed its clinical program such that patients in clinical trials received treatment with afamelanotide during the Spring and Summer months (i.e. when patients are at greatest risk of phototoxic reactions from environmental light exposure). At no time was the Company asked by the Committee to clarify when patients were enrolled in CUV029. This is a fundamental failing of an expert committee to understand clinical trial timelines, which it uses to justify the omission of data from a review.

It is stressed that EPP is not a seasonal disorder exacerbated in Spring and Summer, since patients at various latitudes require treatment all year round. The suggestion that latitude plays a role is invalid and not scientifically supported, since CLINUVEL's and EMA's analyses do not allude to latitude as a determinant to symptomatology. In none of the countries where afamelanotide is being administered is latitude a clinical problem in EPP.

Further, an argument is made in the Report that the results from CUV029 may not reflect the Danish situation due to differences in latitude between the CUV029 study sites and Denmark "where there are presumably more hours of sunshine". This statement lacks scientific merit on two counts.

Firstly, it is widely recognised in the literature that EPP is not merely a disorder of "sunshine". EPP patients experience phototoxic reactions year-round as a result of exposure to visible light, including artificial light and reflected light (such as that from water or snow). While patients do experience greater phototoxicity from environmental light in the spring and summer, most report year-round phototoxicity (Biolcati et al., 2015).

Secondly, the argument on latitude lacks grounding in reality. CUV029 was conducted in Finland (Helsinki, latitude – 60.17° N), France (Paris – 48.86° N), Germany (Dusseldorf – 51.23° N), Ireland (Dublin – 53.35° N), the Netherlands (Maastricht – 50.85° N and Rotterdam – 51.92° N) and the UK (Newport – 41.49° N and Manchester -53.48° N). For clarity, the Company was not asked to clarify the study sites involved in CUV029, but details of investigators and study sites are disclosed in the Langendonk et. al., (2015) paper.

When one considers the latitudes and climates of the CUV029 study sites (mostly in Northern Europe, around the latitude of Copenhagen at 55.68° N) the presumption of the Committee used to justify the omission of the CUV029 study data lacks any merit.

I.I (iv) Use of the Dermatology Life Quality Index

The Committee's Protocol and Report rely heavily on the use of the Dermatology Life Quality Index (DLQI) as a measure of quality of life and the MCID as part of its protocol. Based on the use of the DLQI, the MCID threshold is considered unmet in the Report. The DLQI is acknowledged as an inappropriate tool for fully evaluating quality of life in EPP patients, and its validity goes unchallenged in the Report. By contrast, the Committee cautions the use of the EPP Quality of Life (EPP-QoL) tool as it is partially validated.

The DLQI was not designed to, and does not, capture the impact on quality of life experienced by patients with EPP or any light-induced disorder. The DLQI was designed and validated for dermatological disorders, such as psoriasis and eczema (Finlay & Khan, 1994). EPP, by contrast, is a genetic metabolic disorder for which there is no fully validated, disease-specific quality of life specific tool. Further, the DLQI focuses on skin symptoms (i.e. itch). EPP is characterised by phototoxicity as the primary clinical symptom and patients have conditioned their behaviour to avoid light exposure. The EPP-QoL was developed with clinical experts to ask questions about the specific impact of the disease on patients' lives. In addition, the time window for the DLQI (one-week recall) is not appropriate for a lifelong condition where patients experience reactions infrequently (because of their conditioned behaviour). The EPP-QoL uses a two month recall period, which is more likely to capture the patient experience.

CLINUVEL provided extensive information on the nature of the DLQI to the DMC as part of its feedback on the protocol. By using the DLQI unquestioningly in the Report, the Committee has failed to understand the unique nature of EPP and clinical benefit in the disorder. The overt selectivity by the Committee poses further questions whether it argues towards a desired outcome.

I.I (v) Patient blinding

Possible unblinding was used as a justification for the Report to upgrade the risk of bias in Table 8. Yet the Report makes inconsistent references to the possible impact of blinding and shows a lack of understanding of EPP, its treatment, and the clinical study results.

Section 5.1.5 suggests that the results from CUV039 may have been biased as patients receiving placebo implants would "guess" which therapy they have received due to a lack of hyperpigmentation at the implant injection site. The assumptions made here are that:

1) Patients were aware of the possibility of hyperpigmentation at the injection site as an adverse reaction from active treatment;
2) Patients experienced hyperpigmentation at the injection site as an adverse reaction; and
3) This adverse reaction had an impact upon their clinical benefit, or perception thereof.

CLINUVEL was not asked to comment on the information given to patients as part of the CUV039 study. [redacted]

Even if patients would have been made aware of localised hyperpigmentation, the Report notes that 19% of patients receiving afamelanotide in CUV039 (n=46) reported skin discolouration at the implant site, with one patient also reporting hyperpigmentation. In 81% no hyperpigmentation was observed, which counteracts any alleged bias as confirmed by all investigators involved in the trial(s). Thus, if patients were aware of localised hyperpigmentation – and it influenced their perception of treatment – most patients receiving active treatment in CUV039 would therefore have assumed that they received a placebo.

Finally, the EPAR addresses the issue of blinding and its potential impact upon patient perception of treatment impact, with the expert committee advising the EMA noting that it "did not consider [knowledge of potential active treatment] measurable on the perceived effect". Put simply, even if it was experienced, patients were unlikely to have their perception of treatment benefit influenced by possible localised hyperpigmentation.

The Report's stance on patient blinding is illogical in light of the evidence presented to the Committee.

I.II Characterisation of EPP

There are fundamental errors, inconsistencies and assumptions in the Report which in no way reflect the patients' real world experience of EPP or its treatment, or the current medical literature on the disease. These errors reflect a lack of fundamental knowledge, expertise and diligence on the part of the Committee who is responsible for the Report, addressed below in II.I.

Report content	Comment
Section 3.1 states that "the Committee assumes in this day and age that most parents and healthcare institutions would refer a child displaying symptoms of EPP to a doctor for medical assessment".	[redacted] t is consistently noted in the literature – and by patients themselves – that EPP patients typically undergo a diagnostic odyssey, with extended delay in diagnosis (Lala et al, 2018). It is common for EPP patients to be sent for psychiatric consultation prior to diagnosis due to the lack of belief or understanding of their symptoms from the medical profession.
Section 3.1 states that some patients may choose not to receive treatment as SCENESSE® only provides symptomatic relief but does not alter the potential risk of liver failure.	Only 2-5% of EPP patients experience liver failure as a result of their EPP, while the main clinical impact upon patient quality of life is due to chronic phototoxicity. Over more than 15 years of clinical use, CLINUVEL has never had reports from patients or expert physicians that the lack of reported impact on liver function has been a rationale for not commencing or continuing treatment. Further, the Company has shown throughout its evidence that SCENESSE® provides a clinical benefit to patients, allowing a life previously thought impossible. Rather than "symptomatic relief", this is a prevention of phototoxic symptoms, facilitating a normal life. Since the commencement of the DMC process, Wensink et al (2021) have published on this experience.

Section 3.3 suggests that EPP patients may receive some therapeutic benefit from a "spray-on tan"	The ignorance by the Committee of comparing a "spray-on tan" as a solution in EPP is made shockingly obvious. If one even wanted to contemplate the hypothesis – irrespective how simplistic and not supported by scientific data – the Sponsor would not have developed a hormonal therapy for more than 10 years to treat EPP patients, and the medical community would have administered the "spray-on tan" solutions for decades. There is no medical evidence which supports the use of a cosmetic spray tan to prevent phototoxicity. The – unjustified – suggestion that such an approach may provide a therapeutic benefit illustrates the Committee's biased approach to evaluating the only approved medication for EPP.
The conclusion to Section 5.1.2 draws a direct causation between patient protoporphyrin IX (PPIX) levels and severity of disease symptoms, suggesting that baseline PPIX levels would help assess patients' sensitivity to light.	There is only limited evidence of a correlation between PPIX and disease severity, which is inconsistent and not of sufficient quality to justify PPIX levels constituting a clinical study endpoint. Indeed, the Lecha et al (2009) paper (reference 1 in the Report) notes the lack of correlation between PPIX levels, FECH mutation or disease severity. This correlation claimed in the Report shows a lack of understanding of the disease mechanism of action and the available literature. The Committee does demonstrate that it does not understand the difference of light sensitivity of the (epi)dermis and phototoxicity provoked by protoporphyrin IX.
In a discussion of symptoms in Section 5.1.5, the Report suggests that only some patients experience chronic symptoms.	The Committee is inconsistent in its presentation of the disease. EPP is a lifelong disorder with patients experiencing acute phototoxic reactions from first exposure to light. Later in Section 5.1.5 (Adverse Events) the Report notes that EPP is chronic in nature, necessitating an acceptable safety profile. The draft Health Economic Report also refers to EPP as a "chronic disease" in section 7.

II. Procedural failures

II.I Lack of expertise and disease knowledge

Page 5 of the DMC's process guide for assessing new pharmaceuticals notes that the DMC will establish "… an expert committee consisting of members with specific knowledge about the relevant disease, including physicians, nurses, pharmacists, patients etc." It is clear that the DMC has failed to establish an appropriate Committee for the review of SCENESSE®, despite establishing such a committee for another product under review.

The Report has been overseen by the Council's Drug and therapeutics committee on atopic eczema. When this choice was questioned by the Company early in the review of SCENESSE®, it was advised that no other Committee existed which was relevant to the review. The Company notes that the drug *givosiran* – a newly approved treatment for acute hepatic porphyrias – is being evaluated by a Committee for porphyrias, the same family of metabolic disorders as EPP. It is incomprehensible why this Committee chose to request consultation

from dermatologists whereas porphyria is a genetic metabolic disorder, treated predominantly worldwide by specialists other than dermatologists.

The Committee reviewing SCENESSE® comprised five physicians and two clinical pharmacists. Two regions did not appoint members. No patient representative was appointed – it is unclear why, and this point is discussed in further detail in II.II. Of the five physicians – four dermatologists and one pharmacologist – and two pharmacists, none have ever published research into porphyrias nor, to the Company's knowledge, are recognised experts in the disorder. It is questionable whether these physicians have treated EPP patients clinically, since no treatment currently exists in Denmark. The Company notes, however, that none of the known physicians consulting EPP patients at the recognised Danish porphyria expert centres were involved in the Committee.

As the Report acknowledges, EPP is a metabolic disorder, not a dermatological disorder. Patient care is generally provided by specialist haematologists, specialists in internal medicine, gastroenterologists, geneticists, hepatologists and biochemists. By selecting a Committee focused on atopic dermatitis – a common inflammatory disorder – the DMC has overtly failed to establish a committee with specific knowledge about EPP.

As outlined in Section I above, there are grave errors, assumptions and omissions in the Report, which reflect a lack of understanding or an attempt to deepen the knowledge on EPP and the clinical development of the first ever treatment for these patients.

CLINUVEL had identified [redacted] experts in Denmark with reasonable knowledge about the disease, none of whom have been approached by the Committee.

II.II The seven general principles

The DMC states that it has focused on implementing the seven general principles for prioritising hospital medicine as established by the Folketing.[2] The DMC and the Report has fundamentally failed to address these principles in its review of SCENESSE® for EPP.

Principle: Patient involvement

Despite its own guidance noting that one or two patients are typically part of an expert committee, the DMC did not include a patient representative on its expert committee for the review of SCENESSE®. It is unclear what involvement, if any, the three "contributing" patient representatives mentioned in Section 9 of the report had in the review of the drug. Other than [redacted], there is no evidence that patient views were considered in the drafting of the Report.

Principle: Openness and transparency around assessments and decisions

CLINUVEL has identified above a number of decisions and opinions expressed in the Report which lack transparency.

Principle: Continued rapid introduction of drugs in Denmark

The DMC has extended the review of SCENESSE® beyond all reasonable timelines, having initially rejected its review entirely.

SCENESSE® was approved in Europe in December 2014. The Company first received correspondence from the DMC in 2017. From 2017 to 2019 the DMC maintained that it was not the appropriate body to review SCENESSE®, insisting that the Company engage with the Danish regions. In June 2019 it was decided that the DMC should review the product. In October 2019 the DMC proceeded with an assessment, which is incomplete as at the end of March 2021.

[2] https://www.regioner.dk/sundhed/medicin/prioritering

These give the semblance that the Committee and DMC are not genuinely interested in providing therapy to Danish EPP patients. The delays not only deny EPP patients with access to the only approved medication for their disorder, they also erode CLINUVEL's market exclusivity granted under the marketing authorisation.

Principle: Equal access for patients to medicine

[redacted]

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Medicinrådet

Response to comments regarding afamelanotide

20. april 2021

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Dear Lachlan Hay

Thank you for your response. We appreciate your feedback and have responded to some of your comments below.
We would like to clarify the purpose of the consultation. It is your opportunity to comment on whether you think there are factual errors in the report or conditions the expert committee or the Council has overlooked that could have an impact on DMC's assessment and categorization of your medicine. The fact that you disagree with the assessment of the expert committee, and the DMC's work and methods in general, we will not comment upon those.
We have discussed your consultation letter with the chair of the expert committee, and none of your comments will lead to a change in the categorization nor the overall assessment.
DMC has the following comments to your response:

- We would like to resolve the misunderstanding regarding the process of DMC's assessment of afamelanotide. The DMC only assesses the value of medicines that have been approved by EMA after January 1st, 2017. The DMC has nevertheless chosen to assess afamelanotide because one region approached DMC with a request for such an assessment, as afamelanotide is currently the only treatment option for patients with erythropoietic protoporphyria (EPP). An assessment of a medicinal product on DMCs initiative, is not subject to any requirements for processing times.
- DMC believes that the expert committee regarding atopic eczema was competent to evaluate afamelanotide, as patients with EPP primarily consult dermatologists in Denmark. Furthermore, the expert committee was extended by one clinician who had seen many patients diagnosed with EPP. Furthermore, three patients with EPP were also included in the expert committee in connection with this assessment. We therefore do not find your criticism of our choice of expert committee members justified. Even if you disagree with the expert committee's assessment and conclusions, we find it unjustified to say it is due to the lack of competence of the expert committee, within this area.
- DMC assesses the quality of evidence using GRADE, which is an internationally recognized method for assessing quality of evidence and strength of recommendations in a systematic and transparent manner. Thus, the same system is used in the assessment of all medicines, regardless of whether there may be good reasons, including ethical reasons, for the chosen study design. You can read more about the Council's application of GRADE in DMC's method manual. It is also important to keep in mind that the quality of the evidence does not affect how medicine is categorized.
- Regarding the reduction of phototoxic symptoms reported in CUV039, the data have an uneven distribution. Therefore, you have rightly chosen to present a non-parametric analysis in your application, which is appropriate for skewed data. The methods of the DMC do not allow for a categorization using non-parametric statistics. However, the expert committee has still evaluated the data, as is common procedure when the available data is not suited for categorization.
- Thank you for making us aware of the study period of CUV029. It will be corrected in a new version of the assessment report that will be presented for the Council. Nevertheless, CUV029 is assessed by EMA not to be GCP-compliant, and they conclude that the results are not valid, nor reliable. Thus, this does not change the expert committee's decision of not using data from CUV029 except for the assessment of adverse events.

- Regarding the note on one patient experiencing an allergic reaction, the expert committee has agreed to erase it from the assessment report. The expert committee chose to do so in order to prevent any misunderstanding from external readers regarding safety, as there is no evidence to confirm that it was attributed to the treatment.
- Regarding the assessment of quality of life, the expert committee has taken results from both DLQI and EPP-QoL into account to make a more comprehensive assessment. We think that only focusing on EPP-QoL will deteriorate the assessment.

A few concluding remarks to clarify the process from here:

- The question of whether afamelanotide will be recommended by DMC will be discussed by the council on the 28th of April 2021. The discussion will be based on the assessment report and the price you have negotiated with Amgros. The DMC only makes recommendations and not decisions. Thus, in case of a non-recommendation, the use of afamelanotide will be a decision made by each region in Denmark.
- When the recommendation is published, your response will be published too, along with this letter. If you need to keep anything in your response confidential, please send us a new version in which the relevant paragraphs are clearly marked as such.

Kind Regards

[redacted]

Medicinrådet

Medicinrådets vurdering vedrørende afamelanotid til behandling af erytropoietisk protoporfyri

Version 1.1

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.

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1. Medicinrådets konklusion

Medicinrådet vurderer, at den samlede værdi af afamelanotid sammenlignet med placebo til patienter med erytropoietisk protoporfyri **ikke kan kategoriseres** i henhold til Medicinrådets metoder.

Ser man udelukkende på de randomiserede studier, ses der ingen klinisk relevant effekt hverken på muligheden for at opholde sig længere tid udenfor uden smerter eller på livskvalitet. Inddrager man data fra de observationelle studier, tyder det på, at afamelanotid samlet set potentielt kan forbedre patienternes muligheder for at opholde sig udendørs. Dog er effektens størrelse svær at vurdere.

Medicinrådet har foretaget deres kategorisering på baggrund af et randomiseret studie. Men på baggrund af dette studie er det vanskeligt at udtale sig om effekten af behandlingen. Dette skyldes, at patienterne har en undgående adfærd over for sollys, som er svær at ændre, når studiet er blindet og foregår over en periode, som er for kort til, at der kan ske en adfærdsændring. Medicinrådet lægger desuden vægt på, at der ingen objektive mål findes for sygdommen, og at de selvrapporterede effektmål viser en meget stor spredning, som kan skyldes, at nogle patienter oplever effekt og andre ikke. Det kan også være et udtryk for, at sygdommens sværhedsgrad er meget individuel, eller at forsøgsdeltagernes risikovillighed for at færdes udendørs har været forskellig. Derudover kan spredningen også skyldes store geografiske forskelle og dermed forskelle i antal solskinstimer, patienterne har oplevet.

Medicinrådet har derfor inddraget supplerende observationelle data med længerevarende studieperioder, som viser, at behandlingen gør det muligt for patienterne at færdes mere udendørs, samtidig med at deres livskvalitet forbedres.

Bivirkningerne ved behandlingen vurderer Medicinrådet som værende acceptable. Dette understøttes også af observationelle studier, som viser, at mange patienter fortsætter behandlingen i mange år.

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

AE: *Adverse event*

α-MSH: α-melanocytstimulerende hormon

BMI: *Body-mass index*

CI: Konfidensinterval

DLQI: *Dermatology Life Quality Index*

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

EPAR: *European Public Assessment Report*

EPP: Erytropoietisk protoporfyri

EPP-QoL: *Erythropoietic protoporphyria Quality-of-Life*

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

HR: Hazard ratio

IQR: *Interquatile range*

ITT: *Intention to treat*

MC1R: Melanocortinreceptor

MKRF: Mindste klinisk relevante forskel

OR: Odds ratio

PPIX: Protoporfyrin IX

RCT: *Randomised clinical trial*

RR: Relativ risiko

SD: Standard deviation

TEAE: *Treatment emergent adverse event*

3. Introduktion

Formålet med Medicinrådets vurdering af afamelanotid til patienter med erytropoietisk protoporfyri (EPP) er at vurdere den værdi, lægemidlet har, sammenlignet med dansk standardbehandling.

Vurderingen er udarbejdet, fordi Medicinrådet af egen drift har besluttet at vurdere lægemidlet. Beslutningen blev truffet den 28. august 2019. Virksomheden, som har markedsføringstilladelsen til afamelanotid, er blevet tilbudt at indsende en ansøgning med kliniske data samt sundhedsøkonomiske analyser, hvilket de har gjort. Vi modtog ansøgningen den 19. november 2020.

Det kliniske spørgsmål er:

Hvilken værdi har afamelanotid sammenlignet med placebo til patienter med erytropoietisk protoporfyri?

3.1 Erytropoietisk protoporfyri

Erytropoietisk protoporfyri (EPP) er en metabolisk sygdom, der gør patienterne ekstremt intolerante overfor lys og forårsager fototoksicitet i huden (smerter, hævelse og rødme). Patienterne er intolerante for både UV-lys og synligt lys – også gennem vinduesglas. Yderligere kan kunstigt lys fra f.eks. lamper og billygter også være generende, men graden af intolerance varierer mellem patienterne og kan forværres, hvis patienten har været udsat for lys i længere tid.

EPP er en sjælden sygdom, som hører under en gruppe af arvelige sygdomme kaldet porfyri. Porfyri skyldes genmutationer i enzymer, som i hæmoglobinsyntesen skal danne hæmoglobin (den iltbindende del af røde blodlegemer). Derved ophobes de toksiske forstadier til hæmoglobin (porfyrin) [1,2]. Porfyri opdeles i akutte/ikke-akutte porfyrier og kutane/ikke-kutane porfyrier, afhængigt af hvor defekten i hæmoglobinsyntensen optræder, og hvor ophobningen af porfyriner sker (bl.a. i lever, knoglemarv, de røde blodlegemer og hud). Akutte porfyrier giver symptomer i nerver og indre organer, mens kutane porfyrier giver symptomer i huden i form af lysfølsomhed (fotosensitivitet) på grund af udskillelse af frie radikaler i huden ved lyseksponering.

EPP er en af de mest alvorlige kutane porfyrier. Symptomerne på EPP er ekstrem intolerance for lys, som viser sig ved neuropatiske brændende smerter i huden, rødme, hævelse samt evt. sårdannelse og blødninger i huden (petekkier). Sygdommen manifesterer sig ofte i barndommen og viser sig allerede efter de første soleksponeringer [1]. Symptomerne kommer straks efter lyseksponering (1-30 minutter) og kan vare i op til flere dage. Symptomerne kan variere i sværhedsgrad alt efter varigheden af lyseksponering. Synlig hud, såsom ansigt og hænder, vil typisk være steder, hvor symptomerne opstår [1–3]. Patienterne kan ved lyseksponering opleve, at de får feberlignende symptomer, bliver trætte og bliver følelsesmæssigt påvirkede. Derudover er huden meget følsom for berøring. Gentagne perioder med lyseksponering kan resultere i, at patienterne udvikler fortykkelse af huden, ar og læderhud [1].

Risikoen for symptomer gør, at patienterne undgår at færdes ude i dagtimerne eller kun i meget begrænset omfang kan være udendørs. Dette har store konsekvenser for patienternes dagligdag og kan føre til social isolation, da de begrænses i sociale aktiviteter og oplever manglende forståelse fra omverdenen [4]. Derudover begrænser sygdommen også patienternes jobmuligheder. Alt dette medfører, at patienterne har væsentligt nedsat livskvalitet [1-3].

Patienterne har ofte D-vitaminmangel som følge af, at de undgår sollys. Dette kan betyde risiko for nedsat knogletæthed og vitaminmangel. Derudover vil 5-20 % af patienterne med tiden udvikle levermanifestationer, som potentielt kan føre til akut leversvigt [5]. Af samme grund skal patienterne være tilbageholdende med alkohol og være opmærksomme ved behov for jerntilskud.

Forekomsten af EPP i Danmark anslås at være 13 pr. 1.000.000 indbyggere [2], hvilket stemmer overens med fagudvalgets anslåede 80-100 patienter. Fordelingen af patienter over og under 18 år er ukendt. Der skønnes at være 1-2 nye tilfælde pr. år. Sygdommen forekommer lige hyppigt hos mænd og kvinder [5] og ses sjældent hos personer med mørk hud [3].

EPP diagnosticeres på baggrund af kliniske symptomer samt måling af forhøjet porfyrin i blodet. Hos børn mistænkes EPP, hvis de græder eller klager over smerter i huden under eller efter soleksponering [2]. På grund af sygdommens sjældenhed kan det tage lang tid, før patienterne bliver diagnosticeret; således bliver nogle patienter først som voksne korrekt diagnosticerede [5]. Fagudvalget skønner imidlertid, at forældre i dag vil opsøge læge, hvis et barn udviser symptomer på EPP med henblik på udredning.

Der er formentlig fortsat en gruppe udiagnosticerede patienter, især ældre patienter, som potentielt vil blive opdaget og kan tilbydes behandling med afamelanotid, hvis dette lægemiddel bliver anbefalet som mulig standardbehandling. Det er dog ikke sikkert, at alle patienter ønsker at modtage behandlingen, fordi de har vænnet sig til at leve 'i skyggen', og fordi behandlingen kun virker symptomlindrende og ikke ændrer prognosen med hensyn til eksempelvis leverpåvirkning.

Fagudvalget vurderer, at ca. 40-50 patienter vil have et behandlingsbehov og dermed vil kunne tilbydes behandling med afamelanotid, såfremt det bliver godkendt som standardbehandling.

3.2 Afamelanotid

Afamelanotid (Scenesse®) blev i 2014 godkendt af EMA til forebyggelse af lysintolerance hos patienter ≥ 18 år, som er diagnosticeret med EPP. Lægemidlet er ikke aktuelt markedsført i Danmark. I EMA har lægemidlet status som *orphan drug*.

Afamelanotid er en syntetisk peptid, som er en analog til α-melanocyt-stimulerende hormon (α-MSH). Det er en agonist for melanocortin-receptoren (MC1R) på melanocytceller. Afamelanotid stimulerer, via MC1R, melanocytterne til at producere eumelanin. Eumelanin pigmenterer huden, hvilket beskytter huden mod de fototoksiske reaktioner forårsaget af sollys [5].

Afamelanotid administreres som et subkutant implantat og indsættes under lokalbedøvelse via et kateter i fedtlaget på forsiden af hoftekarmen. Implantatet måler 1,7 cm i længden og 1,5 mm i diameter. Implantatet kan fjernes ved behov, f.eks. hvis der opstår en allergisk reaktion, men absorberes inden for 50-60 dage. Derfor skal der indsættes et nyt efter 60 dage. Der anbefales behandling med tre implantater årligt eller højest fire implantater i de mest solrige måneder. Implantatet indeholder en dosis på 16 mg afamelanotid. Behandlingslængden vurderes af den behandlende læge, men kan i princippet være livslang. Fagudvalget vurderer, at behandlingen vil være livslang, hvis den har effekt og ingen bivirkninger.

Behandlingen anbefales ikke til patienter over 70 år, da behandlingen ikke er tilstrækkeligt undersøgt i denne aldersgruppe [5]. Behandlingen anbefales ikke til gravide og ammende, da behandlingen ikke er undersøgt i denne patientgruppe. Kvinder i den fertile alder bør ikke modtage behandlingen, med mindre de anvender effektiv kontraception, som de bør fortsætte minimum tre måneder efter ophør af en behandling. Derudover bør afamelanotid ikke anvendes til patienter med nedsat lever- og nyrefunktion [5].

3.3 Nuværende behandling

Standardinterventionen er at undgå eksponering for UV-lys og synligt lys i det omfang, det er muligt. Dette involverer, at patienterne skærmer huden ved at påføre sig dækkende tøj samt brug af solafskærmende hatte. Nogle vælger også spraytan, om end effekten er kortvarig.

Der findes aktuelt ingen godkendte lægemidler til behandling af EPP i Danmark, hvorfor der er stort *unmet need* hos disse patienter. Symptomatiske behandlinger involverer brugen af smertestillende medicin, antihistaminer, topikale kortikosteroider samt kold kompression [5]. I mangel af effektiv medicinsk behandling har man anvendt forebyggende behandling med betacaroten, N-acetyl-L-cysteine, zink og C-vitamin. Samtlige ovenstående behandlinger har dog ingen eller ringe dokumenteret effekt på patienternes symptomer [3], og der findes derfor ingen medicinsk standardbehandling.

4. Metode

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

5. Resultater

5.1 Klinisk spørgsmål 1

5.1.1 Litteratur

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

Ansøger har inkluderet studiet publiceret af Langendonk et al. 2015 [3] (herefter; Langendonk), som Medicinrådet har efterspurgt i protokollen. Herudover har ansøger, jf. protokollen, inkluderet tidligere studier i studieprogrammet for afamelanotid, studier vedrørende langtidsbivirkninger samt EMAs *European Public Assessment Report* (EPAR) [5] for afamelanotid. Tabel 1 viser en oversigt over det indsendte data, og hvorledes fagudvalget vil bruge det i vurderingen.

Publikationen af Langendonk rapporterer data fra to kliniske studier; CUV039 og CUV029. Fagudvalget vil desuden benytte de to observationelle studier af Biolcati et al. [6] og Wensink et al. [7] til beskrivelse af effekt og langtidsbivirkninger.

Fra lægemidlets studieprogram har ansøger også inkluderet tre tidligere studier (CUV010, CUV017 og CUV030). Ansøger har dog ikke lagt vægt på resultaterne herfra i ansøgningen. Fagudvalget finder dem ligeledes mindre relevante i forhold til, at det mest tungtvejende randomiserede data kommer fra CUV039 og CUV029. Data fra CUV010, CUV017 og CUV030 vil derfor ikke indgå i fagudvalgets vurdering.

Clinicaltrials.gov er konsulteret ift. lokation af studiecentre i CUV039 og CUV029.

Tabel 1: Datakilder identificeret og udvalgt af ansøger som evidensgrundlag samt fagudvalgets anvendelse i vurderingen af klinisk værdi

Studie NCT nummer		Design Start - afslutningsdato	Antal	Anvendelse i vurderingen af klinisk værdi
Langendonk et al. 2015 [3]	**CUV039** NCT01605136	Dobbeltblindet, randomiseret fase III-studie Maj 2012 – juli 2013 (Vurderet af EMA som det pivotale studie)	93	Primære datakilde for den kliniske vurdering
	CUV029 NCT00979745	Dobbeltblindet, randomiseret fase III-studie September 2009 – maj 2011 (første patient indrulleret i januar 2010)	74	Anvendt som supplement i forhold til bivirkninger

Studie NCT nummer	Design Start - afslutningsdato	Antal	Anvendelse i vurderingen af klinisk værdi
Biolcati et al. 2015 [6] Intet NCT-nummer	Observationelt retrospektivt studie 2006 – 2014	115	Anvendt til at belyse langtidsbivirkninger af afamelanotid
Wensink et al. 2020 [7] Intet NCT-nummer	Prospektivt kohortestudie Juni 2016 – september 2018	117	Anvendt til at belyse langtidsbivirkninger samt til en narrativ beskrivelse af effekten af afamelanotid over flere år
EMAs *European Public Assessment Report* (EPAR) [5]	-	-	Datakilde for den kliniske vurdering
EMAs produkt resumé (SPC)[8]	-	-	Anvendes i afsnittet Andre *overvejelser*
CUV010 Intet NCT-nummer	Ukontrolleret fase II-studie af 5 EPP-patienter. September 2006 – februar 2007	5	Anvendes ikke i den kliniske vurdering som følge af; studiet ikke er randomiseret, studiepopulationen er lille, studiets effektmål er ikke efterspurgt i protokollen
CUV017 NCT04053270	Randomiseret, placebo kontrolleret, fase III-overkrydsningsstudie Maj 2007 – december 2009	100	Anvendes ikke i den kliniske vurdering som følge af; der var tilladt overkrydsning i studiet
CUV030 NCT01097044	Dobbeltblindet, randomiseret fase II-*Confirmatory Study* af 77 patienter April 2010 – januar 2011	77	Anvendes ikke i den kliniske vurdering, eftersom erfaringer fra CUV030 blev bragt videre til CUV029 og CUV039. CUV030 var ikke GCP (good clinical practice) - kompliant if. EPAR

5.1.2 Studie- og baselinekarakteristika for de inkluderede studier

CUV039

CUV039-studiet undersøgte effekt og bivirkninger af afamelanotid sammenlignet med placebo. Studiet inkluderede patienter ≥ 18 år diagnosticeret med EPP og blev udført på syv forskellige centre i USA med lokation i: Alabama, Californien, Michigan, New York,

North Carolina, Texas og Utah. For at undersøge lægemidlets effekt i årets mest solrige måneder blev patienterne kun indrulleret i studiet i forårs- og sommermånederne.

I alt blev 94 patienter randomiseret i en ratio 1:1 til enten 16 mg afamelanotid eller placebo. Der blev anvendt blokrandomisering for at sikre ensartet gruppetildeling på tværs af centrene, som følge af centrenes forskellige geografiske placering, hvor man kan forvente forskelle i muligheden for soleksponering. Inklusionsperioden var 2 måneder (maj og juni 2012). Hvis patienterne opfyldte inklusionskriterierne, kunne de modtage første behandling med afamelanotid inden for 14 dage. Patienterne fik indopereret et implantat med afamelanotid eller placebo hver 2. måned over en periode på seks måneder/180 dage (dvs. totalt tre implantater i behandlingsperioden), hvilket vil sige at, for de, som blev inkluderet sidst, vil sidste implantat være indopereret i november 2012. Der blev foretaget opfølgning på bivirkninger og livskvalitet dag 360.

Studiets primære formål var at undersøge, om afamelanotid tillod patienterne at eksponere dem selv for sollys, uden der forekom smerte eller fototoksiske reaktioner. For at undersøge dette skulle patienterne hver dag udfylde dagbøger, hvori de angav tiden, de havde opholdt sig underdørs i hhv. skygge og/eller direkte sollys, i intervaller af 15 minutter i tidsrummet fra kl. 10 til kl. 18. Samtidig skulle patienter ved hjælp af en Likert-skala (0-10) angive, om de i tiden udendørs havde oplevet smerte. Sekundære effektmål inkluderede livskvalitet, varighed af fototoksiske reaktioner og bivirkninger.

Fagudvalget bemærker, at studiecentrenes geografiske lokation ligger sydligere end Danmark, samt at der mellem de forskellige studiecentre er en stor geografisk spredning, som vil have betydning for, hvor meget forsøgsdeltagerne kan eksponere dem selv for sol. Fagudvalget vurderer, at der i en dansk population ofte vil være tale om tre til fire implantater årligt for at dække den periode, hvor patienterne oplever de værste symptomer.

Fagudvalget finder det hensigtsmæssigt, at studiet primært er udført hen over sommermånederne, som er sammenligneligt med tidspunktet på året, hvor behandlingen potentielt også vil kunne tilbydes danske patienter. Samlet set vurderer fagudvalget, at resultaterne fra CUV039-studiet kan overføres til den danske population, dog med forbehold for den geografiske forskel, som betyder, at deltagerne i studiet potentielt kan udsættes for flere solskinstimer end patienter i Danmark.

CUV029

CUV029-studiet minder meget om CUV039 i design og udførelse. De to studier fulgte også den samme protokol, dog med nogle ændringer i CUV039 baseret på erfaringer fra CUV029. Derfor vil kun de væsentligste forskelle blive gennemgået i det følgende.

CUV029 er udført på otte forskellige centre i Europa med lokation i: Helsinki, Düsseldorf, Dublin, Maastricht, Rotterdam, Paris, Newport og Manchester. *Intention to treat* (ITT)-populationen bestod af 74 patienter (38 fik afamelanotid, mens 36 fik placebo). Inklusionsperioden var 11 måneder (fra september 2009 til og med juli 2010), første patient blev dog først indrulleret i januar 2010. Hvis patienterne opfyldte inklusions-kriterierne, kunne de modtage første behandling med afamelanotid inden for 7 dage. Patienterne fik indopereret et implantat med afamelanotid eller placebo hver 2. måned over en periode på ni måneder/270 dage (dvs. totalt fem implantater i behandlingsperioden), hvilket vil sige, at for de, der blev inkluderet sidst, ville sidste

implantat være indopereret i april 2011. Der var ingen opfølgningsperiode. Tiden, patienterne i behandlingsperioden opholdt sig udendørs, blev angivet i en dagbog. Patienterne skulle angive, hvorvidt de opholdt sig i direkte sollys, indirekte sollys eller skygge i 15-minutters intervaller i tidsrummet kl. 10-15. Smerte skulle angives på samme måde som i CUV039.

Fagudvalget bemærker, at studiecentrene generelt ligger mere sydligt end Danmark, hvor antallet af solskinstimer vurderes at være højere. Derudover bemærker fagudvalget, at studiet er udført over en lang periode, hvilket tillader, at nogle patienter også modtog behandling i vinterhalvåret. Fagudvalget vurderer, at dette er en usikkerhed ved studiet, som ikke vil give et retvisende billede af, hvordan effekten af afamelanotid er i sommermånederne, hvor det er særligt vigtigt at have en effektiv behandling. Ifølge EMAs EPAR er studiet ikke udført i overensstemmelse med *Good Clinical Practise (GCP),* bl.a. som følge af ændringer i analyseplanen. EMA konkluderer, at resultaterne fra studiet ikke er valide og pålidelige [5]. Fagudvalget vurderer på den baggrund, at CUV029 kun kan anvendes som supplement i vurderingen af afamelanotid i forhold til bivirkninger.

Wensink et al. 2020
Studiet af Wensink er et prospektivt kohortestudie, som undersøger sikkerhed og effekt af afamelanotid i klinisk praksis hos EPP-patienter. Studiet inddrager 117 patienter med EPP fra et dagsambulatorium i Rotterdam. Patienterne modtog afamelanotid hver 2. måned, maksimalt fire gange årligt. Data blev indsamlet i perioden juni 2016 til september 2018. Følgende effektmål blev rapporteret: tid opholdt udendørs, livskvalitet, fototoksiske reaktioner (antal, sværhedsgrad og varighed), anvendelse af beskyttende tøj og uønskede hændelser.

Fagudvalget finder studiet brugbart til belysning af effekt og langtidsbivirkninger, på trods af at det ikke er randomiseret. Fagudvalget vurderer, at det både er en fordel og en ulempe, at studiet ikke er randomiseret. Det er en fordel, fordi patienterne ved, at de får en aktiv behandling, som kan få dem til at overvinde frygten for symptomer ved at bevæge sig udendørs. Omvendt er det en ulempe, fordi det ikke er randomiseret og uden nogen kontrolgruppe, og det vides dermed ikke, om noget af effekten kan tilskrives en placebo-effekt. Fagudvalget vil i mangel på bedre data fra randomiserede studier lægge vægt på resultaterne fra studiet.

Studiet foregår i Rotterdam, som vejrmæssigt vurderes sammenligneligt med Danmark. Derudover er data indsamlet over 2 år og inkluderer derved også de mest solrige måneder.

Biolcati et al. 2015
Studiet af Biolcati er et retrospektivt studie, som undersøgte compliance, livskvalitet og sikkerhed af afamelanotid. Studiet rapporterer observationer fra 115 EPP-patienter, som tilsammen blev behandlet med 1023 afamelanotidimplantater over en periode på 8 år (2006-2014). Patienterne blev behandlet på porfyricentre i enten Rom eller Zürich. Studiet inkluderede i starten kun patienter fra CUV010 og CUV017, senere blev der åbnet op for, at øvrige EPP-patienter på de to porfyricentre også kunne indgå.

Fagudvalget finder studiet brugbart til belysning af langtidsbivirkninger, på trods af at det er retrospektivt og ikke randomiseret. I vurderingen vil fagudvalget tage forbehold for den lidt sydligere geografiske placering af studiecentrene, sammenlignet med Danmark.

Tabel 2: Baselinekarakteristika

	CUV039		CUV029		Wensink 2020	Biolcati 2015*
	Afamelanotid (n = 48)	Placebo (n = 45)	Afamelanotid (n = 38)	Placebo (n = 36)	Afamelanotid (n = 117)	Afamelanotid (n = 115)
Alder, middel ± SD	40,4 ± 12,0	39,1 ± 16,2	38,3 ± 13,0	38,6 ± 11,6	43 ± 15,5	38,9 (12,8)
Kvinder, antal (%)	20 (42)	24 (53)	17 (45)	20 (56)	59 (50)	53 (53)
BMI, middel ± SD	26,0 ± 4,8	26,7 ± 5,4	24,0 ± 3,0	26,5 ± 5,2	25,2 + 4,6	-
Kaukasiere, antal (%)	47 (98)	43 (96)	38 (100)	35 (97)	-	99 (99)
Livskvalitet, EPP-QoL, middel ± SD	27 ± 20	26 ± 19	39 ± 26	35 ± 24	30,6 (IQR 18,8 – 45,1)	-
Total PPIX level, median (IQR), µmol/L i de røde blodlegemer	-	-	-	-	40 (7,9- 278)	-
Fitzpatrick** hudtype, antal (%)	-	-	-	-	-	-
I (bliver aldrig brun, altid solskoldet)	13 (27)	10 (22)	6 (16)	12 (33)	-	-
II (bliver med besværlighed brun, ofte solskoldet)	20 (42)	15 (33)	18 (47)	15 (42)	-	-
III (bliver næsten altid brun, sjældent solskoldet)	12 (25)	16 (36)	13 (34)	9 (25)	-	-
IV (bliver sjældent solskoldet, bliver med lethed altid brun)	3 (6)	4 (9)	1 (3)	0	-	-

*Studiet af Biolcalti inkluderer patienter, som deltog i CUV010 og CUV017, baselinekarakteristik er her rapporteret for CUV017 (n = 100), da CUV010 ikke forefindes. Baselinekarakteristikken opgjort for Biolcati er således repræsentativ for 100/115 patienter. ** Kategorisering af hudtyper er baseret på indikation for pigmentering.
Forkortelser: BMI = Body-mass index (vægt i kilogram divideret med højde i meter opløftet i 2); IQR = interquartile range; PPIX = protoporfyrin IX; SD = standard deviation.

Fagudvalget vurderer overordnet, at baselinekarakteristika er velafbalancerede mellem de to arme i både CUV039 og CUV029. I CUV039 ses det, at flere patienter i afamelanotidarmen har sarte hudtyper end i placebo-armen, jf. Fitzpatrick hydtype, hvilket potentielt kan underestimere effekten af afamelanotid. I CUV029 er der flere i placeboarmen, som har den helt sarte hudtype (hudtype I), mens flere har hudtype III og IV i afamelanotidarmen. Der vil ikke blive taget højde for forskelle i Fitzpatrick hudtype i fagudvalgets vurdering. Overordnet har størstedelen af patienterne de to mest sarte hudtyper (I og II), hvilket stemmer overens med danske patienter.

Niveauet for livskvalitet blandt danske patienter kendes ikke, men fagudvalget formoder, at det følger symptomintensiteten og dermed varierer med årstiden. Fagudvalget vurderer overordnet, at baselinekarakteristikken stemmer overens med, hvad man kan forvente hos EPP-patienter i dansk klinisk praksis.

Fagudvalget bemærker, at det havde været nyttigt at kende patienternes protoporfyrin-niveauer ved baseline for CUV029 og CUV039, dette for at kunne vurdere patienternes lysfølsomhed. Disse niveauer er kun rapporteret i Wensink. Fagudvalget bemærker desuden, at det havde været relevant at kende fordelingen af patienterne tilknyttet de forskellige studiecentre i CUV039 og CUV029. Dette som hjælp til at diskutere resultaterne, da både symptomer og livskvalitet hænger sammen med antal solskinstimer, som varierer med den geografiske placering af studiecentrene.

5.1.3 Databehandling og analyse

I dette afsnit er ansøgers datagrundlag, databehandling og analyse for hvert af de tre effektmål (livskvalitet, symptomer og bivirkninger), efterspurgt i protokollen, beskrevet.

Livskvalitet
Fagudvalget ønskede i protokollen livskvalitet opgjort kvantitativt ved brug af DLQI (som gennemsnitlig ændring fra baseline til længst mulig opfølgningstid) og narrativt ved brug af EPP-QoL, som et supplement til DLQI. Disse data har ansøger indsendt, herunder også en sammenlignende analyse for EPP-QoL.

Data for livskvalitetsspørgeskemaet DLQI baserer sig på CUV039-studiet. For det sygdomsspecifikke livskvalitetsspørgeskema, EPP-QoL, baserer data sig også på CUV039. Derudover vil fagudvalget også anvende livskvalitetsdata fra studiet af Wensink, som supplement i vurderingen, om behandlingen har en effekt på livskvalitet.

ITT-populationen for CUV039 for effektmålet livskvalitet består af 90 patienter (afamelanotid n = 47, placebo n = 43). Patienterne udfyldte spørgeskemaerne (DLQI og EPP-QoL) på dag 0, 60, 120 og 180. Derudover blev EPP-QoL yderligere udfyldt ved et *safety follow-up* besøg på dag 360.

Ansøger beskriver, at EPP-QoL er valideret hos Oxford Outcomes på baggrund af data indsamlet i CUV039. Valideringen resulterede i, at tre spørgsmål udgik fra det originale spørgeskema, og det fik en anden scoringsalgoritme. Ansøger beskriver, at EPP-QoL spørgeskemaet er mere sensitivt over for livskvalitetsændringer sammenlignet med DLQI, fordi det er specifikt for patientpopulationen, dette er fagudvalget enige i.

DLQI er imidlertid valideret til patienter med dermatologiske lidelser overordnet og er således udviklet efter metodiske standarder. Der er til gengæld usikkerhed om, hvordan EPP-QoL er blevet udviklet, og der mangler dokumentation for reproducerbarheden.

Livskvalitet er et komplekst effektmål, som påvirkes af mange faktorer, derfor ses der variation over tid. Af den grund giver måling af livskvalitet et øjebliksbillede og er således ikke fyldestgørende for udsving over en længere periode.

I CUV039 bliver livskvalitet målt hver anden måned med de to spørgeskemaer. Ved EPP-QoL spørges der til patientens livskvalitet de seneste 2 måneder. Dette kan være problematisk i forhold til recall bias, hvilket betyder, at det kan være svært at huske, hvordan man havde det på et givent tidspunkt, blandt andet fordi man bliver påvirket af, hvordan man har det aktuelt. Af den grund spørges der normalt ikke længere tilbage end fire uger i spørgeskemaer vedrørende livskvalitet. Ved DLQI spørges der til patientens livskvalitet den seneste uge. Fagudvalget vurderer, at livskvalitet er tilstrækkeligt belyst til at kunne indgå i vurderingen.

Symptomer
Fagudvalget ønskede i protokollen effektmålet *symptomer* opgjort ved hjælp af to deleffektmål: 1) minutter pr. dag udendørs uden eller med milde symptomer og 2) varighed af symptomer efter en periode med soleksponering. Ansøger har anvendt data fra CUV039 til besvarelse af effektmålene. Data er i overensstemmelse med, hvad fagudvalget efterspurgte i protokollen. Som supplement til disse data vil fagudvalget yderligere anvende data fra Wensink og Biolcati til at nuancere besvarelsen af effektmålet.

I CUV039 er varigheden af tiden, patienterne opholdt sig udendørs, opgjort i minutter pr. dag mellem klokken 10-18. Varigheden af fototoksiske reaktioner er opgjort i dage ved en post-hoc analyse, hvor man så på, hvor længe patienterne i en periode efter udsættelse af sollys havde haft en Likert score ≥ 4 point. ITT-populationen for effektmålet udgøres af 89 patienter (afamelanotid n = 46, placebo n = 43).

Bivirkninger
Fagudvalget ønskede, at bivirkninger blev opgjort som andelen, der oplevede grad 3-4 uønskede hændelser (*adverse events*, AE's), og dertil en narrativ beskrivelse af bivirkningsprofilen. Ansøger har opgjort *treatment emergent adverse events* (TEAE's), hvilket fagudvalget accepterer, da det omfatter uønskede hændelser, som er opstået i behandlingsperioden. TEAE's blev i CUV039 klassificeret som enten milde, moderate eller svære. Ansøger oversætter i deres ansøgning svære tilfælde af TEAE's til grad 3-4 uønskede hændelser. Dette skyldes, at en svær TEAE er defineret som en uønsket hændelse, der bevirker, at individet ikke kan udføre sine daglige aktiviteter, kan være livstruende og/eller invaliderende og, som investigator vurderer, er relateret til behandlingen. Opgørelsen af TEAE er baseret på en *safety* population på 93 patienter (afamelanotid n = 48, placebo n = 45), som havde modtaget mindst én behandling med deres tildelte intervention.

Til den narrative beskrivelse af bivirkningsprofilen har ansøger anvendt data fra både CUV029 og CUV039, opgjort som uønskede hændelser. Fagudvalget ønskede i protokollen også en beskrivelse af langtidsbivirkninger, derfor har ansøger leveret data fra Biolcati og Wensink. Bivirkninger i studiet af Biolcati er opgjort som totale antal

uønskede hændelser, der blev rapporteret i hele studiets varighed, derfor kan der ikke sættes tal på, hvor mange af patienterne som oplevede de forskellige hændelser. De uønskede hændelser blev klassificeret i forhold til, om de var relateret eller ikke relateret til afamelanotid.

5.1.4 Evidensens kvalitet

Medicinrådet har anvendt GRADE til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen. Medicinrådet har vurderet publikationen af Langendonk et al. 2015 (som indeholder resultater fra to randomiserede studier; CUV039 og CUV029) ved Cochrane risk of bias tool 2.0. Vurdering af risikoen for bias samt den fuldstændige GRADE-vurdering og begrundelserne er samlet i en GRADE-profil, se bilag 1.

GRADE-profilen er baseret på CUV039, som danner grundlag for kategoriseringen af værdien af afamelanotid. Der er nedgraderet ét niveau, på grund af risiko for bias, idet blindingen i studiet ikke kan opretholdes. Derudover er der nedgraderet ét niveau for inkonsistens, da data kun er baseret på resultater fra ét studie, og data fra det lignende CUV029-studie adskiller sig fra resultaterne i CUV039.

Evidensens kvalitet er vurderet at være lav, hvilket betyder, at nye studier med moderat sandsynlighed kan ændre konklusionen.

5.1.5 Effektestimater og kategorier

Af Tabel 3 fremgår de absolutte og relative effektforskelle, de foreløbige og aggregerede kategorier, den samlede kategori og den samlede kvalitet af evidensen for det kliniske spørgsmål.

Tabel 3: Resultater for det kliniske spørgsmål baseret på data fra EMAs EPAR for afamelanotid vedr. effektmålene livskvalitet og symptomer og fra CUV039-studiet vedr. effektmålet bivirkninger

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	
Livskvalitet	DLQI, gennemsnitlig ændring fra baseline *(4 point)*	Kritisk	0 (-3; 2)*	Kan ikke kategoriseres	Kan ikke beregnes	-	Kan ikke kategoriseres
	EPPQoL, gennemsnitlig ændring fra baseline (fagudvalget ønskede en kvalitativ gennemgang, derfor er MKRF ikke defineret)		Se tekst nedenfor				
Symptomer (fototoksicitet)	Minutter pr. dag udendørs (i indirekte og direkte sollys) uden eller med milde symptomer (smerte < 4 på Likert-skala fra 0-10) *(50 % mere tid udendørs, dog minimum 20 minutter)*	Kritisk	8,4 min (-1,5; 18,9)*	Kan ikke kategoriseres	Kan ikke beregnes	-	Kan ikke kategoriseres
	Varighed af symptomer (moderate-svære med smerte ≥ 4 på Likert-skala fra 0-10) efter episode med udsættelse for sollys *(20 % reduktion af varighed)*		3,4 dage (-1,8; 8,6), svarende til en reduktion på 52 %	Kan ikke kategoriseres	Kan ikke beregnes	-	
Bivirkninger	Andelen af patienter, der oplever uønskede hændelser af grad 3-4 *(5 procentpoint)*	Kritisk	2 %-point (-9; 13)	Kan ikke kategoriseres	RR 1,4 (0,25; 8,03)	Kan ikke kategoriseres	Kan ikke kategoriseres
	Kvalitativ gennemgang af bivirkninger, herunder langtidsbivirkninger – efter mindst 10 år		Se tekst nedenfor				
Konklusion							
Samlet kategori for lægemidlets værdi	Kan ikke kategoriseres						
Kvalitet af den samlede evidens	Lav						

MKRF = mindste klinisk relevante forskel. CI = konfidensinterval, RR = relativ risiko. *Den absolutte forskel er ikke baseret på gennemsnittet i hver arm, da data er skævt fordelt. Derfor har ansøger udregnet den absolutte forskel med de ikke-parametriske metoder Kruskal-Wallis test og Hodges-Lehmann shift. Da Medicinrådets metoder til kategorisering af lægemidlets værdi er baseret på forskelle i gennemsnit, kan værdien ikke kategoriseres.

Livskvalitet

Livskvalitet er et kritisk effektmål for vurderingen af lægemidlets værdi for patienterne, fordi EPP er en kronisk invaliderende sygdom, som kan medføre, at patienterne isolerer sig og hæmmes i deres sociale liv. Fagudvalget ønskede i protokollen livskvalitet opgjort kvantitativt ved brug af DLQI og narrativt ved brug af EPP-QoL.

DLQI

Den gennemsnitlige ændring fra baseline målt ved DLQI var henholdsvis -8,1 point i afamelanotid-armen og -7,3 point i placebo-armen. Dermed var den absolutte forskel 0,8 point, hvilket er under den mindste klinisk relevante forskel på 4 point. Data er dog skævt fordelt, hvorfor ansøger har udført den sammenlignende analyse på den mediane ændring fra baseline ved hjælp af de non-parametriske test Kruskall-Wallis og Hodges-Lehmann shift, som ses af tabel 4.

Tabel 4: Livskvalitet målt ved DLQI ved dag 180

	Afamelanotid	Placebo
Gennemsnitlig ændring fra baseline til dag 180 (SD)	-8,1 (6,2)	-7,3 (5,6)
Median	-7,5	-8,0
Spredning	-26-1	-19-5
95 % CI af gennemsnitlig ændring fra baseline	-9,9; -6,3	-9,0; -5,6
Kruskal-Wallis test	p-værdi = 0,799	
Hodges-Lehmann shift estimat (95 % CI)	0 (2; -3)	

Eftersom den sammenlignende analyse ikke er baseret på gennemsnitlige værdier, hvilket er en forudsætning for kategorisering jf. Medicinrådets metoder, kan værdien af afamelanotid **ikke kategoriseres** vedr. livskvalitet.

Fagudvalget vurderer, at resultaterne tyder på, at afamelanotid ikke har en effekt på livskvalitet. Det kan skyldes, at patienterne fortsat er begrænset i deres hverdag, fordi de ikke kan opholde sig meget længere udendørs, selvom de er i behandling med afamelanotid. Det kan også skyldes, at patienterne endnu ikke har ændret adfærd af frygt for symptomer eller af vane, også selv om de måske godt kunne opholde sig længere tid udendørs, end de har været vant til.

Fagudvalget bemærker, at livskvaliteten er bedst ved besøg 3 og 4 [5]. Dette kan skyldes årstidsvariation, hvor det for nogle patienter på det tidspunkt er blevet vinter, men det kan også være et udtryk for, at nogle patienter synes behandlingen har en effekt. Der er dog en vis usikkerhed ved data vedrørende livskvalitet, som i høj grad er påvirket af antal solskinstimer, dvs. årstid og geografisk placering.

EPP-QoL

Data for EPP-QoL anvendes kun som et kvalitativt supplement til DLQI, jf. protokollen, derfor kan effektmålet ikke kategoriseres jf. Medicinrådets metoder.

Som beskrevet i afsnit 5.1.3 har fagudvalget forbehold for data baseret på EPP-QoL-spørgeskemaet, da det ikke fremgår tydeligt, hvordan EPP-QoL er valideret, og at der er risiko for recall bias.

Livskvalitet målt ved EPP-QoL ved dag 180 og 360 blev i gennemsnit forbedret for både afamelanotid og placebo, som vist i Tabel 5. Ved dag 180 var den absolutte forskel 13,9 (95 % CI 2,8; 27,8).

Ved dag 360 var den gennemsnitlige forbedring faldet sammenlignet med dag 180 i både afamelanotid- og placebogruppen. Ansøger begrunder dette fald med, at patienterne fra 180 til dag 360 ikke længere modtog behandling.

Tabel 5: Livskvalitet målt ved EPP-QoL, dag 180 og 360 [5]

	Dag 180		Dag 360	
	Afamelanotid (n = 46)	Placebo (n = 43)	Afamelanotid (n = 44)	Placebo (n = 40)
Gennemsnitlig ændring fra baseline (95 % CI)	51,1 (42,7; 59,5)	36,8 (29,1; 44,5)	10,9 (2,8; 19,0)	19,4 (12,0; 26,8)
Median	52,8	38,9	1,4	15,3
Spredning	2,8-100	-5,6-88,9	-22,2-100	-13,9-86,1

Fagudvalget bemærker, at der er en meget stor variation i, hvor meget patienterne vurderer, at deres livskvalitet er ændret siden starten af behandlingen. Alle patienterne i afamelanotidgruppen oplever en forbedring ved dag 180. Spændet går dog fra 2,8 til 100, hvilket kan tyde på, at nogle patienter kun oplever en ganske lille forbedring, som ikke vurderes at være klinisk relevant. Ved dag 360, hvor behandlingen er stoppet, er der patienter, der oplever en forværring. Her er spændet størst i afamelanotidgruppen, hvor den oplevede ændring fra baseline går fra -22,2 til 100. Dette kan skyldes, at der har været en reel effekt af afamelanotid, og at det derfor føles værre, når behandlingen ophører, og symptomerne vender tilbage. Ved dag 360 er den mediane ændring fra baseline væsentligt lavere end den gennemsnitlige ændring, især i afamelanotidgruppen. Dette tyder på, at data er skævt fordelt, således at mindst halvdelen af patienterne i afamelanotidgruppen ved dag 360 ligger i spændet mellem en forværring på -22,2 og en forbedring på 1,4, mens den anden halvdel fordeler sig over forbedringer mellem 1,4 og 100. På grund af de skæve data og den store variation bør data fortolkes med forbehold.

Fagudvalget vurderer, at det er plausibelt, at patienterne i behandling med afamelanotid oplever en forbedret livskvalitet, målt ved EPP-QoL. Dette kan dels skyldes, at patienterne er håbefulde og optimistiske over at blive behandlet for deres sygdom, som der ellers ikke findes nogen behandling for, dels en reel effekt af lægemidlet, som betyder, at patienternes frygt for at færdes udendørs mindskes. Der er imidlertid også en relativt stor forbedring i livskvalitet i placebogruppen, vurderet ud fra den gennemsnitlige ændring. Dette kan skyldes, at patienterne i denne gruppe også har håb

for behandlingseffekten. Fagudvalget vurderer dog, at behandlingsperioden af CUV039 er for kort til at opfange en reel og mere permanent ændring i livskvalitet.

Studiet af Wensink støtter op om en forbedret livskvalitet ved behandling med afamelanotid. I studiet, som varede i to år, steg livskvaliteten, målt ved EPP-QoL, med 14 %, hvilket indikerer, at behandlingen er effektiv. Resultaterne viste også, at livskvaliteten var lavere på dage med høj lysintensitet.

Delkonklusion: Fagudvalget vurderer, at der ikke er påvist klinisk relevant effekt på livskvalitet målt ved DLQI. Livskvalitetsspørgeskemaet EPP-QoL antyder, at der er en gruppe af patienter, som oplever forbedret livskvalitet. Data skal dog tolkes med forsigtighed, som følge af at EPP-QoL ikke er valideret, og der ses stor variation i data. Fagudvalget vurderer, at behandlingsperioden i CUV039 er for kort til at kunne opfange en forbedring i livskvalitet. Forbedringen i livskvalitet, som tilsyneladende ses i EPP-QoL, underbygges af resultaterne fra studiet af Wensink. Fagudvalget mener derfor, at behandlingen med stor sandsynlighed tilbyder en forbedring af patienternes livskvalitet.

Symptomer (fototoksicitet)
Effektmålet symptomer er et *kritisk* effektmål i vurderingen af lægemidlets værdi. Dette skyldes, at patienterne frygter at opleve symptomer, da de kan være smertefulde og i nogle tilfælde langvarige. Frygten og smerten ved symptomerne påvirker patienternes livskvalitet.

Effektmålet symptomer er opgjort ved to deleffektmål; 1) tid udendørs uden eller med milde symptomer og 2) varighed af symptomer. Fagudvalget har desuden inddraget data fra Wensink og Biolcati til belysning af langtidseffekt, som beskrives narrativt nedenfor.

Tid udendørs (direkte og indirekte sollys) uden eller med milde symptomer

Af Tabel 6 ses data fra CUV039 vedrørende effektmålet.

Tabel 6: Udendørs ophold mellem kl. 10-18 med ingen eller milde smerter

	Afamelanotid (n = 46)	Placebo (n = 43)
Gennemsnit (SD) – minutter	47,5 (53,4)	27,1 (22,9)
Median	27,3	25,2
Spredning	0,2-263,8	0,7-85,0
95 % CI af gennemsnittene	32,1; 62,9	20,3; 33,9
Hodges-Lehmann shift estimat (95 % CI)	8,4 minutter (-1,5; 18,9)	

Det er ikke hensigtsmæssigt at anvende den gennemsnitlige forskel mellem de to arme i kategoriseringen af effektmålet, eftersom data er skævt fordelt. Dette betyder, at effektmålet *ikke kan kategoriseres,* jf. Medicinrådets metodehåndbog.

Fagudvalget vil i nedenstående i stedet beskrive deres kliniske vurdering af effektmålet ud fra det tilgængelige data fra CUV039.

Ved hjælp af den non-parametriske test (Hodges-Lehmann shift) i tabel 6 estimeres det, at patienter i afamelanotid-armen kan være 8,4 minutter længere tid udendørs pr dag. Der er dog usikkerheder forbundet med estimatet, da konfidensintervallet er meget bredt. Fagudvalget vurderer, at en forskel mellem den gennemsnitlige tid udendørs på 8,4 minutter pr. dag ikke er klinisk relevant.

Der ses også en meget stor spredning hos patienter, som var i behandling med afamelanotid. Dette kan indikere, at nogle har været i stand til at kunne opholde sig meget udendørs, mens andre slet ikke har (den laveste værdi er mindre for afamelanotid-armen sammenlignet med placebo-armen). Spredningen i placebo-armen er mindre. Fagudvalget bemærker, at det muligvis kan skyldes, at patienterne i behandling med placebo har gættet deres behandling, som følge af at de ikke har oplevet hyper-pigmentering ved injektionsstedet. Dette kan lede til, at de bevidst ikke lader sig eksponere mere for solen (både direkte og indirekte) end normalt. Gennemsnitsværdien og medianen for afamelanotid-armen er også meget forskellige, hvilket kan indikere, at nogle få patienter, som kan være udenfor i lang tid, er med til at trække gennemsnittet op.

Fagudvalget vurderer, at det ud fra data i tabel 6 ikke kan udelukkes, at en mindre gruppe af patienter har effekt af behandlingen. Fagudvalget er dog meget forbeholdne over for at konkludere noget om effekten på symptomer på baggrund af dette data. Dette skyldes bl.a., at CUV039 er udført i centre spredt over forskellige geografiske lokationer. Det vides således ikke, om det er patienter tilknyttet centret i f.eks. solrige Texas, som scorer lavt. Derudover er fagudvalget også forbeholdne over for den korte behandlingsperiode (6 måneder), da patienterne har en indøvet adfærd, hvor de undgår solen. Fagudvalget forventer, at der vil gå mere end 6 måneder, før en sådan adfærd ændres. Studiets dobbeltblindede design er muligvis endnu en hindrende faktor i forbindelse med at ændre adfærd. Det er ikke muligt for fagudvalget at vurdere, hvor 'risikovillige' patienterne har været. Her kan alder også spille ind, og det forventes, at unge er mere risikovillige end ældre patienter, der har mange års erfaringer med fototoksiske reaktioner, som har ledt til en mere udtalt undgående adfærd overfor lys.

Varighed af symptomer

Dette deleffektmål har til formål at vurdere, hvorledes afamelanotid har en effekt på varigheden af fototoksiske reaktioner.

Af Tabel 7 ses data fra CUV039 for varighed af symptomer.

Tabel 7: Varighed af symptomer ≥ 4 (fototoksiske reaktioner)

	Afamelanotid (n = 46)	Placebo (n = 43)
Gennemsnit (SD) – dage	3,2 (6,0)	6,6 (16,8)
Median – dage	1,0	1,0
Spredning	0-34	0-98
95 % CI	1,5; 4,9	1,6; 11,6

Den gennemsnitlige varighed af en fototoksisk reaktion var i afamelanotid-armen 3,2 dage og i placebo-armen 6,6 dage. Det er dog ikke hensigtsmæssigt at anvende den gennemsnitlige forskel mellem de to arme i kategoriseringen af effektmålet, eftersom data er skævt fordelt. Dette betyder, at effektmålet ikke kan kategoriseres, jf. Medicinrådets metodehåndbog.

Fagudvalget bemærker, at medianen er ens i de to grupper (1 dags varighed). Det vil sige, at mindst halvdelen har symptomer af mindst en dags varighed i begge arme af studiet. Den sidste halvdel af patienterne har altså en langt større spredning i varigheden af dage med smerter. Dette er mest udtalt i placebo-armen (98 dage). Fagudvalget bemærker, at det ikke er usandsynligt, at der kan gå op til 98 dage, før smerter af en fototoksisk reaktion er borte. Det skyldes, at der er tale om forbrændinger, som kan være lang tid om at hele. Fagudvalget er meget forsigtige med at konkludere noget om effekten af behandlingen på dette effektmål, på baggrund af usikkerhederne forbundet med det.

Delkonklusion: Fagudvalget vurderer, at CUV039-studiet ikke påviser klinisk relevant effekt på symptomer eller varighed af symptomer. Data er skævt fordelt, og der ses en meget stor spredning mellem de enkelte patienters mulighed for at være udenfor og varigheden af deres symptomer, hvilket gør det svært at fortolke data. Desuden spiller patienternes frygt for at eksponere dem selv for sollys også ind på validiteten af data. Fagudvalget vurderer derfor, at det er svært at måle afamelanotids reelle effekt på symptomer på baggrund af data fra CUV039-studiet.

Beskrivelse af resultater fra Wensink for effektmålet *symptomer*

Fagudvalget vælger at inddrage data fra studiet af Wensink til yderligere at belyse, hvorvidt afamelanotid har en effekt på effektmålet *symptomer*.

Resultater fra studiet af Wensink viste, at behandling med afamelanotid førte til, at patienterne kunne opholde sig længere tid udendørs i forhold til deres baselinescore. Den mediane baselinescore var 7,4 [95 % CI 3,6; 15,5] timer pr uge. I uge 5 af en behandlingsperiode kunne patienterne være 6,14 [95 % CI 3,62; 8,67] timer mere udendørs i løbet af en uge sammenlignet med en tilsvarende uge (samme måned og med samme sollysscore) hvor patienten ikke fik behandling – denne forskel estimeres desuden at øges med 0,38 timer per år med behandling (dog ikke statistisk signifikant). Dermed overstiger forbedringen den definerede mindste klinisk relevante forskel på 50 %, dog minimum 20 min. pr. dag.

Der er estimeret en betydelig variation gennem året relateret til tiden, patienterne opholder sig udendørs, med en forskel på 6,4 timer om ugen mellem august og november. Det skal dog bemærkes, at patienterne ikke modtager behandling i november. Det var især i sommermånederne, patienterne oplevede at kunne tilbringe mere tid udendørs i forhold til referencemåneden december. Fagudvalget bemærker, at det kan være med til at underestimere afamelanotids effekt, da december måned er lysfattig, og man derfor vil kunne forvente, at EPP-patienter vil have nemmere ved at komme ud i denne måned. Patienterne modtager dog ikke behandling i december, hvilket kan være et problem i forhold til, en sammenligning af de måneder, hvor man får behandling, med en måned, hvor man ikke får behandling.

Studiet af Wensink rapporterer meget brede konfidensintervaller vedr. tiden, patienterne kan være udendørs med afamelanotid, dette kan betyde, at nogle patienter oplever en større effekt og andre en mindre eller ingen effekt.

Antallet og varigheden af fototoksiske reaktioner steg i starten af studiet men var sæsonbetinget. Stigningen kan betyde, at patienterne i starten skulle finde balancen mellem sollys og tolerance. Studiet af Wensink viser, at respons på behandlingen er afhængig af baselinetolerance, alder, køn, BMI, hudtype, smerteopfattelse og geografisk lokation. Dette stemmer meget godt overens med, hvad fagudvalget forventer.

Delkonklusion: Fagudvalget vurderer, baseret på studiet af Wensink, at afamelanotid i større eller mindre grad mindsker patienternes symptomer ved direkte lyseksponering, hvilket får EPP-patienterne til at opholde sig mere udendørs.

Bivirkninger

Effektmålet bivirkninger er *kritisk* for vurderingen af lægemidlets værdi for patienterne, da forekomsten af bivirkninger har betydning for patienternes i forvejen forringede livskvalitet og for behandlingsophør. Det er vigtigt, at bivirkninger er acceptable set i lyset af sygdommens kroniske natur, og at behandlingen forventes at være langvarig.

Andelen af patienter, som i CUV039 oplevede alvorlige hændelser, var 3 ud af 48 (6 %) i afamelanotid-armen og 2 ud af 45 (4 %) i placebo-armen. Den absolutte forskel er dermed 2 %-point (95 % CI -9; 13). Ingen af de svære TEAE var formodet relateret til studiebehandlingen (i afamelanotid-armen omfattede de: fraktur i humerus, diskusprolaps, mavesmerter og benign nævus, i placebo-armen omfattede de: blodprop i lungerne og melanom). Punktestimatet for den absolutte effektforskel afspejler, at der ikke er flere alvorlige bivirkninger ved afamelanotid sammenlignet med placebo (mindste klinisk relevante forskel er defineret som 5 %-point). Baseret på konfidensintervallet kan den absolutte forskel ikke kategoriseres, da grænserne for konfidensintervallet overskrider mindste klinisk relevante forskel.

Baseret på den relative forskel kan den foreløbige værdi ikke kategoriseres. Konfidensintervallet indeholder værdier, der kan lede til både negative og positive konklusioner (RR 1,4 (0,25; 8,03)).

Delkonklusion: Der er ikke flere uønskede hændelser ved behandling med afamelanotid sammenlignet med placebo.

Kvalitativ gennemgang af bivirkningsprofilen

I Bilag 2 ses der en tabel for, hvilke uønskede hændelser som blev observeret i både CUV029 og CUV039.

De fleste uønskede hændelser var milde til moderate i sværhedsgrad. De hyppigste uønskede hændelser i begge arme og i begge studier var hovedpine (CUV029: afamelanotid 34 % vs. placebo 39 % og CUV039: 40 % vs. 29 %), kvalme (CUV029: 18 % vs. 17 % og CUV039: 19 % vs. 18 %), nasopharyngitis (CUV029: 21 % vs. 22 % og CUV039: 12 % vs. 22 %) og rygsmerter (CUV029 0 % vs 11 % og CUV039: 12 % vs 13 %).

Fagudvalget bemærker, at kun patienterne i afamelanotid-armen oplever misfarvning af huden ved implantatstedet (hhv. 11 % og 19 % i CUV029 og CUV039). Derudover bemærker fagudvalget også, at pigmentforandringer udelukkende ses hos patienter i behandling med afamelanotid (hhv. 8 % og 2 % i CUV029 og CUV039)

Langtidsbivirkninger
Studiet af Biolcati rapporterer, at de hyppigste bivirkninger var kvalme, hovedpine, træthed og reaktioner ved implantatstedet. Dermed adskiller de sig ikke fra de typer af bivirkninger, som blev observeret i CUV029 og CUV039. Dog observerede to patienter i studiet af Biolcati et nyt modermærke, hhv. 2,5 og 5 år efter første dosis af afamelanotid. En af patienterne fik det fjernet, uden det viste tegn på malignitet. Fra samme studie rapporteres det yderligere, at 93 % af patienterne fortsatte deres behandling i flere år, hvilket kan indikere, at bivirkningerne er acceptable for patienterne.

Wensink rapporterer, at 98 % af patienterne i en *real-world praksis* fortsatte behandlingen med afamelanotid, hvilket kan tyde på, at patienterne har oplevet en effektiv behandling. Dog kan det også være et udtryk for, at patienterne, når bivirkningerne er acceptable, føler, at behandling er bedre end ingen behandling. 104/117 patienter oplevede bivirkninger, heraf var de hyppigste rapporterede bivirkninger; kvalme (11,4 %), træthed (9,7 %), rødme (8,8 %) og kvalme med hovedpine (8,4 %). De fleste bivirkninger forsvandt 1 -2 dage efter injektion med implantatet. Der blev ikke rapporteret nogen alvorlige hændelser.

Delkonklusion: Fagudvalget vurderer, at der ikke ses betydelige forskelle mellem afamelanotid og placebo i forhold til bivirkninger, bortset fra risikoen for hyperpigmentering ved implantatstedet ved behandling med afamelanotid. Derfor vurderer fagudvalget, at den overordnede bivirkningsprofil samt langtidsbivirkninger er acceptable og håndterbare.

5.1.6 Fagudvalgets konklusion

Fagudvalget vurderer, at den samlede værdi af afamelanotid sammenlignet med placebo til patienter med erytropoietisk protoporfyri **ikke kan kategoriseres** i henhold til Medicinrådets metoder.

Ser man udelukkende på de randomiserede studier, ses der ingen klinisk relevant effekt hverken på muligheden for at opholde sig længere tid udenfor uden smerter eller på livskvalitet. Inddrager man data fra de observationelle studier, tyder det på, at afamelanotid samlet set potentielt kan forbedre patienternes muligheder for at opholde sig udendørs. Dog er effektens størrelse svær at vurdere.

Fagudvalget har foretaget deres kategorisering på baggrund af et randomiseret studie. Men på baggrund af dette studie er det vanskeligt at udtale sig om effekten af behandlingen. Dette skyldes, at patienterne har en undgående adfærd over for sollys, som er svær at ændre, når studiet er blindet og foregår over en periode, som er for kort til, at der kan ske en adfærdsændring. Fagudvalget lægger desuden vægt på, at der ingen objektive mål findes for sygdommen, og at de selvrapporterede effektmål viser en meget stor spredning, som kan skyldes, at nogle patienter oplever effekt og andre ikke. Det kan også være et udtryk for, at sygdommens sværhedsgrad er meget individuel, eller at forsøgsdeltagernes risikovillighed for at færdes udendørs har været forskellig. Derudover kan spredningen også skyldes store geografiske forskelle og dermed forskelle i antal solskinstimer, patienterne har oplevet.

Medicinrådet har derfor inddraget supplerende observationelle data med længerevarende studieperioder, som viser, at behandlingen gør det muligt for patienterne at færdes mere udendørs, samtidig med at deres livskvalitet forbedres.

Bivirkningerne ved behandlingen vurderer fagudvalget som værende acceptable. Dette understøttes også af observationelle studier, som viser, at mange patienter fortsætter behandlingen i mange år.

6. Andre overvejelser

Opstart, monitorering og seponering
Afamelanotid skal administreres af oplært og akkrediteret sundhedspersonale. Fagudvalget vurderer, at behandlingen med afamelanotid kan administreres på de dermatologiske afdelinger i Danmark.

Opstart: Inden opstart af behandling foretages blodprøvescreening, herunder infektionstal samt tal for nyre- og leverfunktion. Afamelanotid er kontraindiceret ved nedsat nyrefunktion og svær leversygdom. Der bør spørges ind til familiær disposition for modermærkekræft. Fagudvalget opfordrer desuden til helkropsundersøgelse samt fotodokumentation af huden inden opstart. Det skal sikres, at patienten ikke er gravid ved opstart, og at kvinder anvender prævention inden opstart [8].

Monitorering: Det anbefales if. EMAs SPC, at der hver 6. måned foretages en fuld undersøgelse af huden, for at monitorere hvorvidt der er modermærkeforandringer og/eller andre anormaliteter. Dermatologer konsulteres ved fund af anormaliteter i huden [8]. Derudover foretages der for både behandlede og ikke-behandlede rutinemæssige blodprøver én gang årligt. Her testes for lever og nyrepåvirkning samt d-vitamin, hæmoglobin, protoporfyrin, jern, ferritin og transferrin. Blodprøver og monitorering af huden kan foretages i forbindelse med injektion af et implantat. Efter hver administration af afamelanotid skal patienten observeres for bivirkninger indtil 1 time efter administration.

Seponering: Der behandles i sommerhalvåret med enten 3 eller 4 implantater. Behandlingen pauseres i vinterhalvåret.

Fagudvalget bemærker, at det kan tage tid, før patienter med EPP ændrer adfærd, fordi mange patienter har tillært sig et 'liv i skyggen', og mange er bange for at opleve symptomer og derfor ikke tør være i solen. Derfor kan der være usikkerheder forbundet med en tidlig vurdering af effekten. Opstår der uacceptable bivirkninger, skal behandlingen ophøre.

Effekten bør vurderes løbende i forhold til symptomer. Der findes ingen redskaber til at måle effekten, men fagudvalget foreslår, at patienterne fører dagbog i forhold til øget ophold udendørs uden symptomer, antal episoder med symptomer, varighed af symptomer og vurdering af niveauet af smerte på en numerisk rangskala fra 0-10, hvor 10 er værst tænkelige smerte. Behandlingen fortsættes så længe, der er tilfredsstillende effekt.

Risiko for fosterskade
Eftersom behandling med afamelanotid i princippet kan være livslang, er der risiko for, at kvinder kan blive gravide under et behandlingsforløb. Derfor ønskede fagudvalget en beskrivelse af risikoen for fosterskade (teratogenicitet) ved behandlingen.

Ansøger kan ikke udelukke, at der er en risiko for fosterskader, eftersom data vedrørende brug af afamelanotid hos gravide er begrænset [5]. Afamelanotid må derfor ikke gives til gravide eller til kvinder i den fødedygtige alder, medmindre de anvender sikker kontraception, hvilket den behandlende læge skal sikre sig forud for behandlingen.

Risiko for udvikling af hudkræft og modermærkekræft
Fagudvalget ønskede i protokollen en beskrivelse af risikoen for udvikling af hudkræft, da lægemidlet bevirker, at hudens pigmentproduktion stimuleres.

Ifølge EMAs SPC skal huden monitoreres hver 6. måned i forbindelse med behandlingen, som følge af at afamelanotid kan medføre pigmentforandringer i eksisterende modermærker. I CUV039- og CUV029-studierne var der ingen forandringer i huden, som gav anledning til alvorlige hændelser. I studiet af Biolcati fik 2 ud af 115 patienter et nyt modermærke hhv. 2,5 og 5 år efter første administration af lægemidlet. Den ene patient fik det fjernet uden det viste tegn på malignitet. Der er ikke yderligere oplysninger om den anden patient.

Ansøger beskriver, at det er en misforståelse, at afamelanotid kan stimulere udvikling af hudkræft og modermærkekræft. Denne begrundelse skal findes i lægemidlets virkningsmekanisme, hvor lægemidlet stimulerer eumelanin-pigmentproduktionen – den mørke pigmentproduktion. Eumelanin beskytter huden mod UVB-stråling, som ellers er en risikofaktor ved udvikling af hudkræft og malignt melanom.

Variation i resultatet for effektmålet 'antal timer i direkte sollys mellem 10-15 uden smerte' mellem det europæiske studie (CUV029) og det amerikanske studie (CUV039)
Fagudvalget bemærkede i protokollen, at der var en stor variation i resultatet for effektmålet mellem de to studier, og ønskede derfor en redegørelse for, hvordan effektmålet er opgjort. Ansøger forklarer, at det kan skyldes, at patienterne havde forskellig villighed til at eksponere dem selv for sollys. I CUV039 var størstedelen af patienterne villige til at eksponere dem selv for sollys, mens andre slet ikke var. Derudover har ansøger også forklaret, at det kan skyldes forskellige varigheder af studierne.

7. Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning fra Medicinrådet.

8. Referencer

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9. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende atopisk eksem	
Formand	**Indstillet af**
Gabrielle Randskov Vinding *Afdelingslæge*	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
Har ikke specialet	Region Nordjylland
Kan ikke udpege	Region Midtjylland
Evy Paulsen *Overlæge*	Region Syddanmark
Kati Hannele Kainu *Overlæge*	Region Hovedstaden
*En patient/patientrepræsentant**	Danske Patienter
Rasmus Huan Olsen *Afdelingslæge*	Dansk Selskab for klinisk Farmakologi
Charlotte Gotthard Mørtz* *Professor, overlæge*	Inviteret af formanden
Tidligere medlemmer, som har bidraget til arbejdet	**Udpeget af**
Cathrine Nørgaard Peulicke *Klinisk farmaceut*	Dansk Selskab for Sygehusapoteksledelse
Emma Johanna Svedborg *Klinisk farmaceut*	Dansk Selskab for Sygehusapoteksledelse
Andre, der har bidraget	
Kristine Pallesen *Afdelingslæge/dermatolog*	
Tre patientrepræsentanter med sygdommen	

*Har ikke deltaget i arbejdet med at vurdere afamelanotid

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10. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.1	28. april 2021	Ændring i definition af studieperioderne af CUV039 og CUV029.
1.0	24. marts 2021	Godkendt af Medicinrådet.

11. Bilag 1: Evidensens kvalitet

11.1 Cochrane – risiko for bias

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

Tabel 8. Vurdering af risiko for bias. Langendonk et al. 2015, CUV029 (NCT00979745) og CUV039 (NCT01605136)

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	**Lav**	Angivet i artiklen: *A computer-generated randomization list for each site was used to assign patients to a study group. Study investigators, research staff, and patients were unaware of the study-drug assignments.*
Effekt af tildeling til intervention	**Forbehold**	På grund af den øgede pigmentering af huden over afamelanotidimplantatet, forblev patienterne i interventionsgruppen ikke blindede. Dette har sandsynligvis ændret deres adfærd, så de har været mere udendørs, end de ellers ville have været. Med tanke på hvor smertefuld eksponering for lys er for patienter med EPP, er det dog usandsynligt, at de har fastholdt adfærdsændringen, medmindre behandlingen var effektiv. Idet nogle patienter i placebogruppen følte sig overbeviste om, at de fik behandling, må der være nogen grad af placeboeffekt. Der fremgår ikke oplysninger om disse patienter, men formentlig har de enten haft milde symptomer eller ikke ændret adfærd. Resultaterne viser også en stor variation i symptomer og livskvalitet, hvilket tyder på, at nogle patienter ikke har haft en svær grad af EPP.
Manglende data for effektmål	**Lav**	Der er relativt få, der ophører i studiet, og antallene er på samme niveau i interventions- og placebogruppen, både i det amerikanske og det europæiske studie.
Risiko for bias ved indsamlingen af data	**Forbehold**	Idet blindingen formentlig blev brudt for patienterne i interventionsgruppen, er der risiko for bias i forhold til de selvrapporterede effektmål.
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Lav**	Rapportering af effektmål er i overensstemmelse med analyseplanen.
Overordnet risiko for bias	**Forbehold**	Der er risiko for bias, idet blindingen ikke kan opretholdes. Der er risiko for recall bias ved brug af EPP-livskvalitet-spørgeskemaet, hvis psykometriske egenskaber ikke er fuldt belyste. Derfor er der samlet set visse forbehold i tolkningen af resultaterne grundet risiko for bias.

11.2 GRADE

Tabel 9. GRADE evidensprofil for klinisk spørgsmål 1: afamelanotid sammenlignet med placebo til behandling af patienter med EPP (CUV039)

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Afamelanotid	Placebo	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
Livskvalitet, DLQI, gennemsnitlig ændring fra baseline												
1	RCT	Alvorlig[a]	Alvorlig[b]	Ingen	Ingen	Ingen	46	43	-	0 (-3; 2)*	⨁⨁◯◯ LAV	KRITISK
Symptomer, minutter pr. dag udendørs												
1	RCT	Alvorlig[a]	Alvorlig[b]	Ingen	Ingen	Ingen	46	43	-	8,4 min (-1,5; 18,9)*	⨁⨁◯◯ LAV	KRITISK
Symptomer, varighed												
1	RCT	Alvorlig[a]	Alvorlig[b]	Ingen	Ingen	Ingen	46	43	-	3,4 dage (-1,8; 8,6)	⨁⨁◯◯ LAV	KRITISK
Bivirkninger, Andelen af patienter der oplever uønskede hændelser af grad 3-4												
1	RCT	Alvorlig[a]	Alvorlig[b]	Ingen	Ingen	Ingen	48	45	RR 1,4 (0,25; 8,03)	2 %-point (-9; 13)	⨁⨁◯◯ LAV	KRITISK
Kvalitet af den samlede evidens	LAV[e]											

*Den absolutte forskel er ikke baseret på gennemsnittet i hver arm, da data er skævt fordelt. Ansøger har udregnet den absolutte forskel med de ikke-parametriske metoder Kruskal-Wallis test og Hodges-Lehmann shift.
[a] Der er nedgraderet ét niveau, da der er visse forbehold i tolkningen af resultaterne grundet risiko for bias, idet blindingen i studiet ikke kan opretholdes.
[b] Der er nedgraderet ét niveau for inkonsistens, da data kun er baseret på resultater fra ét studie.
[e] Den samlede evidenskvalitet er vurderet ud fra den laveste kvalitet af de kritiske effektmål.

12. Bilag 2: Bivirkningstabel

	CUV029		CUV039	
	Afamelanotide (N = 38)	Placebo (N = 36)	Afamelanotide (N = 48)	Placebo (N = 45)
Totalt antal hændelser	189	166	272	216
Lidelser i mave-tarmsystemet – antal (%)				
Ubehag i maven	0	1 (3)	1 (2)	2 (4)
Mavesmerter	4 (11)	1 (3)	1 (2)	3 (7)
Mavesmerter i øvre del af maven	1 (3)	1 (3)	1 (2)	3 (7)
Diarré	3 (8)	4 (11)	2 (4)	3 (7)
Dyspepsi	0	1 (3)	3 (6)	3 (7)
Kvalme	7 (18)	6 (17)	9 (19)	8 (18)
Tandpine	0	0	3 (6)	3 (7)
Opkast	1 (3)	2 (6)	1 (2)	0
Generelle lidelser og administrations-site tilstand – antal (%)				
Træthed	1 (3)	2 (6)	3 (6)	0
Misfarvning ved implantatstedet	4 (11)	0	9 (19)	0
Smerte	0	0	4 (8)	4 (9)
Infektioner og angreb – antal (%)				
Viral gastroenteritis	1 (3)	2 (6)	0	3 (7)
Influenza	6 (16)	3 (8)	2 (4)	7 (16)
Nasopharyngitis	8 (21)	8 (22)	6 (12)	10 (22)
Sinusitis	0	2 (6)	3 (6)	3 (7)
Infektion i øvre luftveje	3 (8)	1 (3)	1 (2)	0
Muskuloskeletal og bindevævssygdom – antal (%)				
Ledsmerter	0	2 (6)	5 (10)	2 (4)
Rygsmerter	2 (5)	4 (11)	6 (12)	6 (13)
Muskuloskeletal smerter	0	1 (3)	3 (6)	1 (2)
Muskelømhed	1 (3)	2 (6)	3 (6)	1 (2)
Smerte i ekstremiteterne	1 (3)	2 (6)	2 (4)	2 (4)
Lidelser i nervesystemet – antal (%)				
Svimmelhed	0	0	1 (2)	2 (4)
Hovedpine	13 (34)	14 (39)	19 (40)	13 (29)
Migræne	1 (3)	3 (8)	3 (6)	3 (7)
Sinus hovedpine	0	0	1 (2)	2 (4)
Lidelser i hud og subkutane væv – antal (%)				
Eksem	2 (5)	1 (3)	0	1 (2)
Melanocytisk nævus	0	0	2 (4)	1 (2)
Pigmentforandringer	3 (8)	0	1 (2)	0
Kløe	2 (5)	1 (3)	2 (4)	2 (4)

Application for the assessment of afamelanotide (SCENESSE®) for the treatment of erythropoietic protoporphyria

Application to the Danish Medicines Council

22 December 2020

Contents

1 Basic information

TABLE 1: CONTACT INFORMATION

Name	Antonella COLUCCI
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TABLE 2: OVERVIEW OF THE PHARMACEUTICAL. SOURCE: AFAMELANOTIDE SUMMARY OF PRODUCT CHARACTERISTICS (SMPC) (1)

Proprietary name	SCENESSE®
Generic name	Afamelanotide
Marketing authorisation holder in Denmark	CLINUVEL
ATC code	D02BB02
Pharmacotherapeutic group	Emollients and protectives
Active substance(s)	Afamelanotide
Pharmaceutical form(s)	16 mg implant
Mechanism of action	Afamelanotide is a synthetic tridecapeptide and a structural analogue of α-melanocyte stimulating hormone (α-MSH). Afamelanotide is a melanocortin receptor agonist and binds predominantly to the melanocortin-1 receptor (MC1R). Its binding lasts longer than that of α-MSH. This partly results from afamelanotide's resistance to immediate degradation by serum or proteolytic enzymes. It presumably undergoes hydrolysis within a short time; its metabolites' pharmacokinetics and pharmacodynamics are not understood yet. Afamelanotide is thought to mimic the endogenous compound's pharmacological activity by activating the synthesis of eumelanin mediated by the MC1R receptor. Eumelanin contributes to photoprotection through different mechanisms, including: · strong broadband absorption of UV and visible light, where eumelanin acts as a filter. · antioxidant activity through scavenging of free radicals; and · inactivation of the superoxide anion and increased availability of superoxide dismutase to reduce oxidative stress.
Dosage regimen	One implant is administered every 2 months prior to expected and during increased sunlight exposure, e.g. from spring to early autumn. Three

	implants per year are recommended, depending on the length of protection required. The recommended maximum number of implants is four per year. The overall duration of treatment is at the specialist physician's discretion.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	SCENESSE® is indicated for prevention of phototoxicity in adult patients with erythropoietic protoporphyria (EPP).
Other approved therapeutic indications	None.
Will dispensing be restricted to hospitals?	Yes, dispensing is restricted to hospitals. SCENESSE® should only be prescribed by specialist physicians in recognised porphyria centres, and administration should be performed by a physician trained and accredited by the marketing authorisation holder to administer the implant.
Combination therapy and/or co-medication	None.
Packaging – types, sizes/number of units, and concentrations	16 mg implant. Solid white to off-white rod approximately 1.7 cm in length and 1.5 mm in diameter.
Orphan drug designation	Yes.

2 Abbreviations

AE	Adverse event
CI	Confidence interval
CSR	Clinical study report
DLQI	The Dermatology Life Quality Index
DMC	The Danish Medicines Council
EPAR	The European Public Assessment Report
EPP	Erythropoietic protoporphyria
EPP-QoL	The erythropoietic protoporphyria quality of life measure
FECH	Ferrochelatase
GCP	Good clinical practice
ITT	Intention-to-treat
MC1R	Melanocortin-1 receptor
MED	Minimal erythemal dose
MedDRA	Medical dictionary for regulatory affairs
MSD	Minimum symptom dose
PBO	Placebo
SAP	Statistical analysis plan
SmPC	Summary of product characteristics
TEAE	Treatment-emergent adverse event
US	United States of America
QoL	Quality of life

3 Summary

Introduction
The Danish Medicines Council (DMC) has decided to evaluate afamelanotide as standard treatment for patients suffering from EPP. The DMC has invited CLINUVEL to provide clinical data for the evaluation of afamelanotide, which is provided in the present application. The assessment is based on the DMC protocol on EPP. Assessments of efficacy and safety are provided by focusing on quality of life (QoL), symptoms (phototoxicity) and adverse events.

Erythropoietic protoporphyria **(**EPP) is an ultra-rare inherited metabolic disorder, which in most patients are caused, by a deficiency of ferrochelatase (FECH). EPP is associated with acute phototoxicity and patients with EPP experience anaphylactoid reactions, oedema, and erythema along with a deep burning sensation underneath the skin which lasts several days or weeks. These symptoms can lead to excruciating pain and a markedly reduced quality of life. EPP patients modify their behaviour to avoid all forms of light exposure. Afamelanotide (SCENESSE®) is indicated for prevention of phototoxicity in adult patients with EPP and is the only approved treatment for these patients.

Methods
We used the CUV039 (phase III, US) trial to answer the clinical question outlined by the expert committee in the DMC protocol on EPP. The CUV029 (phase III, Europe) trial was used as a supplement. Both trials are published in Langendonk et al. 2015. The CUV039 trial was a phase III, multicentre, randomised, double-blinded, placebo-controlled trial, conducted in two parallel study groups for six months in the United States. The objective of the trial was to investigate the safety and efficacy of 16 mg afamelanotide implants for the reduction of pain and the improvement of the quality of life in EPP patients. QoL was assessed with the DLQI questionnaire and the EPP-QoL questionnaire. Outcome measure for phototoxicity were “minutes per day outdoors without or with mild symptoms” and “duration of symptoms after episode with exposure to sunlight”.

Results
Compared to placebo treatment afamelanotide leads to significant improved quality of life (QoL measured with the EPP-QoL). The DLQI is not an appropriate tool for evaluating quality of life in EPP patients as the DLQI was developed to evaluate the impact of dermatological disorders on patients’ QoL. Consequently, for the outcome “mean change from baseline in QoL measured with the DLQI” a significant difference between the two treatment groups was not estimated. EPP patients treated with afamelanotide experience a clinically relevant improvement in their ability to expose to sunlight (as a proxy for all forms of light). In the outcome “minutes per day outdoors without or with mild symptoms” an absolute mean difference of 20.4 minutes in favour of the afamelanotide group was estimated, which is 75% more time spent outdoors with afamelanotide implants compared to placebo. Compared to placebo we estimated a reduction of 3.4 days in “duration of symptoms after episode with exposure to sunlight” when patients are treated with afamelanotide, which is a reduction of 52%.

In terms of safety, the adverse events observed in the US CUV039 trial were generally mild to moderate in severity. There were no clinically relevant between-group differences in the incidence or severity of adverse events. In addition, the assessment of the long-term safety profile showed that afamelanotide has a good long-term safety profile.

Conclusion

Afamelanotide is well-tolerated in patients with EPP and the observed adverse events are mostly mild and transient. EPP patients treated with afamelanotide experience a clinically relevant improvement in their ability to expose to sunlight (as a proxy for all light), improved QoL and a reduction in the number, duration, and severity of phototoxic reactions. Many patients receiving the afamelanotide implant report being able to lead "normal" lives for the first time. Hence, afamelanotide will be an important treatment option for EPP patients in Denmark.

4 Background

EPP is an ultra-rare inherited metabolic disorder caused, for the majority of patients, by a deficiency of FECH. EPP is associated with acute phototoxicity and patients experience anaphylactoid reactions, oedema, and erythema along with a deep burning sensation underneath the skin which lasts several days to weeks following light exposure. This unbearable and often invisible phenomenon poorly described as "pain" is irresponsive to any analgesics, including opioids. There are currently no other alternative or approved drugs for the prevention or treatment of phototoxicity in EPP patients. Afamelanotide (SCENESSE®) is indicated for prevention of phototoxicity in adult patients with EPP and is the only approved treatment for these patients. The only existing option today for the prevention of phototoxicity, other than SCENESSE®, is the complete avoidance of exposure to visible light (2).

In the application to the DMC we used the US CUV039 trial to answer the clinical question outlined by the expert committee in the DMC protocol on EPP. The CUV029 (phase III, Europe) trial (n=74) was used as a supplement. Both trials are published in Langendonk et al. 2015 (3). The CUV039 trial was a phase III, multicentre, randomised, double-blinded, placebo-controlled trial, conducted in two parallel study groups for six months (n=94) in the United States. The trial investigated the safety and efficacy of 16 mg afamelanotide implants for the reduction of pain and the improvement of the quality of life in EPP patients The primary objective of the CUV039 study was to determine whether afamelanotide can enable EPP patients to expose themselves to sunlight without incurring pain and phototoxic reactions, evaluated in duration of direct sunlight exposure between 10:00 and 18:00 on days when no pain was experienced. Secondary endpoints evaluated duration of sunlight exposure between 10:00 and 18:00 on days when no or mild pain was experienced, and duration of sunlight exposure between 10:00 and 15:00 on days where no pain was experienced. Pain was measured on an 11-point Likert scale (0-10). Direct sunlight exposure was considered a proxy measure for all light exposure in EPP (where visible light causes phototoxic reactions).

QoL, a secondary endpoint, was assessed with the EPP-QoL and the DLQI questionnaires. Throughout the course of the afamelanotide development program it was determined that the DLQI is not an appropriate tool for evaluating quality of life in EPP patients. CLINUVEL worked with global EPP experts to develop the EPP-QoL. While the format – utilising a short questionnaire with a mostly 4-point response scale – is similar to the DLQI, the questions show fundamental differences in the patient experience being evaluated, reflecting the differences in the impact upon patient quality of life. The DLQI focuses on issues relevant to dermatological patients (such as those with atopic dermatitis or psoriasis), where dermatological symptoms are persistent and visible, and treatable, and where it is the skin itself which impacts upon a patient's quality of life within the last week. Conversely, the EPP-QoL asks about the patient's overall wellbeing, and whether EPP has impacted upon the patient's quality of life using specific scenarios within the last two months. In EPP the primary symptom (phototoxicity) and conditioned behaviour of patients to avoid light exposure are

recognised as having the largest impact upon patient QoL. Due to its use in earlier studies, the DLQI was included in the CUV029 and CUV039 as a secondary measure

The CUV039 trial showed a statistically significant difference between the treatment groups with respect to total pain-free direct sun exposure between 10:00 and 18:00 hours (Kruskal-Wallis test, p=0.044). The difference (Hodges-Lehmann estimate with 95% Cl) was 24.0 hours (95% CI: 0.3, 50.3) in favour of afamelanotide across the 6-month study period in the ITT population (n=89). After 6 months in the U.S. trial, the pain-free time in direct sunlight was 70% longer among patients who received afamelanotide than among patients who received placebo (median, 69.4 hours vs. 40.8 hours; P = 0.04). The duration of pain-free time was also significantly longer among patients who received afamelanotide than among those who received placebo after 9 months in the European Union trial (median, 6.0 hours vs. 0.8 hours; P = 0.005). In terms of safety, the adverse events observed in the trial were generally mild to moderate in severity. There were no clinically relevant between-group differences in the incidence or severity of adverse events. In addition, the assessment of the long-term safety profile showed that afamelanotide has a good long-term safety profile.

In study CUV029 a significant rise was observed in the length of time with no pain upon direct exposure to sunlight in the study arm treated with afamelanotide, compared to the placebo arm (p=0.005). In addition, patients who received afamelanotide displayed: 1) a significant reduction in phototoxic reactions compared to placebo (77 compared to 146, p=0.04), 2) a more rapid recovery time after a phototoxic reaction (p=0.04); and 3) an ability to remain in direct sunlight for longer periods of time without experiencing pain (p=0.05).

Studies CUV029 and CUV039 reported a significant clinical and statistical improvement in the amount of exposure to light experienced by patients who received afamelanotide implants, compared to placebo. In addition, a significant improvement in patient quality of life was observed in both studies (QoL measured with the EPP-QoL).

Data are presented in the context of the findings of the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP), which, in granting SCENESSE® marketing authorisation under exceptional circumstances, concluded that: "Under normal conditions of use, the status of current scientific knowledge, tools and instruments, does not allow for sufficient precise measurements of impact of disease and 'visible light' to exposed skin. It is also conceivable that the complexity of the EPP patients behaviour and the dependence of phototoxicity with environmental factors in real life differ to such an extent that the actual benefit cannot be captured in conventional clinical trial designs, for ex. randomised blinded clinical trial design and that no design could address this matter taking into account the current scientific and technical knowledge. It is therefore not foreseeable that the request of additional studies would allow to generate a comprehensive dossier in terms of safety and efficacy. […]

In accordance with Article 14(8) of Regulation (EC) No 726/2004 and Annex I, part II of Directive 2001/83/EC the applicant applied for a marketing authorisation under exceptional circumstances based on the inability to provide comprehensive data on the efficacy and safety under normal conditions of use because the indication for which afamelanotide is intended is encountered so rarely that the applicant cannot reasonably be expected to provide a comprehensive dossier. The applicant also argued that it would be contrary to generally accepted principles of medical ethics to collect such information and that in the present state of scientific knowledge, comprehensive information cannot be provided. The applicant justified that he is unable to provide comprehensive data on the efficacy and safety under normal conditions of use, due to the fact that:

1. EPP is an extremely rare condition and there are insufficient naïve patients available who are able and willing to join a clinical trial;

2. It would be medically unethical to collect such efficacy data owing to the fact that EPP patients are unwilling to expose themselves to light sources or sunlight based on past preconditioning from ingrained anxiety of burning;
3. There is no existing satisfactory assessment tool to capture meaningful and comprehensive efficacy data for afamelanotide; […]"

In conclusion:

"[…] SCENESSE's benefits are greater than its risks and recommended that it be given marketing authorisation. The CHMP noted that SCENESSE led to an increase in the amount of time patients could spend in direct sunlight without experiencing pain. Although the additional time spent in sunlight was small, the Committee considered the possible improvements in quality of life, the unmet medical need in patients with EPP, and the mild side effects seen during short-term treatment with the medicine in deciding to recommend approval for SCENESSE in the EU. The Committee also consulted individual patients and experts on their experience with SCENESSE."

5 Presentation of studies

A systematic literature search has not been performed, because the Danish Medicines Council (DMC) specifies in the DMC protocol on EPP that the DMC searched for peer-reviewed full-text articles directly comparing afamelanotide with placebo in the preparation of the protocol. The DMC identified one article by Langendonk et al. 2015 (3), which contains the following two trials comparing afamelanotide head-to-head with placebo:

- CUV039
- CUV029

In addition to Langendonk et al. 2015 (3), the European Public Assessment Reports (EPAR) for afamelanotide were consulted (4). The identified relevant studies are presented in Table 3 and more thoroughly described in section 4.1. The expert committee requests follow-up data on the long-term safety profile of afamelanotide, which is described in Biolcati et al. 2015 and Wensink et al. 2020 (5,6).

TABLE 3: RELEVANT STUDIES INCLUDED IN THE CURRENT ASSESSMENT

Reference (authors, title, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)
Authors: J.G. Langendonk, M. Balwani, K.E. Anderson Title: Afamelanotide for Erythropoietic Protoporphyria Journal, year: The New England Journal of Medicine, 2015 Reference: (3)	CUV039: A Phase III, Multicentre, Double-Blind, Randomised, Placebo-Controlled Study to Confirm the Safety and Efficacy of Subcutaneous Bioresorbable Afamelanotide Implants in Patients with Erythropoietic Protoporphyria (EPP)	NCT01605136	Start: 12 May 2012 End: July 2013
Authors: J.G. Langendonk, M. Balwani, K.E. Anderson Title: Afamelanotide for Erythropoietic Protoporphyria Journal, year: The New England Journal of Medicine, 2015 Reference: (3)	CUV029: A Phase III, Multicentre, Double-Blind, Randomised, Placebo-Controlled Study to Confirm the Safety and Efficacy of Subcutaneous Bioresorbable Afamelanotide Implants in Patients With Erythropoietic Protoporphyria (EPP)	NCT00979745	Start: September 2009 End: May 2011
Authors: G. Biolcati, E. Marchesini, F. Sorge, L. Barbieri, X. Schneider-Yin and E.I. Minder Title: Long-term observational study of afamelanotide in 115 patients with erythropoietic protoporphyria Journal, year: British journal of Dermatology, 2014 Reference: (5)	Long-term observational study of afamelanotide in 115 patients with erythropoietic protoporphyria	NA	2006 to 2014
Authors: D. Wensink, A.E.M. Wagenmakers, J Barman-Aksozen, et al. Title: Association of Afamelanotide With Improved Outcomes in Patients With Erythropoietic Protoporphyria in Clinical Practice	Post-authorisation safety study for the use of SCENESSE® (afamelanotide 16mg) in patients with erythropoietic protoporphyria (EPP)	NA	Start: June 2016, ongoing

Journal, year: Journal of the American Medical Association Dermatology, 2020 Reference: (X)			

In addition to the CUV039 and CUV029 trials, three other trials were conducted, and the expert committee requests data on efficacy outcomes from these previous studies in the clinical trial program of afamelanotide. They are briefly described in the following and in
Table 4.

TABLE 4: INFORMATION ABOUT PREVIOUS STUDIES IN THE EPP CLINICAL TRIAL PROGRAM

	Study design	Objectives	Study period	Treatment arms	Sample size	Results
CUV010	Multicentre, phase II, open-label study evaluating the safety and efficacy of subcutaneous CUV1647 implants (20 mg afamelanotide) in EPP patients	To reduce the susceptibility to photoprovocation with a standardised light source, effect on melanin density and effect on use of rescue medication.	09/2006 to 02/2007	Afamelanotide 20 mg implant S.C. every 2nd month, 6 doses in total.	5	Average minimum time to response after photoprovocation from 1.9 min (SD 1.3) at baseline to 13.3 min (SD 2.6) at day 120. Melanin density increased, with an increase of approximately 1 MD unit. Safety: implant site reactions, headache, somnolence, nausea.
CUV017	Phase III, multicentre, randomised, placebo-controlled crossover study to evaluate the safety and efficacy of CUV1647 (afamelanotide) implants in patients with EPP	To reduce the number of phototoxic reactions, quality of life (SF- 36), Safety and Tolerability.	05/2007 to 12/2009	Group A: Afamelanotide 16 mg implant S.C. at days 0, 120 and 240, and placebo implant at days 60, 180 and 300. Group B: Treatment alternated as above but starting with placebo.	100	Distribution of frequency of days with pain of different severity differed between active and placebo (p=0.0042; Cochran-Mantel-Haenszel test). Significantly more sun exposure in patients receiving afamelanotide (p = 0.0136; Cochran-Mantel-Haenszel test). No marked effects on QoL (SF-36 questionnaire). Safety: nausea, flushing.
CUV030	Multicentre, phase II, double-blinded, randomised, placebo-controlled study	Number and severity of phototoxic reactions in patients with EPP QoL (DLQI and	04/2010 to 01/2011	Afamelanotide 16 mg or placebo implant S.C. every 60 days,	77	Active group experienced more direct sunlight exposure between 10:00 and 15:00 hours at days when

	evaluating the safety and efficacy of subcutaneous afamelanotide implants in EPP patients	EPP- QoL), susceptibility to photoprovocation (subset) and Safety and Tolerability		3 doses in total.		no pain was experienced (pain score of 0; p=0.012), no difference between groups for overall time spent outdoors. No difference between groups in the number and severity of phototoxicity reactions. Safety: nausea, fatigue, pyrexia, nasopharyngitis.

Note: MD: melanin density, SD: standard deviation, s.c.: subcutaneous.

The CUV017 trial was the first phase III EPP trial after the CUV010 trial, which was a phase II trial. During data analysis for the CUV017 trial, it became apparent that EPP patients remain reluctant to change their conditioned behaviour of sun/light avoidance. Given that exposure to the sun or bright light triggers the chemical reactions that cause the incapacitating pain characteristic of EPP, it is not surprising that the lifelong anxiety of experiencing phototoxicity prevents EPP patients from exposing themselves to sunlight. Consequently, there were few reports of phototoxicity-related pain. The CUV030 trial followed the CUV017 trial and was a phase II study, and it was originally intended that phototoxicity-related pain should be the primary endpoint for the CUV030 trial. During the initial stages of data analysis, and to determine the clinically relevant impact of afamelanotide treatment, the sequence of the study objectives in the CUV030 trial was adapted to assess whether the study subjects could modify their lifelong conditioned behaviour. This was assessed by evaluating time spent in direct sunlight while remaining pain free or experiencing only mild pain during spring and summer months. The phase III European trial CUV029 followed the CUV030 trial. Lessons from the CUV030 and CUV029 trials were incorporated into the CUV039 protocol and statistical analysis plan (SAP) and CUV039 is considered by EMA to be the pivotal study. Information on the three previous studies can be found in Table 4.

5.1 Main characteristics of included studies

The assessment of afamelanotide compared to placebo is primarily based on the US CUV039 trial. The European CUV029 trial is used as a supplement. Both studies are published in Langendonk et al. 2015 (3). The European trial was concluded before the US trial was initiated and changes to the US study protocol were made based on results from the European trial. The two trials are presented below and an overview of main study characteristics is given in Table 5 and Table 6.

The US CUV039 trial (pivotal)

The US CUV039 trial was a phase III, multicentre, randomised, double-blinded, placebo-controlled safety and efficacy trial, conducted in two parallel study groups for six months. Enrolment was restricted to spring and summer. Subjects underwent a screening evaluation up to 14 days prior to administration of the first dose. 97 patients were screened at seven US sites, and 94 patients were randomly assigned to receive either a 16 mg afamelanotide implant or a placebo implant, in a 1:1 ratio. Randomisation was done using a computer-

generated randomisation list for each study site used to assign each subject to a treatment group. To ensure that treatment was balanced within study sites, the randomisation method used a small block size (four). Five individually sealed sets of computer-generated randomisation codes (each set containing 48 randomised numbers) were provided to the pharmacy. The study pharmacist chose one of the five sealed envelopes and the selected randomisation list was used to randomise the subjects in the study. For each study site, subjects who satisfied the inclusion criteria were allocated subject randomisation numbers, sequentially and chronologically, based on the timing of their attendance at the clinic for the first study implant administration. Patients, care provider, investigator and outcome assessor were blinded to treatment assignment.

Hence, 93 patients received at least one dose of the study drug and comprised the safety population (48 subjects in afamelanotide group and 45 in the placebo group). The intention-to-treat (ITT) population included 89 subjects (46 subjects in the afamelanotide group and 43 subjects in the placebo group), because three subjects terminated early without returning any diary and one completed all three doses but did not return the diary at visit four.

The ITT population for the quality of life endpoints comprised 90 subjects (47 subjects from the afamelanotide group and 43 subjects from the placebo group). This population contains more subjects than the ITT population for the diary card endpoints since more subjects completed quality of life assessments than returned diary cards.

The placebo implants contained poly (DL-lactide-co-glycolide) polymer and the implants were identical in size to those in the active treatment group. The 16 mg afamelanotide implant and placebo implant were administered every 60 days over a period of six months, with a total of three implants (day 0, 60 and 120). Additional information about outcomes and study and patient characteristics are presented in Table 5.

TABLE 5: MAIN CHARACTERISTICS OF THE US CUV039 TRIAL

Trial name	Phase III, Multicentre, Double-Blind, Randomised, Placebo-Controlled Study to Confirm the Safety and Efficacy of Subcutaneous Bioresorbable Afamelanotide Implants in Patients With Erythropoietic Protoporphyria (EPP)
NCT number	NCT01605136
Objective	Primary objective: · To determine whether afamelanotide can enable EPP patients to expose themselves to sunlight without incurring pain and phototoxic reactions. Secondary objectives: · To determine whether afamelanotide implants can improve the quality of life of EPP patients and reduce the susceptibility to provocation with a standardised light source (minimum symptom dose) in patients with EPP. · To evaluate the safety and tolerability of afamelanotide by measuring treatment-emergent adverse events (TEAEs) in patients with EPP and investigate the reversibility of afamelanotide-induced increase in dermal pigmentation.
Publications – authors, title, journal, year	Authors: Langendonk JG, Balwani M, Anderson KE, Bonkovsky HL, Anstey AV, Bissell DM, Bloomer J, Edwards C, Neumann NJ, Parker C, Phillips JD, Lim HW, Hamzavi I,

	Deybach JC, Kauppinen R, Rhodes LE, Frank J, Murphy GM, Karstens FPJ, Sijbrands EJG, de Rooij FWM, Lebwohl M, Naik H, Goding CR, Wilson JHP, Desnick RJ Title: Afamelanotide for Erythropoietic Protoporphyria Journal, year: The New England Journal of Medicine, 2015
Study type and design	Phase III, multicentre, double-blind, randomised, placebo-controlled study. Patients were randomised in a 1:1 ratio. The study is complete. Patients and investigators were blinded. This has been described more thoroughly above.
Follow-up time	Treatment period was 180 days with a safety follow-up at day 360, which included: · examination of the skin and oral mucosa by a dermatologist; · 12 lead ECG record; · review of diary for AEs and concomitant medication use; · review of diary for phototoxic reactions; · measurement of QoL assessment with EPP-QoL questionnaire; and · pregnancy test by urine dipstick. Total follow-up time: 360 days.
Population (inclusion and exclusion criteria)	Inclusion criteria (7): · Male or female subjects with characteristic symptoms of EPP phototoxicity and a biochemically confirmed diagnosis of EPP · Aged 18 years old and above (inclusive) · Able to understand and sign the written informed consent form · Willing to take precautions to prevent pregnancy until completion of the study (day 180) Exclusion criteria (7): · Any allergy to afamelanotide or the polymer contained in the implant or to lidocaine or other local anaesthetic to be used during the administration of the study medication · EPP patients with significant hepatic involvement · Personal history of melanoma or dysplastic nevus syndrome · Current Bowen's disease, basal cell carcinoma, squamous cell carcinoma, or other malignant or premalignant skin lesions · Any other photodermatosis, such as polymorphic light eruption, actinic prurigo, discoid lupus erythematosus, chronic actinic dermatitis or solar urticaria · Any evidence of clinically significant organ dysfunction or any clinically significant deviation from normal in the clinical or laboratory determinations · Acute history of drug or alcohol abuse (in the last 6 months) · Patient assessed as not suitable for the study in the opinion of the Investigator (e.g. noncompliance history, allergic to local anaesthetics, faints when given injections or giving blood) · Participation in a clinical trial for an investigational agent within 30 days prior to the screening visit

<table>
<tr><td></td><td>· Prior and concomitant therapy with medications which may interfere with the objectives of the study, including drugs that cause photosensitivity or skin pigmentation
· Female who is pregnant (confirmed by positive serum β-HCG pregnancy test prior to baseline) or lactating
· Females of child-bearing potential (pre-menopausal, not surgically sterile) not using adequate contraceptive measures (i.e. oral contraceptives, diaphragm plus spermicide, intrauterine device)</td></tr>
<tr><td>Intervention</td><td>One 16 mg subcutaneous afamelanotide implant every 2 months for 6 months.
Three implants in total.</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th>Variable</th><th>Afamelanotide (N=48)</th><th>Placebo (N=45)</th></tr>
<tr><td>Age in years – mean±SD</td><td>40.4±12.0</td><td>39.1±16.2</td></tr>
<tr><td>Female – no. (%)</td><td>20 (42)</td><td>24 (53)</td></tr>
<tr><td>Body mass index – mean±SD*</td><td>26.0±4.8</td><td>26.7±5.4</td></tr>
<tr><td>White race – no. (%) **</td><td>47 (98)</td><td>43 (96)</td></tr>
<tr><td>Fitzpatrick skin type – no. (%)
I (never tans, always burns)
II (tans less than average (with difficulty), mostly burns)
III (tans at average level, sometimes has mild burn)
IV (rarely burns, tans more than average (with ease)</td><td>
13 (27)
20 (42)
12 (25)
3 (6)</td><td>
10 (22)
15 (33)
16 (36)
4 (9)</td></tr>
<tr><td>Early discontinuation – no. of patients
Protocol violation
Suspected pregnancy
Withdrawal of consent
Lost to follow-up
Sponsor decision
Physician decision</td><td>3
0
0
2
0
0
1</td><td>4
0
0
0
2
1
1</td></tr>
<tr><td>Adverse events
Adverse events that occurred during the study period – no.
Patients with any adverse event that occurred during the study period – no. (%)
Severity of adverse events that occurred during the study period – no. (%)
Mild
Moderate
Severe
Most frequent adverse events that occurred during the study period – no. (%)
Nausea</td><td>
272
45 (94)

17 (35)
25 (52)
3 (6)

9 (19)</td><td>
216
39 (87)

14 (31)
23 (51)
2 (4)

8 (18)</td></tr>
</table>
</td></tr>
</table>

	Headache Nasopharyngitis Serious adverse events – no. (%) *** Patients who completed the study and received all implants – no. (%) ****	19 (40) 6 (12) 3 46 (96)	13 (29) 10 (22) 2 42 (93)

Source: Langendonk et al. 2015 (3).
* Body-mass index is the weight in kilograms divided by the square of the height in metres.
** Race was self-reported.
*** Serious adverse events in the afamelanotide group were herniated disk, abdominal pain, and benign compound nevus. Serious adverse events in the placebo groups were pulmonary embolus and melanoma. All serious adverse events were deemed by the investigators not to be related to study drugs.
**** Patients in the US study received 3 implants.

Primary and secondary endpoints	Primary outcome measure (7): · Duration of direct sunlight exposure between 10:00 and 18:00 hours at days when no pain was experienced (Pain Score of 0) (time frame: daily for 6 months). The amount of direct sunlight exposure between 10:00 and 18:00 hours at days when no pain was experienced (e.g. 11-point Likert pain score of 0). Time was recorded in a patient diary using 15-minute time blocks. The pain score is measured by the 11-point Likert Pain scale with minimum of 0 and maximum of 10. Likert pain scale of 0 represents no pain and 10 represents worst imaginable pain. Secondary outcome measures (7): · Combined sun exposure and phototoxic pain (time frame: daily for 6 months). Time in direct sunlight exposure between 10:00 and 18:00 hours at days when no or mild pain was experienced (Likert scores of 0 to 3). The pain score is measured by the 11-point Likert Pain scale with minimum of 0 and maximum of 10. Likert pain scale of 0 represents no pain and 10 represents worst imaginable pain. · Sun exposure (time frame: daily for 6 months). Duration of direct sunlight exposure between 10:00 and 18:00 hours during the study. · Quality of Life Score (time frame: day 60, day 120 and day 180 or early termination). The quality of life of participants is measured using the Dermatology Life Quality Index (DLQI) and the erythropoietic protoporphyria quality of life measure (EPP-QoL). The DLQI ranges from 0 (no impact on life) to 30 (significant impact on life). EPP-QoL scores range from 0 (worst imaginable QoL) to 100 (best possible QoL). · Photoprovocation (time frame: day 0, day 30, day 60, day 90 and day 120). A subset of subjects was photoprovoked on the dorsal surface of the hand

	(predilection place) and lower back and the minimum symptom dose (MSD) determined at days 0, 30, 60, 90 and 120. The amount of radiation required to provoke the first clinical symptom was recorded. · Maximum severity of phototoxic reaction experienced by participants (time frame: daily for 6 months). The phototoxicity – phototoxic pain secondary endpoint has been divided into two secondary outcome measures. The days on which the participant experienced pain because of phototoxic reactions (caused by exposure to natural light) was recorded in a study diary. On each day where such a reaction occurred, the participant scored the level of pain using an 11-point Likert pain scale, with a minimum value of 0 and maximum of 10. On the 11-point Likert pain scale, a value of 0 represents no pain and 10 represents worst imaginable pain. The maximum severity of a phototoxic reaction was determined by the highest daily 11-point Likert scale score that occurred during that phototoxic reaction. · Total number of phototoxic reactions experienced by participants (time frame: daily for 6 months). The phototoxicity – phototoxic pain secondary endpoint has been divided into two secondary outcome measures. The number of episodes was the endpoint. The days on which the participant experienced pain because of phototoxic reactions (caused by exposure to natural light) was recorded in a study diary. On each day where such a reaction occurred, the participant scored the level of pain using an 11-point Likert pain scale, with a minimum value of 0 and maximum of 10. The 11-point Likert pain scale with a value of 0 represents no pain and 10 represents worst imaginable pain. The number of phototoxic reactions was determined by counting the number of episodes on which participants report a 11-point Likert scale score of 4 or more for one or more consecutive days.
Method of analysis	The efficacy analyses were performed on an intention-to-treat basis. The ITT population included all randomised and treated subjects who provided at least one post-dose efficacy assessment. The methods used to analyse the efficacy endpoints are listed in the following. The following information was available from the CUV039 clinical study report (CSR). <u>Direct sunlight exposure</u> Analysed with patient-recorded exposure times in a study-specific diary. Time outdoors was recorded separately as being time in direct sunlight or time in the shade in each 15-minute block from 10:00 to 18:00. Differences were assessed with the Kruskal-Wallis test, Hodges-Lehmann estimate and 95% confidence intervals. <u>Phototoxic reactions</u> Subjects recorded their daily phototoxic pain intensity (caused by exposure to natural light) in the study diary. A phototoxic reaction was deemed to have occurred if a reaction resulted in a patient reporting a Likert scale severity score of 4 and above for one or more consecutive days. Days on which the patient experienced pain because of phototoxic reactions (caused by exposure to natural light) was recorded

	in a study diary. On each day where such a reaction occurred, the patient scored their level of pain using an 11-point Likert Pain Intensity Scale. The total severity of an individual phototoxic reaction was determined by adding the Likert scale severity scores for all days in an individual phototoxic reaction. The maximum severity of a phototoxic reaction was determined by the highest daily Likert scale score that occurred during that phototoxic reaction. The number of phototoxic reactions was determined by counting the number of episodes on which patients reported a Likert scale score of 4 or more for one or more consecutive days. Differences between groups were assessed with the Kruskal-Wallis test. <u>The quality of life</u> Was determined using the EPP-QoL and DLQI questionnaire. Both questionnaires were completed at the site at days 0, 60, 120 and 180. The EPP-QoL was also completed at the day 360 safety follow-up visit. The treatment groups were compared with respect to the change from baseline to each post-baseline DLQI assessment using the Kruskal-Wallis test, Hodges-Lehmann estimate and 95% confidence interval. <u>Photoprovocation</u> An area of approximately 33 mm in diameter was irradiated with light filtered to transmit radiation between 400 nm and 650 nm up to a maximum irradiation dose of 300 J/cm2 using a standardised and calibrated light source. Irradiation from the light source can vary over time, so it was calibrated before the test was performed. The time it takes for the patient to first experience symptoms together with the radiation output from the light source was used to calculate the "Minimum Symptom Dose". The treatment groups were compared with respect to the change from baseline to each post-baseline assessment using the Kruskal-Wallis test, Hodges-Lehmann estimate and 95% confidence interval. <u>Adverse events</u> The number of participants with treatment-emergent adverse events (TEAEs, including clinically significant changes in laboratory parameters) was summarised by MedDRA preferred term and body system for each treatment group. TEAEs were further summarised by intensity, seriousness, outcome, and relationship to study drug. Relationship to study is presented in terms of the Investigator assessment and additionally in terms of a blinded central assessment.
Subgroup analyses	A subgroup of 21 patients from the primary population underwent Photoprovocation testing (11 afamelanotide and 10 placebo). The Photoprovocation was performed on the dorsal surface of the hand and lower back to determine the minimum symptom dose at days 0, 30, 60, 90 and 120. The analysis was prespecified and not performed post-hoc.

The European CUV029 trial (supplementary)

The European CUV029 trial was a Phase III, multicentre, randomised, double-blinded, placebo-controlled safety and efficacy trial, conducted in two parallel study groups for nine months. To determine eligibility for study inclusion, subjects underwent a screening evaluation seven days prior to the administration of the first dose (day 0). Patients were randomly assigned to receive either a 16 mg afamelanotide implant or a placebo

implant, in a 1:1 ratio. A computer-generated randomisation list for each study site was used to assign each subject to a treatment arm. For each study site, subjects who satisfied the inclusion/exclusion criteria were allocated subject randomisation numbers sequentially and chronologically, based on the timing of their attendance at the clinic for the first study implant.

The ITT population comprised of 74 subjects who received at least one dose of study treatment (38 in the afamelanotide group and 36 in the placebo group). 68 of these subjects received all required doses of study treatment and completed the study. Five subjects discontinued prematurely: two in the afamelanotide group withdrew consent, 1 in the afamelanotide group was withdrawn by physician's decision for clinical reasons not related to the study, 1 in the afamelanotide group was withdrawn due to a serious violation of the protocol, and 1 in the placebo group was withdrawn by sponsor decision. Furthermore, one subject in the placebo group received all required study medication but did not complete the final study assessment visit and was lost to follow-up.

The implants used in the placebo arm were identical in size to the afamelanotide implant but contained only poly (DL-lactide-co-glycolide) polymer. The implants were administered every 60 days over a period of 9 months, with a total of five implants. Subjects visited the clinic at days 0, 60, 120, 180 and 240 for dose administration and a final visit at day 270 or at premature termination, if applicable. Additional information about outcomes and study and patient characteristics are presented in Table 6.

TABLE 6: MAIN STUDY CHARACTERISTICS OF THE EUROPEAN CUV029 TRIAL

Trial name	A Phase III, Multicentre, Double-Blind, Randomised, Placebo-Controlled Study to Confirm the Safety and Efficacy of Subcutaneous Bioresorbable Afamelanotide Implants in Patients With Erythropoietic Protoporphyria (EPP)
NCT number	NCT00979745
Objective	To determine whether afamelanotide can reduce the severity of phototoxic reactions in patients with EPP.
Publications – title, author, journal, year	Authors: Langendonk JG, Balwani M, Anderson KE, Bonkovsky HL, Anstey AV, Bissell DM, Bloomer J, Edwards C, Neumann NJ, Parker C, Phillips JD, Lim HW, Hamzavi I, Deybach JC, Kauppinen R, Rhodes LE, Frank J, Murphy GM, Karstens FPJ, Sijbrands EJG, de Rooij FWM, Lebwohl M, Naik H, Goding CR, Wilson JHP, Desnick RJ Title: Afamelanotide for Erythropoietic Protoporphyria Journal and year: The New England Journal of Medicine, 2015
Study type and design	Phase III, multicentre, double-blind, randomised, placebo-controlled study. The study is complete. Patients and investigators were blinded.
Follow-up time	270 days (9 months).
Population (inclusion and exclusion criteria)	Inclusion (8): · Male or female subjects with a diagnosis of EPP (confirmed by elevated free protoporphyrin in peripheral erythrocytes) of sufficient severity that they have requested treatment to alleviate their symptoms · Aged 18-70 years (inclusive)

<table>
<tr><td></td><td>
· Written informed consent prior to the performance of any study-specific procedures

Exclusion (8):
· Any allergy to afamelanotide or the polymer contained in the implant or to lignocaine or other local anaesthetic to be used during the administration of study medication
· EPP patients with significant hepatic involvement
· Personal history of melanoma or dysplastic nevus syndrome
· Current Bowen's disease, basal cell carcinoma, squamous cell carcinoma, or other malignant or premalignant skin lesions
· Any other photodermatosis such as PLE, DLE or solar urticaria
· Any evidence of clinically significant organ dysfunction or any clinically significant deviation from normal in the clinical or laboratory determinations
· Acute history of drug or alcohol abuse (in the last 12 months)
· Patient assessed as not suitable for the study in the opinion of the Investigator (e.g. noncompliance history, allergic to local anaesthetics, faints when given injections or giving blood)
· Female who is pregnant (confirmed by positive serum β-HCG pregnancy test prior to baseline) or lactating
· Females of child-bearing potential (pre-menopausal, not surgically sterile) not using adequate contraceptive measures (i.e. oral contraceptives, diaphragm plus spermicide, intrauterine device)
· Sexually active men with partners of childbearing potential not using barrier contraception during the trial and for a period of three months thereafter
· Participation in a clinical trial of an investigational agent within 30 days prior to the screening visit
· Prior and concomitant therapy with medications which may interfere with the objectives of the study, including drugs that cause photosensitivity or skin pigmentation
</td></tr>
<tr><td>Intervention</td><td>Patients were administered afamelanotide 16 mg subcutaneous implants at days 0, 60, 120, 180 and 240.</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th>Variable</th><th>Afamelanotide
(N=38)</th><th>Placebo
(N=36)</th></tr>
<tr><td>Age in years – mean±SD</td><td>38.3±13.0</td><td>38.6±11.6</td></tr>
<tr><td>Female – no. (%)</td><td>17 (45)</td><td>20 (56)</td></tr>
<tr><td>Body mass index – mean±SD*</td><td>24.0±3.0</td><td>26.5±5.2</td></tr>
<tr><td>White race – no. (%) **</td><td>38 (100)</td><td>35 (97)</td></tr>
<tr><td>Fitzpatrick skin type – no. (%)
I (never tans, always burns)
II (tans less than average (with difficulty), mostly burns)
III (tans at average level, sometimes has mild burn)
</td><td>
6 (16)
18 (47)
13 (34)
1 (3)</td><td>
12 (33)
15 (42)
9 (25)
0 (0)</td></tr>
</table>
</td></tr>
</table>

	IV (rarely burns, tans more than average (with ease)		
	Early discontinuation – no. of patients ***	4	2
	Protocol violation	1	0
	Suspected pregnancy	1	0
	Withdrawal of consent	2	1
	Lost to follow-up	0	0
	Sponsor decision	0	0
	Physician decision	0	1
	Adverse events		
	Adverse events that occurred during the study period – no.	189	166
	Patients with any adverse event that occurred during the study period – no. (%)	34 (89)	32 (89)
	Severity of adverse events that occurred during the study period – no. (%)		
	Mild	19 (50)	17 (47)
	Moderate	12 (32)	14 (39)
	Severe	3 (8)	1 (3)
	Most frequent adverse events that occurred during the study period – no. (%)		
	Nausea	7 (18)	6 (17)
	Headache	13 (34)	14 (39)
	Nasopharyngitis	8 (21)	8 (22)
	Serious adverse events – no. (%) ****	1	0
	Patients who completed the study and received all implants – no. (%) *****	34 (89)	34 (94)

* Body-mass index is the weight in kilograms divided by the square of the height in meters.
** Race was self-reported.
*** In the European Union trial, a physician decided to withdraw one patient from the study because of worsening of pre-existing severe headaches.
**** There was only one serious AE, a fractured humerus requiring surgery, which was not considered to be related to study medication.
***** Patients in the European Union study received five implants.

Primary and secondary endpoints	Primary outcome measure (8): · Severity of phototoxic reaction measured by visual analogue scale (time frame: 9 months) Secondary outcome measures (8): · Number of phototoxic reactions (time frame: 9 months) · Quality of life measured by patients completed questionnaire (time frame: 9 months) · Free protoporphyrin IX level (time frame: 9 months)

	· Treatment emergent adverse events (time frame: 9 months)
Method of analysis	<u>Direct sunlight exposure:</u> The difference between treatment groups in the amount of sun exposure (direct sunlight) between 10:00 and 15:00 was compared using a Kruskal-Wallis test for days on which patients experienced no pain (pain score of 0). The amount of time spent outdoors during the day with sunlight exposure was recorded in a patient diary. <u>Phototoxic reactions:</u> The days on which the subject experienced pain because of phototoxic reactions (caused by exposure to natural light) were recorded in a study diary. On each day where such a reaction occurred, the subject scored the level of pain using an 11-point Likert pain intensity scale. The total severity of an individual phototoxic reaction was determined by adding up the Likert scale severity scores for all days in an individual phototoxic reaction. The maximum severity of a phototoxic reaction was determined by the highest daily Likert scale score that occurred during that phototoxic reaction. The number of phototoxic reactions was determined by counting the number of episodes on which patients reported a Likert scale score of 4 or more for one or more consecutive days. Differences were compared using a Kruskal-Wallis test. The median number of phototoxic reactions was compared between treatment groups using a Wilcoxon rank sum test. The proportions of patients in each group who experienced a phototoxic reaction with a minimum Likert scale score of ≥ 4 and ≥ 7 were compared using a Chi-square test. <u>Quality of Life:</u> QoL was measured with the DLQI questionnaire and supplementary EPP-specific questions. The DLQI questionnaire was completed every 7 days from day 0 to 270 using a call centre. Changes in quality of life for each treatment group from day 0 to days 60, 120, 180, 240 and 270 were compared between groups using a Wilcoxon rank sum test. <u>Free protoporphyrin IX levels</u> Free protoporphyrin IX levels at baseline and changes from baseline to days 60, 120, 180, 240 and 270 were measured using a conventional analytical method. Between group comparison was done using the Wilcoxon rank sum test. <u>Minimum symptom dose (MSD) and minimal erythemal dose (MED):</u> In a subset of patients, MSD following photoprovocation on the lower back and dorsal surface of the hand and MED following photo testing on the lower back were compared between treatment groups at days 0, 30, 60, 90, 120, 180, 240 and 270 using the Wilcoxon rank sum test. <u>Safety analyses:</u> Descriptive methods were used to summarise the safety data. The number of subjects with TEAEs (TEAEs, including any clinically significant changes in laboratory parameters) was summarised by MedDRA preferred term and body system for each

	treatment group. TEAEs were further summarised by intensity, seriousness, outcome, and relationship to study drug.
Subgroup analyses	A subset of patients underwent photoprovocation on the lower back and dorsal surface of the hand and were photo tested on the lower back for determination of the MSD and MED, respectively, at days 0, 30, 60, 90, 120, 180, 240 and 270.

6 Clinical questions

6.1 Clinical question: What is the value of afamelanotide compared to placebo for patients with erythropoietic protoporphyria?

6.1.1 Presentation of relevant studies

The relevant study to answer the clinical question is the US CUV039 trial. The European CUV029 trial will also be used for a qualitative description of quality of life (QoL) and adverse events. The main characteristics of these two studies are presented in section 5.1. In the following subsections, the results are presented per study (the CUV039 trial and the CUV029 trial, respectively) and each of the relevant outcome in the studies are addressed. Most information and data were available from the afamelanotide EPAR and the publication by Langendonk et al. 2015 (3,4). If data was not available in the EPAR or publication by Langendonk et al. 2015, the clinical study reports (CSRs) were consulted (9,10). In the DMC protocol on EPP, the expert committee states that they wish to receive data for the longest possible follow-up time, which we have accommodated by taking results from the longest follow-up time in our assessments.

6.1.2 Results per study – CUV039 trial

Quality of life – Critical outcome

In the DMC protocol on EPP, the expert committee requests results on QoL assessed with the DLQI questionnaire as the average change in QoL from baseline. Furthermore, the expert committee requests that the EPP-QoL questionnaire is used as a supplement to the DLQI questionnaire in a qualitative description.

To assess the average change from baseline measured with the DLQI, the CUV039 trial was used with available data from the afamelanotide EPAR (4). Supplementary EPP-QoL data from the CUV039 and CUV029 trials were used. A psychometric validation work on the EPP-QoL instrument was undertaken by Oxford Outcomes (an ICON public company) in the CUV039 trial. This allowed the prospective analysis of QoL in the CUV039 trial to be conducted using both an original scoring algorithm and a revised scoring algorithm which was a result of the validation work undertaken by Oxford Outcomes. Results on the revised scoring algorithm will be presented in this application.

The expert committee has requested data for DLQI and supplementary data on EPP-QoL. The DLQI – as a tool developed for dermatological disorders – has severe limitations as an appropriate tool for evaluating QoL in EPP, a metabolic disorder characterised by phototoxicity. We have further described this in section 7.1 and advise the expert committee to apply the EPP-QoL in the assessment of QoL as the primary tool to measure QoL.

Definition/operationalisation of the outcomes: DLQI and EPP-QoL

The DLQI is a generic questionnaire for dermatological conditions, designed to measure the health-related quality of life of patients suffering from skin disorders and their treatments. The possible DLQI score ranges from 0-30, with lower scores indicating better QoL. The DLQI consists of 10 questions related to symptoms, feelings, daily activities, work or school, relations and inconvenience of treatment.

EPP-QoL is a disease-specific questionnaire and two versions of the EPP-QoL questionnaire exist: the original version and a revised version. The original version of the EPP-QoL is a 15-question tool with a particular scoring algorithm. The total scores range from -10 (best possible) to 35 (worst imaginable), which means that the lower the score, the better the QoL (11). This tool was sent to the then Oxford Outcomes (an ICON public company) for validation. Following the first review, it was recommended that three questions should be deleted and that the scoring algorithm should be modified. In the revised EPP-QoL version, twelve of the original questions were retained and the scores for each question were modified such that higher scores were attributed to answers that suggested better quality of life. Using the revised scoring algorithm, 0 represented worst quality of life and 100 the best quality of life i.e. a higher score indicating better QoL.

Results from each version are comparable. If you put the results obtained from both side by side, the meanings are the same if you interpret the results against the scoring range for the version used. An improvement in one version relates to the same improvement in the other, although the numerical changes in score will be a little different.

Method of data collection and analysis: DLQI and EPP-QoL

The ITT population for the quality of life endpoint comprised 90 subjects (47 subjects from the afamelanotide group and 43 subjects from the placebo group). This population contains more subjects than the ITT (Direct sunlight exposure) population since more subjects completed quality of life assessments than returned diary cards. The DLQI questionnaire was completed at the sites that conducted the trial at days 0, 60, 120 and 180, or at early termination visit, if applicable. EPP-QoL was also completed on trial days 0, 60, 120 and 180 and at the safety follow-up visit at day 360. Assessment of the results of the EPP-QoL was performed prospectively against the original scoring algorithm, and a revised scoring algorithm was developed during the EPP-QoL validation work.

Inter-group comparisons of changes in DLQI total score and EPP-QoL score over time in relation to baseline were performed with the Kruskal-Wallis test statistics and Hodges-Lehmann shift estimates (4).

Results: DLQI

The mean DLQI scores decreased (indicating improved QoL) in both treatment groups throughout the six-month duration of the study. Numerically, the mean scores decreased (improved) more in the afamelanotide group compared with the placebo group (-8.1 and -7.3 at visit 4 at day 180, respectively.). Results in Table 7 are presented as the mean change from baseline in the QoL ITT population at the longest follow-up time, which was at visit 4 (day 180). Furthermore, the p-value estimated with the Kruskal-Wallis test and the Hodges Lehmann shift estimate with 95% CI are presented. The formula for calculations of the 95% CI of the means are presented in appendix section 9.4.

TABLE 7: CHANGE FROM BASELINE ON THE DLQI QUESTIONNAIRE MEASURED AT DAY 180 (ITT QOL POPULATION)

	Afamelanotide (n=46)	Placebo (n=43)	Source
Mean change from baseline to visit 4, day 180 (SD)	-8.1 (6.2)	-7.3 (5.6)	EPAR (4)

Median	-7.5	-8.0	
Range	-26 – 1	-19 – 5	
95% CI of mean change from baseline	-9.9; -6.3	-9.0; -5.6	Own calculations
Kruskal-Wallis test	p-value = 0.799		EPAR (4)
Hodges-Lehmann shift estimate (95% CI)	0 (2; -3)		EPAR (4)

Results: EPP-QoL

The mean EPP-QoL revised score increased (indicating improved QoL) in both treatment groups throughout the six-month duration of the study. Numerically, the mean score increased more in the afamelanotide group compared with the placebo group (51.1 and 36.8, respectively, at visit 4, day 180). The results in Table 8 are presented as the mean change from baseline in the QoL ITT population at visit 4, day 180. Furthermore, the Kruskal-Wallis p-value and Hodges-Lehmann shift estimate with 95% CI are presented. The formula for calculations of the 95% CI of the means are presented in appendix section 9.4.

TABLE 8: RESULTS FROM THE EPP-QOL QUESTIONNAIRE (OXFORD OUTCOMES SCORES), DAY 180

	Afamelanotide (n=46)	**Placebo (n=43)**	**Source**
Mean change from baseline to visit 4, day 180 (SD)	51.1 (29.1)	36.8 (25.7)	EPAR (4)
Median	52.8	38.9	
Range	2.8 – 100.0	-5.6 – 88.9	
95% CI of mean change from baseline	42.7; 59.5	29.1; 44.5	Own calculations
Kruskal-Wallis p-value	0.021		EPAR (4)
Hodges-Lehmann shift (95% CI)	13.9 (2.8; 27.8)		

Moreover, results on EPP-QoL are also available at a safety follow-up at day 360 (240 days after last dose) (Table 9). The mean EPP-QoL decreased after day 180, but the mean EPP-QoL was still higher at day 360 than at day 0 in both the afamelanotide group and the placebo group. This may reflect the raised expectation of quality of life during afamelanotide treatment and the subjects' response to having the treatment withdrawn (4).

TABLE 9: RESULTS FROM THE EPP-QOL QUESTIONNAIRE (OXFORD OUTCOMES SCORES), DAY 360 (SAFETY VISIT)

	Afamelanotide (n=44)	**Placebo (n=40)**	**Source**
Mean change from baseline to follow-up visits, day 360 (SD)	10.9 (27.3)	19.4 (23.9)	EPAR (4)
Median	1.4	15.3	
Range	-22.2 – 100 .0	-13.9 – 86.1	
95% CI	2.8; 19.0	12.0; 26.8	Own calculations
Kruskal-Wallis p-value	0.050		EPAR (4)
Hodges-Lehmann shift (95% CI)	-11.1 (-19.4; 0.0)		

Symptoms (phototoxicity) – Critical outcome

In the DMC protocol on EPP, the expert committee requests that symptoms (phototoxicity) are assessed by two measures, the duration of sun exposure and phototoxic reactions. The CUV039 trial was used to assess these outcomes, because the CUV039 trial assessed exposure to sunlight between 10:00 and 18:00 during the spring and summer months, which was requested by the expert committee. Information was available in the afamelanotide EPAR (4) and the publication by Langendonk et al. 2015 (3). We also present results on the primary outcome in the CUV039 "Duration of pain-free sun exposure in direct sunlight expressed in hours" because this as a crucial outcome when assessing the effect of afamelanotide in EPP patients.

Definition/operationalisation of outcomes: Duration of sun exposure and phototoxic reactions
These outcomes are operationalised in the EPP protocol as minutes per day outdoors (in direct or indirect sunlight) without or with mild symptoms (pain <4 on a Likert scale from 0-10) and duration of symptoms (moderate to severe with pain ≥4 on a Likert scale from 0-10) after an episode with exposure to sunlight.
The CUV039 trial assessed the duration of exposure to sunlight between 10:00 and 18:00 at days when no or mild pain was experienced (Likert score of 0-3). The mean daily duration is expressed in minutes, while the mean duration of phototoxic reactions is expressed in days. The mean daily duration of sun exposure in minutes was determined by dividing the total exposure over the entire study by the number of days the subject was on the study drug. A post-hoc assessment of the number of days on which subjects reported pain of each possible severity scores using a 11-point Likert scale was used to assess the duration of phototoxic reactions (Likert score >4).

Method of data collection and analysis: Duration of sun exposure and phototoxic reactions
Subjects recorded their daily sun exposure in a diary. Time outdoors was recorded separately as being time in direct sunlight or time in the shade in each 15-minute block from 10:00 to 18:00. Subjects also recorded their daily phototoxic pain intensity (caused by exposure to natural light) in the study diary. On each day where such a reaction occurred, the subject scored the level of pain using an 11-point Likert pain intensity scale where a score of 0 represented "no pain" and a score of 10 was "worst imaginable pain". Phototoxicity was deemed to have occurred when a subject recorded a Likert pain scale score of ≥ 4. An individual phototoxic reaction was comprised of one or more consecutive days with a Likert pain scale score of ≥ 4. The total severity of an individual phototoxic reaction was determined by adding the Likert pain scale scores for all days in an individual phototoxic reaction.

Inter-group comparisons of duration of sun exposure and phototoxic reactions were performed with the Kruskal-Wallis test statistics and Hodges-Lehmann shift estimates (4).

Results: Duration of sun exposure
Results on the mean daily duration of sun exposure between 10:00 and 18:00 with no or mild pain are presented for the ITT population in Table 10. The mean daily duration of sun exposure was 47.5 minutes (SD: 53.4 minutes) in the afamelanotide group compared with 27.1 minutes (SD: 22.9 minutes) in the placebo group. Furthermore, the Kruskal-Wallis p-value and Hodges-Lehmann shift estimate with 95% CI are presented. The formula for calculations of the 95% CI are presented in appendix section 9.4.

TABLE 10: DAILY DURATION OF SUN EXPOSURE FROM 10:00 TO 18:00 (ITT POPULATION)

	Afamelanotide (n=46)	Placebo (n=43)	Source
Mean (SD) – minutes	47.5 (53.4)	27.1 (22.9)	EPAR (4)

Median - minutes	27.3	25.2	
Range	0.2 – 263.8	0.7 – 85.0	
95% CI of means	32.1; 62.9	20.3; 33.9	Own calculations
Kruskal-Wallis p-value	0.094		EPAR (4)
Hodges-Lehmann shift estimate (95% CI)	8.4 minutes (-1.5; 18.9)		

Results: Duration of phototoxic reactions

Results on the mean duration of phototoxic reactions are presented for the ITT population in Table 11. The mean duration of phototoxic reactions was 3.2 days (SD: 6.0 days) in the afamelanotide group compared with 6.6 days (SD: 16.8 days) in the placebo group. The formula for calculations of the 95% CI are presented in appendix section 9.4.

TABLE 11: DURATION OF PHOTOTOXIC REACTIONS IN DAYS (ITT POPULATION)

	Afamelanotide (n=46)	Placebo (n=43)	Source
Mean (SD) – days	3.2 (6.0)	6.6 (16.8)	Langendonk et al. 2015 (3)
Median - days	1.0	1.0	
Range	0-34	0-98	
95% CI of means	1.5; 4.9	1.6; 11.6	Own calculations

Results: Duration of pain-free sun exposure in direct sunlight expressed in hours

Results on the mean duration of pain-free sun exposure from 10:00 and 18:00 hours in direct sunlight across the 6-month study period expressed in hours are presented for the ITT population in Table 12. The mean duration of pain-free direct sun exposure across the 6-month study period was 115.6 hours (SD: 140.6 hours) in the afamelanotide group compared with 60.6 hours (SD: 60.6 hours) in the placebo group. There was a statistically significant difference between the treatment groups with respect to total pain-free direct sun exposure (Kruskal-Wallis test, p=0.044). The difference (Hodges-Lehmann estimate) was 24.0 hours (95% CI: 0.3, 50.3) in favour of afamelanotide across the 6-month study period in the ITT population.

TABLE 12: DURATION OF PAIN-FREE SUN EXPOSURE FROM 10:00 TO 18:00 HOURS IN DIRECT SUNLIGHT ACROSS THE 6-MONTHS STUDY PERIOD. ITT POPULATION.

	Afamelanotide (n=46)	Placebo (n=43)	Source
Mean (SD)	115.6 hours (140.6)	60.6 (60.6)	EPAR (4)
Median	69.4	40.8	
Range	0-650.5	0-224.0	
Kruskal-Wallis p-value	0.044		
Hodges-Lehmann shift (95% CI)	24.0 hours (0.3; 50.3)		

Adverse events – Critical outcome

In the DMC protocol on EPP, the expert committee requests data on adverse events (AEs) assessed as the proportion of patients experiencing grade 3-4 AEs. To accommodate this, the CUV039 trial was used. Furthermore, the expert committee requests a qualitative description of AEs, including long-term AEs. Both

the CUV029 and CUV039 trials were used in the qualitative description of the safety profile of afamelanotide, and Biolcati et al. 2015, Wensink et al. 2020 and data on file were used to assess the long-term AEs (5,6,12). The primary safety outcome in the CUV039 trial was type and incidence of TEAEs. Secondary endpoints were any significant abnormalities detected in electrocardiography (ECG), physical examination changes from screening, changes in blood pressure and heart rate from screening to all subsequent visits and changes in clinical chemistry, haematology and urinalysis parameters from screening to all subsequent visits. It was not possible to identify any afamelanotide trials that categorised AEs as grade 3-4. Grade refers to the severity of an AE and ranges from grade 1 to 5. A grade 3 AE is defined as severe or medically significant, but not immediately life-threatening. Grade 4 AEs are defined as life-threatening.

Definition/operationalisation of the outcome: Adverse events

The CUV029 and CUV039 trials both categorise AEs as mild, moderate, or severe. TEAEs categorised as severe are presented in the present application because it is assumed that this is most similar to what the expert committee requests in the EPP protocol (grade 3 and 4). Information regarding the proportion of patients experiencing a severe TEAE was available in the publication by Langendonk et al. 2015 (3). AEs were categorised for severity in the following way:

- **Mild:** The AE was transient and easily tolerated by the subject. Specific action was optional.
- **Moderate:** The AE caused the subject discomfort and interrupted the subject's usual activities.
- **Severe:** The AE caused considerable interference with the subject's usual activities and may be incapacitating or life-threatening.

In the CUV039 trial, a TEAE was defined as:

- an event that was not present prior to or on the day of the first study medication administration but was present after study medication was administered;
- an event that was present prior to first administration of study medication and continued to occur after the administration of the first dose at an increased level of severity; or
- an event that was present prior to administration of study medication and was documented as completely resolved and re-emerged after the administration of the first dose.

Method of data collection and analysis: Adverse events

During the study, subjects were monitored for any signs or symptoms of treatment-emergent toxicity. Safety was assessed through the following:

- focused medical history and physical examination, including vital signs, full body anterior and posterior high-resolution photography to provide a baseline, including suspicious, pre-existing skin lesions and sun-damaged fields;
- adverse event and concomitant medication query;
- clinical laboratory investigations including haematology, blood chemistry and urinalysis; and
- electrocardiograms.

The number of participants with TEAEs (including clinically significant changes in laboratory parameters) was summarised by MedDRA preferred term and body system for each treatment group. TEAEs were further summarised by intensity, seriousness, outcome, and relationship to study drug. Relationship to study is presented in terms of the investigator assessment and additionally in terms of a blinded central assessment.

Results: Adverse events

Safety results are presented for the safety population. Afamelanotide was safe and well tolerated in this study. TEAEs were generally mild or moderate in severity and not considered to be related to study medication. There were few serious AEs, but none considered related to study medication. There were no clinically relevant differences between groups in the incidence or severity of AEs, or in results of physical exam, vital signs, clinical chemistry, urinalysis, or haematology evaluations. Results on number of subjects with severe TEAEs are presented in Table 13. There were 3 severe TEAEs in the afamelanotide group and 2 severe TEAEs in the placebo group. The severe TEAEs in the afamelanotide group were herniated disk, abdominal pain, and benign compound nevus. The severe TEAEs in the placebo group were pulmonary embolus and melanoma.

TABLE 13: NUMBER OF SUBJECTS WITH A SEVERE TREATMENT-EMERGED ADVERSE EVENT (TEAE)

	Afamelanotide (N=48)	Placebo (N=45)	Source
Severe TEAE - no. (%)	3 (6%)	2 (4%)	Langendonk et al. 2015 (3)

6.1.3 Results per study – CUV029 trial

Quality of life – Critical outcome

The CUV029 trial assesses changes in QoL with DLQI and EPP-QoL. The CUV029 trial was not used to assess the outcome changes from baseline in DLQI, as some subjects did not have DLQI responses at baseline, and so the change from baseline could not be meaningfully analysed. Therefore, the CUV029 trial was only used in the qualitative description of QoL based on EPP-QoL data and in the qualitative description of AEs as a supplement to the CUV039 data. Results from the longest follow-up time (270 days) is presented. Data was available from the CUV029 CSR (9).

Definition/operationalisation of the outcome: EPP-QoL

The EPP-QoL questionnaire was described in section 6.1.2.

Method of data collection and analysis: EPP-QoL

The EPP-QoL were completed at the site at days 0, 60, 120, 180, 240 and 270 and a p-value was estimated with a 2-sided Wilcoxon test. The revised version of the EPP-QoL was used in the CUV029 as well. For further explanation see section 6.1.2.

Results: EPP-QoL

Results are presented as mean absolute scores at day 270 (9 months) and presented for the ITT population. The mean absolute score in EPP-QoL at day 270 in the afamelanotide group was 79.9 and 67.2 in the placebo group. Table 14 shows that the absolute score in EPP-QoL approaches significance (p-value = 0.06).

TABLE 14: MEAN ABSOLUTE SCORE IN EPP-QOL AT DAY 270 (ITT POPULATION)

	Afamelanotide (N=38)	Placebo (N=36)	Source
n	32	34	Langendonk et al. 2015 (3)
Mean (SD)	79.7 (16.1)	67.2 (25.7)	
P-value	0.06		

Adverse events – Critical outcome

Definition/operationalisation of the outcome: Adverse events
AEs in the CUV029 trial was defined in the same way as in the CUV039 trial.

Method of data collection and analysis: Adverse events
Subjects were monitored during the study for any signs or symptoms of treatment-emergent phototoxicity. The primary safety endpoint was the incidence of any phototoxicity as judged from observed AEs. Secondary safety endpoints included:

- type and incidence of TEAE;
- physical examination changes from screening;
- changes in blood pressure and heart rate from screening to all subsequent visits; and
- changes in clinical chemistry, haematology, and urinalysis parameters from screening to all subsequent visits.

Results: Adverse events
Results are presented for the safety population. Most subjects in both groups experienced at least one TEAE. For most of these subjects, the greatest severity of any TEAE was mild or moderate, as shown in Table 15. Very few subjects experienced severe TEAEs.

TABLE 15: TEAE FROM THE CUV029 TRIAL (SAFETY POPULATION)

	Afamelanotide (N=38)	Placebo (N=36)	Source
Subjects with any TEAE	34 (89%)	32 (89%)	Langendonk et al. 2015 (3)
Severity among TEAE			
Mild	19 (50%)	17 (47%)	
Moderate	12 (32%)	14 (39%)	
Severe	3 (8%)	1 (3%)	

6.1.4 Comparative analyses

In this section, we present the comparative analysis of afamelanotide and placebo based on results from the CUV039 trial on the outcomes presented in the DMC protocol on EPP. In addition to the outcomes requested by the expert committee in the DMC protocol on EPP, we present a comparative analysis of pain-free duration in direct sunlight expressed in hours, the unit used in the analysis of the studies as presented to the EMA and following the statistical analysis plan of the study as agreed by CLINUVEL and the expert physicians conducting the trial. We regard these results as highly relevant because this was the primary analysis conducted in the CUV039 trial, while “minutes per day” was completed as a post-hoc analysis. The “minutes per day” approach must average the total exposure time over the duration of the study (as captured in patient diaries, recorded in 15 minute “blocks”), rather than reflecting the actual number of minutes and/or days that EPP patients exposed themselves to sunlight.

The comparative analysis we present is a head-to-head comparison based on the CUV039 study. The purpose of the comparative analysis is to assess how afamelanotide performs on the different outcomes outlined by the expert committee in the DMC protocol on EPP. The expert committee has requested data on the

following outcomes: QoL, symptoms (phototoxicity) and adverse events. Dichotomic outcomes will be presented in both absolute and relative values, while continuous outcomes will be presented only in absolute values (mean differences).

The QoL outcome is assessed by measuring the mean change from baseline in DLQI with the DLQI questionnaire. The QoL outcome is also described qualifiedly using measurements from the EPP-QoL questionnaire. The symptoms (phototoxicity) outcome is assessed by measuring the change in minutes per day outdoors between 10:00 and 18:00 without or with mild pain measured on a Likert scale. Symptoms (phototoxicity) outcome is also assessed by measuring change in the number and the duration (severity) of phototoxic reactions.

The AE outcome is assessed by measuring the proportion of patients who experience a severe TEAE and qualitatively described with focus on the long-term safety profile of afamelanotide. The qualitative descriptions are supplemented with information from the European CUV029 trial. Results of the comparative analysis is described in the following and presented in Table 16.

Change from baseline in QoL measured with DLQI

In the outcome "mean change from baseline in QoL measured with the DLQI", we did not estimate a difference between the two treatment groups. This supports our position that DLQI is an inappropriate tool for measuring changes in QoL in EPP patients, which is presented later in this application (see 7.1). The expert committee has outlined a minimal clinically relevant difference of 4 points in the DMC protocol on EPP. This is not achieved by afamelanotide, but this is not surprising, given that the DLQI questionnaire lacks specificity for EPP and has not been validated for use in this disorder. The outcome is a continuous outcome, and no data on the relative difference in effect is presented, only the absolute difference in effect.

It is clear from the use of the EPP-QoL tool – which was designed by EPP experts specifically to evaluate the impact of EPP on patients' quality of life – that intervention with afamelanotide has a significant positive impact on patient quality of life (see below). This is supported by the overwhelming clinical benefit reported by experts in the clinical literature over the years of use of the product in this rare condition (3,5,6,18,19) .

Minutes per day outdoors without or with mild pain (10:00 to 18:00)

In the outcome "minutes per day outdoors (in direct or indirect sunlight) without or with mild symptoms (pain < 4 on a Likert scale of 0-10)", we estimated an absolute mean difference of 20.4 minutes (95% CI: 2.9; 37.9), in favour of the afamelanotide group, which means that patients are able to spend 75% more time outdoors if they are treated with afamelanotide compared with the placebo group. The expert committee outlines a minimal clinically relevant difference in the DMC protocol on EPP of 50% more time outdoors in minutes (minimum 20 minutes). Afamelanotide achieves this minimal clinically relevant difference and demonstrates a strong performance on this outcome. The outcome is a continuous outcome, and no data on the relative difference in effect is presented, only the absolute difference in effect.

Duration of symptoms after an episode with exposure to light

In the outcome "duration of symptoms (moderate to severe with pain ≥4 on a Likert scale from 0-10) after episode with exposure to sunlight", we estimated a mean difference of -3.4 days, which is a reduction of 52% compared with placebo. The expert committee outlines a minimal clinically relevant difference of 20% reduction in the duration of symptoms. Afamelanotide achieves this minimal clinically difference and demonstrates a strong performance on this outcome. The outcome is a continuous outcome and no data on the relative difference in effect is presented, only the absolute difference in effect.

Duration of pain-free time (hours) spend in direct sunlight

In the outcome "duration of pain-free sun exposure from 10:00 to 18:00 hours in direct sunlight across the 6-months study period" the pain-free time in direct sunlight was 70% longer among patients who received afamelanotide than among patients who received placebo (median, 69.4 hours vs. 40.8 hours; P = 0.04). We estimated a mean difference of 55 hours in favour of the afamelanotide group).

It is important to contextualise these results. EPP patients are lifelong conditioned to avoid exposure to environmental light (sunlight) and, until the afamelanotide clinical development program, had been offered no effective treatments that would offer photoprotection. As a result, it is understandable that few patients were prepared to challenge their condition over the course of a six-month study, knowing that they may have received a placebo (i.e. no possible protection). Requests to patients to expose themselves would be unethical, given the risk of phototoxicity. As a result, the number of hours of exposure over the course of the study was deemed the most appropriate endpoint for the CUV039 study, and patient diaries were established as a data capture tool to reflect this.

In the CUV039 study, the majority of sunlight exposure data were recorded by a minority of patients who were prepared to risk exposure during the study period (this had been understood from previous studies as well, and is a unique challenge in evaluating treatment in EPP). Some patients – receiving both placebo and active – recorded fewer than five hours of exposure throughout the entire study due to their unwillingness to challenge their conditioned behaviour.

Adverse events

The expert committee requests data on the outcome "Proportion of patients who experience AEs of grade 3 to 4". We were not able to identify any trial categorising adverse events into such categories. Therefore, we present data on the proportion of patients who experience severe TEAEs, as we assume that this is the best alternative to accommodate the expert committee's request. We found a very small proportion of severe TEAEs in both treatment arms. We estimated an absolute difference of two percentage points. The expert committee has outlined a minimal clinically relevant difference of five percentage points in the DMC protocol on EPP. Afamelanotide does not achieve this; however, it should be noted that the proportion of patients who experience severe TEAEs on afamelanotide treatment is very low. Later in this section, we have described the safety profile of afamelanotide qualitatively.

Summary of comparative analyses

In order to provide an overview of our comparative analysis of afamelanotide and placebo, we have summarised the results of the comparative analyses presented above in Table 16.

TABLE 16: COMPARATIVE ANALYSIS BASED ON THE HEAD-TO-HEAD CUV039 TRIAL

Outcome	Study arm	N	Results (CI)	Estimated absolute difference	Estimation method	Source

				Difference	95% CI	p-value		
Minutes per day outdoors (in direct or indirect sunlight) without or with mild symptoms (pain <4 on a Likert scale from 0-10)	Afamelanotide	46	47.5 (32.1; 62.9)	20.4 minutes (75% reduction)	(2.9; 37.9)	0.094	The mean difference is calculated by subtracting the two means. The 95% CI for the mean difference was calculated with an online calculator (13)	EPAR (4)
	Placebo	43	27.1 (20.3; 33.9)					
Duration of symptoms (moderate to severe with pain ≥4 on a Likert scale from 0-10) after episode with exposure to sunlight	Afamelanotide	46	3.2 (1.5, 4.9)	-3.4 days (52% reduction)	(-8.6; 1.8)	0.503	The mean difference is calculated by subtracting the two means. The 95% CI for the mean difference was calculated with an online calculator (13)	EPAR (4)
	Placebo	43	6.6 (1.6, 11.6)					
DLQI, mean change from baseline	Afamelanotide	46	-8.1	-0.8	(-3.3; 1.7)	0.799	The mean difference is calculated by subtracting the two means The 95% CI for the mean difference was calculated with an online calculator (13)	EPAR (4)
	Placebo	43	-7.3					
Proportion of patients who experience severe TEAEs	Afamelanotide	48	3 (6%)	2 percent point	NA	NA	The difference was calculated by subtracting the two percentages.	Langendonk et al. 2015 (3)
	Placebo	45	2 (4%)					

Note: The comparative analyses performed in the table are based on the outcomes defined in the DMC EPP protocol.

Qualitative description of quality of life estimated with EPP-QoL

In this section, we present the qualitative description of changes in QoL measured with the EPP-QoL questionnaire and published in Langendonk et al. 2015 (3) and the CRSs belonging to the CUV039 trial and CUV029 trial (9,10).

As described in section 7.1, the DLQI questionnaire has severe limitations as a method of measuring QoL in patients suffering from EPP. The DLQI questionnaire focuses on how dermatological symptoms impact patients' QoL, which is relevant for skin conditions, rather than the overall well-being of patients, which is relevant in metabolic diseases such as EPP. Uniquely, EPP patients are lifelong conditioned to avoid light exposure, which causes the greatest impact upon their QoL. The limitations of the DLQI become apparent when we compare the changes in QoL measured by DLQI with those measured by EPP-QoL.

In the CUV039 trial, the mean change from baseline in QoL measured with the EPP-QoL questionnaire was significantly improved at day 180 in the afamelanotide group compared with the placebo group (p= 0.021), as shown in Table 8. Table 17 shows that the improvement in mean change from baseline in the afamelanotide group was significant, compared with the placebo group at all visits during the study period (p-values from <0.001 at day 60 and 120 and 0.02 at day 120). A similar improvement was shown in the CUV029 trial, with a mean absolute improvement of QoL measured with the EPP-QoL questionnaire that approached significance at day 270 (p-value = 0.06) and significant differences estimated in QoL during the study period (p-values from 0.005 to 0.01 from day 120 to 240) (see Table 18). The same improvement in QoL was not shown when measuring QoL with the DLQI questionnaire, as shown in Table 7 (a mean difference of 0.8 and a p-value of 0.799). These findings clearly show the lack of specificity of the DLQI questionnaire for measuring changes in QoL of EPP patients.

TABLE 17: MEAN CHANGE FROM BASELINE IN QOL MEASURED WITH THE EPP-QOL, CUV039

	Afamelanotide		Placebo		P-value
	Score	No. of patients	Score	No. of patients	
Baseline score at day 0, before dose 1	26.6±19.9	47	26.2±19.4	43	-
Change at day 60, before dose 2	44.0±25.8	47	23.4±24.6	43	<0.001
Change at day 120, before dose 3	49.8±26.4	46	30.4±25.4	42	<0.001
Change at day 180	51.1±29.1	46	36.8±25.7	43	0.02
Scores at day 360 (240 days after last dose)	38.4±27.0	44	45.4±29.6	40	-

*± are standard deviations. Scores on EPP-QoL questionnaire range from 0 to 100, with higher scores indicating a better QoL. P values are determined by means of the Kruskal–Wallis test.
Source: Langendonk et al. 2015.

TABLE 18: MEAN QOL SCORES MEASURED WITH THE EPP-QOL, CUV029

	Afamelanotide		Placebo		
	Score	No. of patients	Score	No. of patients	P-values
Baseline score at day 0, before dose 1	39.0±25.8	37	35.3±23.7	34	0.39
Score at day 60, before dose 2	68.0±19.1	37	60.1±22.0	35	0.09
Score at day 120, before dose 3	78.8±16.2	37	63.6±23.9	35	0.005

Score at day 180, before dose 4	84.6±12.6	35	73.5±24.3	35	0.03
Score at day 240, before dose 5	84.8±10.7	34	73.1±24.1	34	0.01
Score at day 270, final visit	79.7±16.1	32	67.2±25.7	34	0.06

*± values are means ±SD. Scores on the EPP-QoL questionnaire range from 0 to 100, with higher scores indicating a better QoL. In the European Union trial, P values for the comparison of afamelanotide with placebo were determined by means of the paired Wilcoxon rank-sum test.
Source: Langendonk et al. 2015.

Qualitative description of adverse events

In our qualitative description of the AEs associated with afamelanotide treatment we have used the publication by Langendonk et al. 2015 (3). There were no deaths during the CUV029 trial and the CUV039 trials. Four serious adverse events (SAEs) in the afamelanotide groups (sub capital humerus fracture, herniated disk, abdominal pain, and benign compound nevus) and two serious adverse events in the placebo groups (pulmonary embolus and melanoma) were reported in the two trials. These SAEs were considered by the principal investigator to be unrelated to the study drug. AEs occurring during the study period were generally mild to moderate in severity in both trials, the most common AEs were headache, nausea, nasopharyngitis and back pain (see Table 19). There were no clinically relevant between-group differences in the incidence or severity of AEs, except for mild hyperpigmentation at the implant site in one third of the patients who received afamelanotide and pre-existing naevi that darkened in a few patients who received this drug (localised hyperpigmentation). We present the reported AEs from Langendonk et al. 2015 in Table 19.

TABLE 19: ADVERSE EVENTS FROM THE EUROPEAN CUV029 AND US CUV039 TRIALS

	European trial CUV029		**US trial CUV039**	
	Afamelanotide (N=38)	**Placebo (N=36)**	**Afamelanotide (N=48)**	**Placebo (N=45)**
Total no. of events	189	166	272	216
Ear and labyrinth disorder: ear pain – no. (%)	1 (3)	2 (6)	2 (4)	0
Gastrointestinal disorder – no. (%)				
Abdominal discomfort	0	1 (3)	1 (2)	2 (4)
Abdominal pain	4 (11)	1 (3)	1 (2)	3 (7)
Upper abdominal pain	1 (3)	1 (3)	1 (2)	3 (7)
Diarrhoea	3 (8)	4 (11)	2 (4)	3 (7)
Dyspepsia	0	1 (3)	3 (6)	3 (7)
Nausea	7 (18)	6 (17)	9 (19)	8 (18)
Toothache	0	0	3 (6)	3 (7)
Vomiting	1 (3)	2 (6)	1 (2)	0
General disorder and administration site conditions – no. (%)				
Fatigue	1 (3)	2 (6)	3 (6)	0
Implant-site discoloration	4 (11)	0	9 (19)	0
Pain	0	0	4 (8)	4 (9)
Infection and infestation – no. (%)				
Viral gastroenteritis	1 (3)	2 (6)	0	3 (7)
Influenza	6 (16)	3 (8)	2 (4)	7 (16)
Nasopharyngitis	8 (21)	8 (22)	6 (12)	10 (22)
Sinusitis	0	2 (6)	3 (6)	3 (7)

Upper respiratory tract infections	3 (8)	1 (3)	1 (2)	0
Abnormal laboratory result – no. (%)				
Blood urine	2 (5)	2 (6)	0	0
Increase in ϒ-glutamyltransferase levels	0	3 (8)	0	0
Musculoskeletal and connective-tissue disorder – no. (%)				
Arthralgia	0	2 (6)	5 (10)	2 (4)
Back pain	2 (5)	4 (11)	6 (12)	6 (13)
Musculoskeletal pain	0	1 (3)	3 (6)	1 (2)
Myalgia	1 (3)	2 (6)	3 (6)	1 (2)
Pain in extremity	1 (3)	2 (6)	2 (4)	2 (4)
Nervous system disorder – no. (%)				
Dizziness	0	0	1 (2)	2 (4)
Headache	13 (34)	14 (39)	19 (40)	13 (29)
Migraine	1 (3)	3 (8)	3 (6)	3 (7)
Sinus headache	0	0	1 (2)	2 (4)
Respiratory, thoracic, and mediastinal disorder – no. (%)				
Cough	5 (13)	2(6)	1 (2)	1 (2)
Oropharyngeal pain	6 (16)	2 (6)	2 (4)	2 (4)
Skin and subcutaneous tissue disorder – no. (%)				
Eczema	2 (5)	1 (3)	0	1 (2)
Melanocytic nevus	0	0	2 (4)	1 (2)
Pigmentation disorder	3 (8)	0	1 (2)	0
Pruritus	2 (5)	1 (3)	2 (4)	2 (4)

*listed events were reported by three or more patients in either of the studies.
Source: Langendonk et al. 2015.

Qualitative description of the long-term safety profile

In our qualitative description of the long-term safety profile of afamelanotide, we used Biolcati et al. 2015, CLINUVEL data on file and Wensink et al. 2020 (5,6,12). Biolcati et al. 2015 investigated the long-term (8 years) safety profile of prolonged use of afamelanotide in 115 patients. However, to accommodate the expert committee's wish for 10+ years of data, CLINUVEL data on file for 11 patients is also used. The long-term retrospective observational study by Biolcati et al. 2015 showed that 97% of patients considered afamelanotide to be effective in ameliorating EPP symptoms and 93% adhered to treatment for a prolonged time if there were no compelling reasons to discontinue. We regard this as an indication of good clinical effectiveness. The study supports a good safety profile for afamelanotide, as even in long-term usage, only minor adverse events were observed. In total, 680 events were reported in the study, 401 related and 279 not related to afamelanotide. The most frequent adverse events were gastrointestinal disorders (n [1]= 212), and among them nausea (n = 156, 146 times related, 10 times unrelated) was the most frequent. The second most frequent adverse events were nervous system disorders (n = 164), with headache as the most frequent (n = 125; 81 times related, 44 times unrelated), and general disorders and administration site conditions (n =

[1] n= Adverse Events reported

107), with fatigue being reported most frequently (n = 59; 33 times related and 26 times unrelated). Two patients noted a new melanocytic naevus, appearing 2.5 and 5 years after the first dose of afamelanotide, respectively. One of them was removed and showed no signs of malignancy.

The 10+ years of data on file showed no serious adverse events in the 11 patients treated for more than 10 years in Switzerland. The longest continuous treatment period for a single patient to date is 14 years (66 SCENESSE® implants). The most frequently reported non-serious AEs were nausea, which was reported 43 times, and headache, which was also reported 43 times, similar to what was observed in Biolcati et al. 2015. Fatigue was reported 11 times. Based on these findings, we conclude that afamelanotide has a good long-term safety profile.

Wensink et al. 2020 investigated the effectiveness of afamelanotide treatment in a total of 117 patients with EPP (59 women [50.4%]; mean [SD] age, 43.0 [15.5] years). In this single-centre, prospective, post-authorisation safety and effectiveness cohort study, data were collected from patients with EPP treated with afamelanotide at the Erasmus Medical Centre in Rotterdam (The Netherlands) between June 2016 and September 2018 to evaluate the association of afamelanotide treatment with outcomes in patients with EPP in regular practice during long-term follow-up. The strength of this study is the large number of treated patients with EPP with a relatively long duration of follow-up under real-world conditions of use and the 98% continuation rate equivalent to 115 patients. Compared with baseline, mean time spent outside during treatment increased significantly by 6.1 hours per week. Mean quality of life score improved significantly by 14.0% and phototoxic reactions were less painful. The number of phototoxic reactions increased during treatment with a positive association with light intensity and a negative association of the duration of treatment with the number of reactions. There was no significant association of treatment with the duration of phototoxic reactions, but there was seasonal variation resulting in longer phototoxic reactions during spring and summer, duration varied by 45.7 hours between the month with the lowest (January) and highest (July) number of hours.

Adverse events occurred in 104 patients (88.9%). Regular laboratory test results showed no significant abnormalities. The most reported AEs were nausea (n=60 [11.4%]), fatigue/malaise (n=51 [9.7%]), flushing (n= 46 [8.8%]) and nausea with headache (n=44 [8.4%]). All were self-limiting with a mean duration of 1 to 2 days, occurring directly after implantation. There were no related serious AEs. “Lack of effectiveness” (reported to CLINUVEL as MedDRA coded “therapeutic response decrease”) was reported 38 times (7.2%), indicating that the association of the implant with outcomes lasted less than 60 days.

This post-authorisation study demonstrates that afamelanotide is effective at reducing EPP-related symptoms and phototoxic reactions in clinical practice. The treatment is associated with variable but sustained increase in quality of life and duration of light exposure and is associated with less severe phototoxic reactions and a good safety profile.

7 Other considerations

7.1 Discussion on the use of the DLQI questionnaire as a QoL measure in EPP

The expert committee has based the assessment of quality of life in EPP patients on the DLQI questionnaire and states that the DLQI questionnaire can be supplemented with a qualitative description based on the EPP-QoL questionnaire. The committee’s reason for this is that the EPP-QoL questionnaire is not validated. According to the expert committee, this raises questions about the psychometric properties of the

questionnaire, which is why a minimal clinically relevant difference cannot be established for EPP-QoL. It is noted that the DLQI is not validated for use in EPP or other metabolic disorders, but in common dermatological conditions, such as psoriasis and atopic dermatitis.

It is our position that the EPP-QoL questionnaire is a more appropriate tool to assess the QoL of EPP patients. The fundamental rationale behind this statement is that EPP is not a dermatological condition. EPP is a metabolic disorder with phototoxicity as the primary clinical symptom (anaphylactic reactions and burns *underneath* the skin) where the long-term impact upon the patient is to withdraw from society to prevent symptoms (conditioned behaviour). The EPP-QoL was developed by expert physicians responsible for the healthcare of EPP patients and has undergone psychometric validation by Oxford Outcomes (an ICON public company). The format is similar to the DLQI, but the questions are fundamentally different, as it is the patient's experience being evaluated, reflecting the differences in the impact on patient's quality of life.

The DLQI questionnaire is a generic dermatology QoL assessment tool, developed to evaluate the health-related quality of life of patients with dermatologic conditions as well as their treatment. The DLQI questionnaire focuses on issues relevant to dermatological patients with persistent and visible dermatologic symptoms, and their relationship with their skin. Here, it is the skin itself that has an impact on the patient's quality of life. The EPP-QoL questionnaire concerns the patient's overall well-being and whether EPP has an impact on the patient's quality of life, using specific scenarios that would be relevant to EPP patients including their relationship to light (as the cause of phototoxicity) and their immediate environment. Moreover, the impacts that are relevant for dermatologic patients, e.g. impact on sexual life and impact of messy treatments, are not relevant for EPP patients.

Furthermore, the DLQI utilises a one-week recall period, i.e. "over the last week". It is noted that, due to their learnt behaviour, EPP patients avoid all forms of light exposure. As a result, the clinical symptom which may elicit a higher DLQI impact (phototoxicity, where their skin may experience some of the sensations described in the DLQI) are relatively rare (patients experience 3-10 reactions per year (2) and unlikely to be captured during the recall period. The EPP-QoL, by contrast, relies on a two-month recall period, when the impact on patient QoL is more likely to be captured. The challenges of using the DLQI in EPP and photodermatoses has been highlighted in the literature, with one study amending the DLQI recall period to 12-months due to the inadequacy of the short one-week recall (14).

The CUV039 trial showed a significant improvement in QoL following treatment with afamelanotide, measured with the EPP-QoL questionnaire at days 60, 120 and 180 (p-values of <0.001 on all days as presented in Table 17). These results demonstrate that afamelanotide treatment significantly improved patients' quality of life when QoL is measured with this EPP-specific questionnaire. These effects were not seen when the DLQI questionnaire was used to measure changes in QoL. The differences in results seen with the two assessment tools are not surprising, as the DLQI is established as a QoL instrument in dermatological diseases. In EPP, it lacks the specificity of the EPP-QoL, e.g. it does not contain any questions that measure the impact of light on the skin, and thus no differences in quality of life assessment between the afamelanotide group and the placebo group were detected. This also becomes very apparent in our qualitative description of QoL measured with the EPP-QoL, provided in section 6.1.4.

We strongly encourage the DMC to take the above comments into account when evaluating afamelanotide.

7.2 Considerations on teratogenicity

In this section, we respond to the expert committee's request for a description of the teratogenicity associated with afamelanotide treatment, based on the life-long treatment and the fact that some patients might get pregnant while receiving treatment with afamelanotide. According to the afamelanotide summary of product characteristics (SmPC) (1), there is limited or no data on the use of afamelanotide in pregnant women and therefore, we cannot rule out the possibility that there could be a risk to new-borns/infants. Therefore, afamelanotide implants should not be used in pregnant women or women of childbearing potential not using effective contraception (1). SCENESSE® is only administered by trained and accredited healthcare professionals in expert centres. Training includes discussion on counselling patients on family planning.

7.3 Considerations on skin carcinogenesis

As requested by the expert committee, we have described the risk of developing skin cancer. According to the SmPC (1) of afamelanotide, the skin should be monitored during treatment, because afamelanotide may induce darkening of pre-existing pigmentary lesions due to the pharmacological effect of the drug. A full body skin examination every 6 months is recommended to monitor all pigmentary lesions and skin abnormalities. If any skin changes are consistent with skin cancer or precursors, or are ambiguous to the porphyria specialist, a dermatology specialist should be consulted. (1) In the CUV039 trial, any suspicious pre-existing skin lesions and sun-damaged fields were photographed at screening and re-photographed at day 180 or at early termination. Patients returned at day 360 for a safety follow-up, where they had their skin examined by a dermatologist and were photographed once more. In the CUV029 trial, patients were also photographed at screening (Day -7) and re-photographed at day 270 or at early termination. No changes in moles, freckles, birthmarks, or other pigmentation conditions giving rise to an adverse event were identified in any of the trials.

Afamelanotide stimulates the production of pigment in the skin. However, it is a possible misunderstanding that α-MSH or an analogue such as afamelanotide might stimulate the development of melanoma. The primary risk factors for melanoma are genetic predisposition and exposure to ultraviolet B (UVB) irradiation, which can induce DNA damage and lead to acquisition of pro-proliferative and anti-senescence mutations (15). α-MSH drives increased eumelanin production, inhibits production of pro-inflammatory cytokines and reduces the expression of vascular-cell adhesion molecule 1 and E-selectin (16,17). Melanocortin 1 receptor (MC1R) signalling in response to α-MSH binding also stimulates DNA repair (18). Eumelanin provides protection against melanoma by reducing UVB penetration of the skin and scavenging oxygen radicals generated as a result of exposure to UVB irradiation (15). Moreover, since the MC1R receptor is not expressed in melanocyte stem cells in the hair follicle, such stem cells would not be activated by α-MSH or an α-MSH analogue (16). It is noted that CLINUVEL is now evaluating afamelanotide in patients with xeroderma pigmentosum to assess its ability to assist in nucleotide excision repair and provide photoprotection to these patients who are at 10,000-fold risk of skin cancer.

7.4 Considerations on large variation in "number of hours in direct sunlight between 10-15 without pain" outcome in European trial vs US trial

The DMC noticed the large variation in the outcome "number of hours in direct sunlight between 10:00-15:00 without pain" in the CUV029 trial and the CUV039 trial in Langendonk et al. 2015 (3). The large variation may be explained by CLINUVEL data on file, that showed a large variation among patients in their willingness to

expose themselves to sunlight in the CUV039 trial. A proportion of patients in the US trial were willing to challenge their disease and spend time outside, and most data in the US trial were based on these patients. The same willingness to challenge the disease was not apparent in the CUV029 trial, which can explain the large variation in number of hours in direct sunlight between the US trial and European trial in Langendonk et al. 2015 (3). Another explanation could be the different trial durations, which was 9 months in the CUV029 trial and 6 months in the CUV039 trial.

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9 Appendices

9.1 Literature search

Not applicable. No literature search was conducted in the present application to the DMC because it was not requested in the EPP protocol.

9.2 Results per study

TABLE 20: RESULTS OF THE US CUV039 TRIAL

Trial name:	**CUV039**										
NCT number:	**NCT01605136**										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value		
Mean daily duration of sunlight exposure between 10:00 and 18:00	Afamelanotide	46	47.5 (32.1; 62.9)	8.4 minutes	-1.52; 18.88	0.094	NA	NA	NA	The intergroup difference in effect is estimated with the Kruskal-Wallis test and Hodges-Lehmann shift with 95% CI.	EPAR. 95% CI of mean are own calculations. EPAR. 95% CI of mean are own calculations.
	Placebo	43	27.1 (20.3; 33.9)								
Daily duration of phototoxic reactions	Afamelanotide	46	3.2 (1.5; 4.9)	NA	NA	0.503	NA	NA	NA	NA	Langendonk et al. 2015
	Placebo	43	6.6 (1.6; 11.6)								Langendonk et al. 2015
Mean change in QoL from baseline, measured with	Afamelanotide	46	-8.1 (-9.9; -6.3)	0	-3; 2	0.799	NA	NA	NA	The intergroup difference in effect is	EPAR. 95% CI of means are own calculations

the DLQI questionnaire	Placebo	43	−7.3 (-9.0; -5.6)							estimated with the Kruskal-Wallis test and Hodges-Lehmann shift with 95% Cl.	EPAR. 95% Cl of means are own calculations.
Mean change from baseline in QoL measured with the EPP-QoL questionnaire	Afamelanotide	46	51.1 (42.7; 59.5)	13.9	2.8; 27.8	0.021	NA	NA	NA	The intergroup difference in effect is estimated with the Kruskal-Wallis test and Hodges-Lehmann shift with 95% Cl.	EPAR. 95% Cl of mean are own calculations EPAR. 95% Cl of mean are own calculations.
	Placebo	43	36.8 (29.1; 44.5)								
Number of subjects with a severe TEAE - no. (%)	Afamelanotide	48	3 (6%)	2 % point	-0.094; 0.129	Not reported.	1.406	0.246; 8.031	0.701	NA	Langendonk et al. 2015
	Placebo	45	2 (4%)								

TABLE 21: RESULTS OF THE EUROPEAN CUV029 TRIAL

Trial name:	**CUV029**								
NCT number:	**NCT00979745**								
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Results	Difference	95% CI	*P* value	Hazard/Odds/Risk ratio	95% CI	*P* value	
Mean absolute score in EPP-QoL at day 270.	Afamelanotide	32	79.7	NA	NA	0.06	NA	NA	NA	2-sided Wilcoxon test
	Placebo	34	67.2							
Subjects who experience a mild TEAE – no. (%)	Afamelanotide	38	19 (50%)	2 subjects (3 % points)	-0.190; 0.242	Not reported	1.059	0.662; 1.693	0.811	Absolute difference in proportions and relative difference expressed as risk ratio.
	Placebo	36	17 (47%)							
Subjects who experience a moderate TEAE – no. (%)	Afamelanotide	38	12 (32%)	2 subjects (7 % points)	-0.139; 0.278	Not reported	0.857	0.458; 1.604	0.630	Absolute difference in proportions and relative difference expressed as risk ratio.
	Placebo	36	14 (39%)							
Subjects who experience a severe TEAE – no. (%)	Afamelanotide	38	3 (8%)	2 subjects (5 % point)	-0.074; 0.182	Not reported	2.842	0.301; 26.085	0.355	Absolute difference in proportions and relative difference
	Placebo	36	1 (3%)							

			expressed as risk ratio.

9.3 Results per PICO (clinical question 1)

TABLE 22: PICO RESULTS REFERRING TO CLINICAL QUESTION 1

Results per outcome		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	Difference	CI	*P* value	Hazard/Odds/Risk ratio	CI	*P* value	
Minutes per day outside (in indirect or direct sunlight) without or with mild symptoms (pain <4 on a Likert scale)	The CUV039 trial	20.4 minutes (75% increase)	(2.9; 37.9)	0.094	Not calculated	Not calculated	Not calculated	Mean difference. 95% CI of mean difference is estimated with an online calculator from (13)
Duration of symptoms (moderate-to-severe with pain ≥ 4 on a Likert scale from 0-10) after episode with light exposure	The CUV039 trial	-3.4 days (52% reduction)	(-8.6; 1.8)	0.503	Not calculated	Not calculated	Not calculated	Mean difference. 95% CI of mean difference is estimated with an online calculator from (13)

Mean change from baseline in QoL measured with the DLQI	The CUV039 trial	-0.8	(-3.3; 1.7)	0.799	Not calculated	Not calculated	Not calculated	Mean difference. 95% Cl of mean difference is estimated with an online calculator from (13)
Number of subjects with a severe TEAE	The CUV039 trial	2 percentage point	-0.094; 0.129	Not reported	1.406	0.246; 8.031	0.701	Estimation of difference in percentage points and the relative difference expressed as a risk ratio.

9.4 Calculation of 95% confidence intervals

Calculations of 95% confidence intervals were done using this formula:

$$95\%\ Cl = \left[mean - 1.96 * \frac{\sigma}{\sqrt{n}}; mean + 1.96 * \frac{\sigma}{\sqrt{n}}\right]$$

Cost-per-patient and budget impact analysis of afamelanotide (SCENESSE®) for the treatment of erythropoietic protoporphyria

Application to the Danish Medicines Council

13 November 2020

Table of Contents

List of abbreviations

AE	Adverse event
α-MSH	Alpha-melanocyte stimulating hormone
ATC	Anatomical Therapeutic Chemical Classification System
DMC	Danish Medicines Council
DLQI	Dermatology Life Quality Index
DRG	Diagnosis Related Group
EC	European Commission
EPP	Erythropoietic protoporphyria
FECH	Ferrochelatase
OS	Overall survival
SmPC	Summary of Product Characteristic
s.c	Subcutaneous
UV	Ultraviolet

1 Background

Erythropoietic protoporphyria (EPP) is a rare metabolic disorder belonging to a group of serious diseases called porphyrias (1). Porphyrias are caused by abnormal functioning of haem biosynthesis enzymes and characterized by the excessive accumulation and excretion of porphyrins and their precursors. EPP results from a deficiency of ferrochelatase (FECH), the last enzyme in the haem biosynthetic pathway. FECH deficiency is associated with increased concentrations of protoporphyrin in erythrocytes, plasma, skin, and liver (1). The mutated FECH enzymes cause toxic haemoglobin precursors (protoporphyrin) to accumulate. Protoporphyrin accumulates in superficial vessels in the skin of EPP patients. When exposed to specific wavelengths of light (UVA and visible, peaking at 408nm), protoporphyrin reacts resulting in phototoxicity (anaphylactoid reactions) underneath the skin of EPP patients. Phototoxic reactions can be provoked by direct exposure to light/UV, but also indirectly through windows. Symptoms of a phototoxic reaction are oedema (swelling), erythema, and capillary bleeding (petechiae). A deep burning sensation underneath the skin is typical of the disorder, an unbearable and often invisible ordeal irresponsive to any analgesics, including opioids. Symptoms have a fast onset (1 to 30 minutes after light exposure) and may last for days (2–4). EPP is one of the most serious cutaneous porphyrias with severe symptomatology appearing since childhood. In addition, 2-5% of these patients will develop liver impairment which eventually results in liver failure (5). Protoporphyrin is eliminated via the liver, and when the capacity of the biliary excretion pathway is exceeded, excess protoporphyria may result in the formation of gallstones and cholestatic liver damage (6).

The degree of light intolerance varies among patients and can become worse with prolonged exposure to light. Recurrent periods with light exposure can cause lichenification and scarring of the skin (2,7). EPP is associated with a large disease burden and reduction in quality of life among patients, because the risk of symptoms causes patients to develop a lifelong behaviour of limiting or completely avoid time spent outdoors and expose themselves to light. EPP also has a high impact on the patient's social life and job opportunities and can cause patients to isolate (8).

In Denmark, no medical treatments are currently on the market for EPP patients and the standard intervention is to avoid UV-light and light through windows, and to wear protective clothes. In general, preventive treatment with beta-carotene, N-acetyl-L-cysteine, zinc, and vitamin C has been used in the absence of other effective medical treatments. Adherence to these treatment attempts is poor, with patients reporting limited clinical benefit. A comprehensive review of treatments (9), where a systematic database search on studies related to treatment of EPP identified a total of 25 relevant studies. This publication identified a lack of safe and effective treatment for EPP patients.

1.1 Afamelanotide (SCENESSE®)

Afamelanotide is a melanocortin receptor agonist and a structural and potent analogue of α-melanocyte stimulating hormone (α-MSH), with a greater binding affinity and longer half-life. Afamelanotide stimulates the production of eumelanin in the skin, without the cell damage that usually occurs when the melanin production in the skin is stimulated by UV-light (10,11). Eumelanin contributes to photoprotection through different mechanisms such as strong broadband absorption of UV and visible light, and antioxidant activity through scavenging of free radicals (12). SCENESSE® is a 16mg controlled release subcutaneous injectable implant formulation of afamelanotide, approved by the European Commission (EC) in December 2014. Information on SCENESSE® is given in Table 1.

Table 1 **Afamelanotide**

Name	SCENESSE®
Active ingredient	Afamelanotide
Indication	Prevention of phototoxicity in adult patients with EPP
Strength and dosing	16 mg subcutaneous implant
ATC-code	D02BB02
Packages	1 implant
EC-date of approval	22 December 2014

Source: EPAR (13)

1.2 Clinical question

The DMC protocol for assessment of afamelanotide for the treatment of EPP lists the following clinical question:

What is the value of afamelanotide compared to placebo for patients with erythropoietic protoporphyria?

1.3 Patient population

EPP is diagnosed based on clinical symptoms and elevated blood levels of protoporphyrin. EPP usually presents in childhood, but cases with development in adulthood have been detected (1). The prevalence of EPP is equal among men and women and rarer among people with dark skin. The Danish EPP prevalence is estimated to be 13 per 1.000.000 inhabitants and the DMC expert committee expects a prevalence of 80-100 Danish EPP patients. The incidence is estimated to be

1-2 patients each year (7,14). The expert committee states that up to 50 Danish EPP patients would benefit from treatment with afamelanotide (7).

The clinical question (section 1.2) should be answered for a population of patients ≥18 years who have a diagnosis of EPP and who have reduced quality of life, defined as a Dermatology Life Quality Index (DLQI) score ≥10 points. We perform the budget impact analysis on the patient population of 40-50 patients the expert committee assesses would benefit from treatment with afamelanotide. It is assumed that these patients have DLQI scores ≥10 points.

2 Methods: Cost per patient analysis

The purpose of the cost per patient analysis is to estimate the incremental cost of treating patients with afamelanotide compared to placebo.

The comparison is informed by the phase III, randomised, double-blinded and placebo-controlled trials reported in Langendonk et al. 2015 and the summary of product characteristics (SmPC) of afamelanotide (12,15). Currently (October 2020), one patient is being treated with afamelanotide in Denmark. We have reached out to the clinical expert treating the patient to get information about current Danish practice and course of treatment for patients treated with afamelanotide and patients not treated with afamelanotide. Due to hospital policy, the clinical expert was not able to provide any details.

Hence, information about current practice (i.e. the practice for EPP patients not treated with afamelanotide) in a Danish setting was not retrieved. We therefore assume that the only difference in costs between "afamelanotide patients" and "placebo patients" are

- the cost of afamelanotide implants (drug costs)
- hospital administration costs associated with the treatment/insertion of an afamelanotide implant
- patient and transportation costs associated with the treatment/insertion of an afamelanotide implant

Based on the above, we assume that treatment with afamelanotide is not displacing any costs.

2.1 Applied model

The health economic model developed for the cost per patient analysis is a simple cost model. The rationale for choosing a simple cost model is the relatively simple treatment pathway of EPP, excluding the need for more complex health state models.

The cost model is developed in Excel and the Excel model is submitted along with this application.

2.2 Intervention

The intervention is a subcutaneous (s.c) afamelanotide implant. One implant contains 16 mg of afamelanotide. According to the SmPC for afamelanotide, one implant should be administered every two months, prior to expected and during increased sunlight exposure (e.g. spring to early autumn). The SmPC do not limit the treatment to specific months or seasons but recommends three implants per year with a recommended maximum of four implants per year (12). Experience from other countries show that some patients are treated continuously with six implants per year. The overall duration of treatment is at the physician's discretion and can be lifelong. The implants should be administered in adipose tissue above the supra-iliac crest.

2.3 Comparator

The comparator in the cost per patient analysis is placebo because no approved medical treatment alternatives exist for EPP patients. In Langendonk et al. 2015, placebo consisted of an implant identical to the afamelanotide implant, containing poly (D,L-lactide-co-glycolide) instead of afamelanotide (15).

2.4 Applied perspective

The cost per patient analysis has a limited societal perspective in accordance with the DMC guideline (16).

All costs and results are reported in a 2020 price level.

2.5 Time horizon

The health economic model applies a time horizon of one year in the base-case analysis. The time horizon is based on the DMC guideline where it is described that the time horizon should be long enough to capture all relevant differences in costs. As mentioned in section 2.2, the treatment duration for the average EPP patient with afamelanotide implants is at the physician's discretion and potentially lifelong. However, there is no data on the actual average treatment duration of afamelanotide implants in EPP patients. Because the treatment-cause of afamelanotide implants is the same every year a patient receive treatment, we assume that the costs of the intervention and comparator will be the same every treatment year and therefore, a time horizon of one year is applied. The model is flexible, and the user can choose longer time horizons, implying a life-long perspective can be applied.[1]

[1] The age distribution and hence the average age of EPP patients in Denmark is unknown (7).

2.6 Discounting

Costs are not discounted in the base-case analysis because the time horizon is one year. The model is flexible for the user to choose time horizons longer than one year. In this case, costs incurred after year 1 are discounted. In years 2-35, costs are discounted by 4% each year. From year 36, costs are discounted by 3% (17).

2.7 Resource use and unit costs

The cost analysis of afamelanotide to EPP patients includes drug costs, hospital administration costs and patient and transportation costs.

Cross-sectorial costs, costs to background treatments such as beta-carotene and N-acetyl-L-cysteine, and adverse event (AE) costs are not included in the present analysis. These costs are excluded because it is assumed that there will be no cost difference between afamelanotide and placebo in these cost categories. EPP increases mortality for 2-5% of patients who experience terminal liver disease (5), but this does not have a material impact upon the model and thus end-of-life cost is not included in the analysis.

Drug costs

The price of the afamelanotide implant (pharmacy purchasing price) was informed by CLINUVEL. According to the SmPC, local anaesthesia can be applied to the insertion area if necessary. Drug costs associated with local anaesthesia are included in the applied DRG-tariff for hospital administration costs. Information about drug costs can be seen in Table 2.

Table 2 **Drug costs**

	Strength (mg)	Package size	Price (DKK)
Afamelanotide (SCENESSE®)	16	1 implant	104,911

Source: CLINUVEL; valutakurser.dk (visited: 6 October 2020).

Hospital administration costs

As a unit cost estimate for the hospital administration costs related to afamelanotide treatment, we applied a DRG-tariff of DKK 1,540 (see Table 3).

Afamelanotide is a subcutaneous implant and according to the SmPC, the administration should be performed by a physician who is trained to administer the implant. The insertion of the implant is assumed to take 10 minutes in an outpatient setting. The SmPC states that patients must be observed for 30 minutes after insertion of the implant, to make sure the patient is not developing an allergic or hypersensitivity reaction. This resource use (10+30 minutes) is included in the applied DRG-tariff.

According to the SmPC, a regular full body skin examination (every 6 months) is recommended to monitor all pigmentary lesions and other skin abnormalities (12). We assume that these skin examinations are performed when the patient is in the hospital for the subcutaneous implantation of afamelanotide. Hence, we assume that the cost of the skin examination is included in the applied DRG-tariff (see Table 3).

Furthermore, since implantation of afamelanotide is a relatively simple procedure and described in detail in the SmPC, we assume that there are no extra start-up costs or initial introduction costs associated with the treatment.

Table 3 **Hospital administration costs per treatment**

Resource	Tarif (DKK)	DRG group
Administration (implantation)	1,540	10MA98

Source: www.drg.dk. An outpatient contact with EPP as the primary diagnosis (ICD10-code: DE800) is grouped to DRG group 10MA98.

Adverse events

The most common AEs observed in Langendonk et al. 2015 were headache, nausea, nasopharyngitis and back pain (15). These are mostly transient in nature and occur within 24-48 hours of implant administration.

There were no clinically relevant differences between groups in the incidence or severity of the AEs. All serious AEs were deemed by the investigators to not be related to study drugs (afamelanotide or placebo) (15). One-third of the patients who received afamelanotide experienced mild hyperpigmentation at the implant site and moles that darkened in a few patients (15). We assume that hyperpigmentation (including darkening of pre-existing pigmentary expressions such as naevi or lentigo) does not require any treatment. #add from comment.

Hence, similar safety profiles for the afamelanotide and placebo group were observed, implying no difference in primary care sector or hospital costs associated with treatment of AEs. Based on this, we have not included costs associated with treatment of AEs in the analysis.

An overview of AEs observed in the US CUV039 trial published in Langendonk et al. 2015 (15) are presented in Table 4.

Table 4 **Number and severity of AEs that occurred during study period (180 days) of the US CUV039 trial**

Events	Afamelanotide (N=48)	Placebo (N=45)
Total no. of events	272	216
Patients with any adverse event – no. (%)	45 (94)	39 (87)
Severity of adverse events – no. (%)		
Mild	17 (35)	14 (31)
Moderate	25 (52)	23 (51)
Severe	3 (6)	2 (4)

Source: Langendonk et al. 2015 (15)

Patient and transportation costs

Patient and transportation costs were included in accordance with the DMC guideline (16). We based the estimation of patient and transportation costs on unit costs listed in the DMC document "Valuation of unit costs". A unit cost of DKK 179 per hour was used in the estimation of cost of patient time and a unit cost of 3.52 DKK per km was used in the estimation of transportation costs. Two hours of patient time associated per treatment was assumed, including an hour of transportation time in total, potential waiting time, time for insertion of the implant and observation time (10 min. + 30 min.). An average driving distance of 14 km each way was assumed, summarizing to a total of 28 km (18). The total patient and transportation costs per treatment are presented in Table 5.

Table 5 **Patient and transportation costs associated with afamelanotide treatment and placebo, undiscounted (DKK)**

	Afamelanotide	Placebo
Patient cost	358	0
Transportation	99	0
Total per treatment	**457**	**0**

Source: DMC document "Valuation of unit costs" (18) and calculations.

2.8 Sensitivity analysis

The DMC protocol states that an afamelanotide implant should be administered every two months from 1 April to 1 October, leading to four implants per year. Based on this, we conducted a sensitivity analysis with four implants per year instead of three as in the base-case. The result of the sensitivity analysis can be seen in section 3.1. As mentioned in section 2.2, up to six implants per year have been observed in other countries. We will not present a sensitivity analysis where six implants per year have been applied, because theprotocol from the DMC on afamelanotide

states that afamelanotide treatment would only be offered from 1 April to 1 October in Denmark. Based on this, we assume that six implants per year are not be relevant in a Danish clinical setting.

2.9 Overview of base-case settings in the model

Table 6 provides an overview of the base-case settings and alternative settings in the cost per patient analysis.

Table 6 **Overview of base-case settings and possible alternative settings in the cost per patient model**

	Base-case	Alternative settings/comments
Applied model	Simple cost model	
Intervention	Afamelanotide	
Comparator	Placebo	None
Time horizon	One year	Flexible
Discounting rate	Not applied	Flexible given the time horizon, 4% (year 2-35), 3% (year 36-70)
Perspective	Limited societal	None
Included costs	Drug costs Hospital administration costs Patient and transportation cost	All included costs can be varied in the model
Applied unit costs	Pharmacy purchasing price DRG-tariffs DMC unit prices (18)	Other costs are assumed to be equal for the afamelanotide and placebo group
Dose and number of treatments	16 mg implant three times per year	Flexible. A sensitivity analysis assuming four 16 mg implants per year was conducted
Administration form	Subcutaneous	None
Inclusion of waste	No	None
OS modelling	Not applied/not relevant	

3 Results: Cost per patient analysis

In this section, we present the results of the cost per patient analysis. We have estimated the cost of treating an average EPP patient with afamelanotide compared to placebo. The incremental cost of treating EPP patients with afamelanotide implants compared to placebo is app. DKK 321,000 over a time horizon of one year. The results of the cost analysis are presented in Table 7, which shows that the cost driver in the analysis is the cost of the afamelanotide implant.

Table 7 **Costs-per-patient analysis, undiscounted (DKK)**

	Afamelanotide	Placebo	Incremental cost
Drug costs	314,734	0	314,734
Hospital costs	4,620	0	4,620
Patient and transportation costs	1,370	0	1,370
Total	320,724	0	320,724

3.1 Sensitivity analysis results

As mentioned earlier, we conducted a sensitivity analysis where we increased the number of implants per year from three to four. The sensitivity analysis shows that the incremental cost of afamelanotide increases from app. DKK 321,000 per year to DKK 428,000 per year. This shows that the incremental cost is highly dependent on the number of implants per year. The results are shown in Table 8.

Table 8 **Costs-per-patient analysis: One-way sensitivity analysis, undiscounted (DKK)**

	Afamelanotide	Placebo	Incremental cost
Drug costs	419,646	0	419,646
Hospital costs	6,160	0	6,160
Patient and transportation costs	1,827	0	1,827
Total	427,632	0	427,632

4 Methods: Budget impact analysis

The purpose of the budget impact analysis is to estimate the impact on the Danish regions' budget if afamelanotide is recommended as standard treatment to EPP patients. The budget impact is estimated per year in the first five years after the recommendation. The budget impact analysis compares the costs in the scenario where afamelanotide is recommended as possible standard treatment and the scenario where afamelanotide is not recommended as possible standard treatment for EPP patients. The total budget impact per year is the difference between the two scenarios. The budget impact is based on the cost per patient analysis but excludes patient and transportation costs and applies undiscounted costs (16). Thus, our budget impact analysis only includes drug costs and hospital administration costs.

4.1 Patient numbers and market shares

The DMC protocol states that the prevalence of EPP in Denmark has been estimated at 13 per 1,000,000 inhabitants, which is consistent with the expert committee's estimate of 80-100 patients. The incidence of EPP is estimated to be one to two new cases each year (7).

The expert committee estimates that around 40 to 50 patients would benefit from treatment with afamelanotide and could be offered the therapy if it is approved as standard treatment in Denmark (7). Thus, we have estimated a prevalence of 45 patients in the budget impact analysis. In addition, we have estimated an average of 0.75 incident patients each year that would need treatment and could be offered afamelanotide therapy (half of the expert committee's estimate of the incidence of EPP). The estimated number of patients eligible for treatment is presented in Table 9.

Table 9 **Number of patients eligible for treatment each year in the budget impact analysis**

	Year 1	Year 2	Year 3	Year 4	Year 5
Prevalence (rounded)	45	46	47	47	48

Source: Calculations based on the DMC protocol (7).

If afamelanotide is recommended as standard treatment, we assume an increasing uptake over the five years starting with 20% in year 1 and ending with a market share (or patient uptake) of 100% in year 5 (see Table 10).

Table 10 **Market shares each year in the budget impact analysis**

	Year 1	Year 2	Year 3	Year 4	Year 5
Recommended	20%	40%	60%	80%	100%
Not recommended	0%	0%	0%	0%	0%

Source: Assumption.

Given the total number of treatment-eligible patients (Table 9) and the assumed market shares (Table 10), the total number of patients treated with afamelanotide is estimated. The estimates, with or without recommendation, are shown in Table 11. For simplicity, we have assumed that all treated patients are treated for the full year (i.e. half-cycle correction is not applied).

Table 11 **Number of patients treated with afamelanotide**

	Year 1	Year 2	Year 3	Year 4	Year 5
Recommended	9	18	28	37	47
Not recommended	0	0	0	0	0

Source: Own calculations.

4.2 Sensitivity analysis

Similar to the cost per patient analysis, we have conducted a sensitivity analysis of the budget impact with four implants per year instead of three.

5 Results: Budget impact analysis

In this section we present the results of the budget impact analysis.

Table 12 shows the results of the budget impact in the first five years with and without a positive recommendation for afamelanotide. The budget impact in the first year is an incremental cost of DKK 2.9 million. In year 5, the total budget impact is estimated to be DKK 15 million.

Table 12 **Total budget impact each year with and without recommendation of afamelanotide (million DKK)**

	Year 1	Year 2	Year 3	Year 4	Year 5
With recommendation	2.9	5.7	8.9	11.8	15.0
Without recommendation	0.0	0.0	0.0	0.0	0.0
Budget impact	2.9	5.7	8.9	11.8	15.0

5.1 Sensitivity analysis results

The result of the budget impact sensitivity analysis where we increased the number of implants per year from three to four, are presented in Table 13. In year 1, the total budget impact is estimated at DKK 3.8 million – an increase of DKK 0.9 million compared to the base-case result. In year 5, the total budget impact is estimated to DKK 20 million, which is an increase of DKK 5 million compared to the base-case.

Table 13 **Total budget impact: One-way sensitivity analysis (million DKK)**

	Year 1	Year 2	Year 3	Year 4	Year 5
With recommendation	3.8	7.7	11.9	15.8	20.0
Without recommendation	0.0	0.0	0.0	0.0	0.0
Budget impact	3.8	7.7	11.9	15.8	20.0

6 Discussion

In this analysis we have estimated the cost per patient and budget impact of introducing afamelanotide as standard treatment for patients diagnosed with EPP in Denmark. We have applied a relatively simple cost model assuming that the only differences in costs between "afamelanotide patients" and "placebo patients" are the cost of the afamelanotide implant, hospital administration costs and patient and transportation costs.

Given these assumptions, the cost per patient per year is estimated to DKK 320,000 in the base-case, and the total budget impact is estimated to DKK 15 million five years after the introduction.

For patients diagnosed with EPP, treatment with afamelanotide improves the quality of life markedly. Furthermore, there is no medical treatment alternatives available for patients suffering from EPP and if afamelanotide is recommended, it would be the only treatment alternative available for these patients.

These results are associated with uncertainty. The sensitivity analysis proved the number of afamelanotide implants per year is a cost driver. In addition, in terms of budget impact, it is self-evident that the total number of treatment eligible EPP patients has an impact on the costs. However, EPP being a rare disease, there is an upper limit of the overall budget impact for the Danish regions.

No other studies estimating the cost per EPP patient treated with afamelanotide have been identified.

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Medicinrådet

Medicinrådets protokol for vurdering af afamelanotid til behandling af lysintolerance (erytropoietisk protoporfyri, EPP)

Versionsnr.: 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 deres endelige ansøgning. Til hvert spørgsmål knytter sig en definition af patientgruppen, det lægemiddel vi undersøger, den behandling vi 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, 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 ansøgende virksomhed få besked.

Godkendt af Medicinrådet 17. august 2020
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Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
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Indhold

1 Begreber og forkortelser

α-MSH:	α-melanocyt stimulerende hormon
CI:	Konfidensinterval
DLQI:	*Dermatology Life Quality Index*
EMA:	*European Medicines Agency*
EPAR:	*European public assessment report*
EPP:	Erytropoetisk protoporfyri
EPP-QoL:	*Erythropoetic protoporphyria Quality-of-Life*
GRADE:	System til vurdering af evidens (*Grading of Recommendations Assessment, Development and Evaluation*)
HR:	*Hazard ratio*
OR:	*Odds ratio*
RR:	Relativ risiko

2 Introduktion

Medicinrådet besluttede den 28. august 2019, af egen drift, at vurdere afamelanotid til patienter med diagnosen erytropoetisk protoporfyri, som er en svær form for lysintolerance. Afamelanotid blev inden Medicinrådets etablering godkendt af det Europæiske Lægemiddelagentur (EMA), men blev aldrig markedsført i Danmark, lægemidlet skal derfor principielt ikke vurderes af Medicinrådet. Afamelanotid forventes imidlertid at kunne anvendes til ca. 40-50 danske patienter, Tværregionalt Forum for koordination af Medicin har derfor bedt Medicinrådet om at tage lægemidlet op af egen drift. Markedsføringsindehaver af lægemidlet er Clinuvel (herefter omtalt; firmaet), har tilkendegivet, at de gerne vil bidrage med de kliniske og sundhedsøkonomiske data, der normalt indsendes i en endelig ansøgning.

2.1 Erytropoietisk protoporfyri (EPP)

Erytropoietisk protoporfyri (EPP) er en kronisk invaliderende hudsygdom, der gør patienterne ekstremt intolerante overfor lys og forårsager fototoksicitet i huden (smerter, hævelse og rødme). Patienterne er intolerante for både UV-lys og synligt lys – også gennem vinduesglas. Yderligere kan kunstigt lys fra f.eks. lamper og billygter også være generende, men graden af intolerance varierer mellem patienterne og kan forværres, hvis patienten har været udsat for lys i længere tid.

EPP er en sjælden sygdom, som hører under en gruppe af arvelige sygdomme kaldet porfyri. Porfyri skyldes genmutationer i enzymer, som i hæmoglobinsyntesen skal danne hæmoglobin (den iltbindende del af røde blodlegemer). Derved ophobes de toksiske forstadier til hæmoglobin (porfyrin) [1,2]. Porfyri opdeles i akutte/ikkeakutte porfyrier og kutane/ikkekutane porfyrier, afhængigt af hvor defekten i hæmoglobinsyntensen optræder, og hvor ophobningen af porfyriner sker (bl.a. i lever, knoglemarv, de røde blodlegemer og hud). Akutte porfyrier giver symptomer i nerver og indre organer, mens kutane porfyrier giver symptomer i huden i form af lysfølsomhed (fotosensitivitet) på grund af udskillelse af frie radikaler i huden ved lyseksponering.

EPP er en af de mest alvorlige kutane porfyrier. Symptomerne på EPP er ekstrem intolerance for lys, som viser sig ved neuropatiske brændende smerter i huden, rødme, hævelse samt evt. sårdannelse og blødninger i huden (petekkier). Sygdommen manifesterer sig ofte i barndommen og viser sig allerede efter de første soleksponeringer [1]. Symptomerne kommer straks efter lyseksponering (1-30 minutter) og kan vare i op til flere dage. Symptomerne kan variere i sværhedsgrad alt efter varigheden af lyseksponering. Synlig hud, såsom ansigt og hænder, vil typisk være steder, hvor symptomerne opstår [1–3]. Patienterne kan ved lyseksponering opleve, at de får feberlignende symptomer, bliver trætte og bliver følelsesmæssigt påvirkede. Derudover er huden meget følsom for berøring. Gentagne perioder med lyseksponering kan resultere i, at patienterne udvikler fortykkelse af huden, ar og læderhud [1].

Risikoen for symptomer gør, at patienterne undgår at færdes ude i dagtimerne eller kun i meget begrænset omfang kan være udendørs. Dette har store konsekvenser for patienternes dagligdag og kan føre til social isolation, da de begrænses i sociale aktiviteter og manglende forståelse fra omverdenen [4]. Derudover begrænser sygdommen også patienternes jobmuligheder. Alt dette medfører, at patienterne har væsentligt nedsat livskvalitet [1–3].

Patienterne har ofte D-vitaminmangel som følge af, at de undgår sollys. Dette kan betyde risiko for nedsat knogletæthed og vitaminmangel. Derudover vil 5-20 % af patienterne med tiden udvikle levermanifestationer, som potentielt kan føre til akut leversvigt [5]. Af samme grund skal patienterne være tilbageholdende med alkohol og være opmærksom ved behov for jerntilskud.

Forekomsten af EPP i Danmark anslås at være 13 pr. 1.000.000 indbyggere [2], hvilket stemmer overens med fagudvalgets anslåede 80-100 patienter. Fordelingen af patienter over og under 18 år er ukendt. Der

skønnes at være 1-2 nye tilfælde pr. år. Sygdommen forekommer lige hyppigt hos mænd og kvinder [5] og ses sjældent hos personer med mørk hud [3].

EPP diagnosticeres på baggrund af kliniske symptomer samt måling af forhøjet porfyrin i blodet. Hos børn mistænkes EPP, hvis de græder eller klager over smerter i huden under eller efter soleksponering [2]. På grund af sygdommens sjældenhed kan det tage lang tid, før patienterne bliver diagnosticeret; således bliver nogle patienter først som voksne korrekt diagnosticerede [5]. Fagudvalget skønner imidlertid, at forældre og institutioner i dag vil opsøge læge, hvis et barn udviser symptomer på EPP med henblik på udredning.

Der er formentlig fortsat en gruppe udiagnosticerede patienter, især ældre patienter, som potentielt vil blive opdaget og kan tilbydes behandling med afamelanotid, hvis denne bliver anbefalet som mulig standardbehandling. Det er dog ikke sikkert, at alle patienter ønsker at modtage behandlingen, fordi de har vænnet sig til at leve 'i skyggen', og fordi behandlingen kun virker symptomlindrende og ikke ændrer prognosen med hensyn til eksempelvis leverpåvirkning.

Fagudvalget vurderer, at ca. 40-50 patienter vil have et behandlingsbehov og dermed vil kunne tilbydes behandling med afamelanotid, såfremt det bliver godkendt som standardbehandling.

2.2 Afamelanotid

Afamelanotid (Scenesse®) blev i 2014 godkendt af EMA til forebyggelse af lysintolerance hos patienter ≥ 18 år, som er diagnosticeret med EPP. Lægemidlet er ikke markedsført i Danmark. I EMA har lægemidlet status som *orphan drug*.

Afamelanotid er et syntetisk peptid, som er en analog til α-melanocyt stimulerende hormon (α-MSH). Det er en agonist for melanocortin-receptoren (MC1R) på melanocytceller. Afamelanotid stimulerer, via MC1R, melanocytterne til at producere eumelanin. Eumelanin pigmenterer huden, hvilket beskytter huden mod de fototoksiske reaktioner forårsaget af sollys [5].

Afamelanotid administreres som et subkutant implantat og indsættes under lokalbedøvelse via et kateter ind i fedtlaget på forsiden af hoftekarmen. Implantatet måler 1,7 cm i længden og 1,5 mm i diameter og skal udskiftes hver 60. dag. Der anbefales behandling med tre implantater årligt eller højest fire implantater i de mest solrige måneder. Implantatet indeholder en dosis på 16 mg afamelanotid. Behandlingslængden vurderes af den behandlende læge, men kan i princippet være livslang.

Behandlingen anbefales ikke til patienter over 70 år, da behandlingen ikke er tilstrækkeligt undersøgt i denne aldersgruppe [5]. Behandlingen anbefales ikke til gravide og ammende, da behandlingen ikke er undersøgt i denne patientgruppe. Kvinder i den fertile alder bør ikke modtage behandlingen, med mindre de anvender effektiv kontraception, som de bør fortsætte minimum tre måneder efter ophør af en behandling [5].

2.3 Nuværende behandling

Standardinterventionen er at undgå eksponering for UV-lys og synligt lys i det omfang, det er muligt. Dette involverer, at patienterne skærmer huden ved at påføre sig dækkende tøj samt brug af solafskærmende hatte. Nogle vælger også spraytan, om end effekten er kortvarig.

Der findes aktuelt ingen godkendte lægemidler til behandling af EPP i Danmark. Symptomatiske behandlinger involverer brugen af smertestillende medicin, antihistaminer, topikale kortikosteroider samt kold kompression [5]. I mangel af effektiv medicinsk behandling har man anvendt forebyggende behandling med betacaroten, N-acetyl-L-cysteine, zink og C-vitamin. Samtlige ovenstående behandlinger har dog ingen eller ringe dokumenteret effekt på patienternes symptomer [3], og der findes derfor ingen medicinsk standardbehandling.

3 Kliniske spørgsmål

Medicinrådet bruger kliniske spørgsmål til vurdering af lægemidlers værdi for patienterne. Til hvert spørgsmål knytter sig en definition af patientgruppen (population), af det lægemiddel vi undersøger (interventionen), af den behandling vi sammenligner med (komparator(er)) og af effektmålene.

3.1 Klinisk spørgsmål 1

Hvilken værdi har afamelanotid sammenlignet med placebo til patienter med erytropoietisk protoporfyri?

Population
Patienter ≥ 18 år diagnosticeret med erytropoietisk protoporfyri (EPP), der har væsentlig reduceret livskvalitet, defineret som en Dermatology Life Quality Index (DLQI) score ≥ 10 point.

Intervention
Afamelanotid, 16 mg administreret som et subkutant implantat der udskiftes hver 2. måned fra den 1. april til 1. oktober hvert år.

Komparator
Da der ikke anvendes medicinsk behandling som standard, er komparator placebo.

Effektmål
De valgte effektmål står i Medicinrådet mener, at vurderingen af lægemidlets værdi bliver bedst understøttet af de effektmål nævnt i Tabel 1. For hvert effektmål har Medicinrådet fastsat en mindste klinisk relevant forskel (MKRF). I det følgende afsnit argumenterer vi for valget af effektmål og de mindste klinisk relevante forskelle.

Tabel 1.

3.2 Effektmål

Medicinrådet mener, at vurderingen af lægemidlets værdi bliver bedst understøttet af de effektmål nævnt i Tabel 1. For hvert effektmål har Medicinrådet fastsat en mindste klinisk relevant forskel (MKRF). I det følgende afsnit argumenterer vi for valget af effektmål og de mindste klinisk relevante forskelle.

Tabel 1. Oversigt over valgte effektmål.

Effektmål*	**Vigtighed**	**Effektmålsgruppe**	**Måleenhed**	**Mindste klinisk relevante forskel**
Livskvalitet	*Kritisk*	*Livskvalitet, alvorlige symptomer og bivirkninger*	DLQI, gennemsnitlig ændring fra baseline	4 point
			EPPQoL, kvalitativ gennemgang	-
Symptomer (fototoksicitet)	*Kritisk*	*Livskvalitet, alvorlige symptomer og bivirkninger*	Minutter pr. dag udendørs (i indirekte og direkte sollys) uden eller med milde symptomer (smerte < 4 på Likert-skala fra 0-10)	50 % mere tid udendørs (minutter) for patienter i behandling med afamelanotid, dog minimum 20 minutter

			Varighed af symptomer (moderate-svære med smerte ≥ 4 på Likert-skala fra 0-10) efter episode med udsættelse for sollys	20 % reduktion af varighed for patienter i behandling med afamelanotid
Bivirkninger	*Kritisk*	*Livskvalitet, alvorlige symptomer og bivirkninger*	Andelen af patienter der oplever uønskede hændelser af grad 3-4	5 procentpoint
			Kvalitativ gennemgang af bivirkninger, herunder langtidsbivirkninger (efter mindst 10 år)	-

* For alle effektmål ønsker vi data med længst mulig opfølgningstid, med mindre andet er angivet.

3.2.1 Kritiske effektmål

Livskvalitet
Fagudvalget vurderer, at livskvalitet er et kritisk effektmål, da EPP er en kronisk, ikkedødelig sygdom, som ofte medfører, at patienterne isolerer sig for at undgå sollys og dermed bliver hæmmet i deres sociale liv. Livskvalitet ønskes opgjort ved brug af to spørgeskemaer:

- Det generiske spørgeskema til dermatologiske lidelser, Dermatology Life Quality Index (DLQI). DLQI er er udviklet til at vurdere den helbredsrelaterede livskvalitet i forbindelse med dermatologiske sygdomme og deres behandling. DLQI indeholder 10 spørgsmål relateret til symptomer, følelser, daglige aktiviteter, tøj, arbejde eller skole, fritidsaktiviteter, relationer og gener af behandlingen [15]. Fagudvalget vurderer, at DLQI kan anvendes til at give et overordnet billede af livskvaliteten hos patienter med EPP, men at de spørgsmål, der indgår, ikke giver fyldestgørende informationer om patienternes specifikke symptomer. Den maksimale score er 30, hvor højere score indikerer dårligere helbredsrelateret livskvalitet [6,7]. Den mindste klinisk relevante forskel er i litteraturen rapporteret til 4 point for DLQI [8]. Livskvalitet ønskes opgjort som gennemsnitlig ændring fra baseline for patienter, der har fået henholdsvis afamelanotid og placebo. Forskellen mellem ændringerne skal være 4, før det anses som klinisk relevant.
- Det sygdomsspecifikke spørgeskema Erythropoietic Protoporphyria Quality-of-Life (EPPQoL), som scores fra 0-100, hvor en høj score indikerer bedre livskvalitet [3]. Firmaet, som markedsfører afamelanotid, har udviklet EPPQoL på baggrund af DLQI til brug i kliniske forsøg. EPPQoL er tilsyneladende mere sensitivt til at detektere ændringer end DLQI, men da EPPQoL ikke er valideret, er der usikkerhed om spørgeskemaets psykometriske egenskaber. Det er derfor heller ikke muligt at fastsætte den mindste klinisk relevante forskel. Fagudvalget ønsker, at data baseret på EPPQoL udelukkende anvendes til narrativt at nuancere resultater for livskvalitet målt ved DLQI.

Symptomer (fototoksicitet)
Symptomer ved EPP forekommer som fototoksiske reaktioner efter lyseksponering, hvor patienterne oplever en slags forbrænding af huden, som har været lyseksponeret, med smerte, hævelse og rødme. Symptomlindring kan anses som udtryk for respons på behandlingen, hvilket også formodes at blive afspejlet i livskvaliteten. Fagudvalget vurderer derfor, at symptomer bør være et kritisk effektmål i vurderingen.

Der findes ingen objektive mål for symptomlindring, og der er mange usikkerheder forbundet med måling af symptomer. For bedst at kunne vurdere lægemidlets effekt på symptomer vurderer fagudvalget, at det er nødvendigt at kombinere symptomer med ophold i sollys. Fagudvalget ønsker symptomer målt i både direkte og indirekte sollys, da begge typer lys giver symptomer. Dog er direkte sollys værst, og giver symptomer efter kortere tids eksponering. Nedenfor beskrives de forskellige måder, fagudvalget ønsker symptomer opgjort på.

Minutter pr. dag udendørs (i direkte eller indirekte sollys) uden eller med milde symptomer (smerte < 4 på skala fra 0-10)
Fagudvalget ønsker, at firmaet belyser den tid, patienterne kan opholde sig udendørs uden eller med milde symptomer. Fagudvalget vurderer, at patienterne er villige til at opleve milde symptomer for at kunne opholde sig lidt længere tid udendørs, da selv en lille forbedring vil have stor betydning. Det er imidlertid meget individuelt, hvor længe patienter kan opholde sig udendørs. Fagudvalget vurderer derfor, at den mindste klinisk relevante forskel er en 50 %'s øgning (i minutter) af den gennemsnitlige tid, patienterne i behandling med afamelanotid kan være udendørs pr. dag sammenlignet med placebo. Dog skal forbedringen være på mindst 20 minutter.

Fagudvalget ønsker, at data for effektmålet er målt i tidsrummet kl. 10-18 i årets mest solrige måneder, som i Danmark vil være fra april til september, hvilket også vil være den periode, behandling vil kunne tilbydes i Danmark.

Varighed af symptomer (moderate-svære med smerte ≥ 4 på skala fra 0-10) efter episode med udsættelse for sollys
Fagudvalget ønsker at vide, i hvilken grad afamelanotid kan reducere varigheden af moderate til svære symptomer efter episoder med udsættelse for sollys. Varigheden af symptomerne efter sollys er individuel, men kan vare i mange dage, hvorfor det for patienterne vil betyde meget, om de moderate til svære symptomer kan reduceres. Fagudvalget vurderer derfor, at den mindste klinisk relevante forskel er en 20 % reduktion af den gennemsnitlige varighed af symptomer for patienter i behandling med afamelanotid, sammenlignet med placebogruppen.

Bivirkninger

Fagudvalget vurderer, at bivirkninger er et kritisk effektmål, da det har betydning for den enkelte patients livskvalitet og for behandlingsophør. Det er vigtigt, at bivirkningsprofilen belyses og er acceptabel, særligt i den unge patientpopulation, da sygdommen ikke er livstruende, og behandlingen ikke er kurativ og forventes at være langvarig. Fagudvalget vurderer dog, at villigheden til at acceptere bivirkninger i forhold til effekten kan variere med f.eks. alder og interesser.

Fagudvalget ønsker bivirkninger opgjort som andelen, der oplever uønskede hændelser af grad 3-4. Fagudvalget vurderer, at tolerancen for grad 3-4 uønskede hændelser er lav for patienter med EPP, eftersom sygdommen er kronisk og ikke livstruende, og behandlingen forventes at være langvarig. Den mindste klinisk relevante forskel vurderes at være 5 procentpoint.

Fagudvalget ønsker som supplement til effektmålet uønskede hændelser af grad 3-4 at foretage en narrativ vurdering af den generelle bivirkningsprofil, herunder også langtidsbivirkninger (efter mindst 10 år), for at vurdere bivirkningernes alvorlighed og håndterbarhed.

4 Litteratursøgning

Medicinrådet har undersøgt, om der findes et eller flere peer-reviewede publicerede fuldtekstartikler, hvor afamelanotid er sammenlignet direkte med placebo.

Medicinrådet fandt følgende artikel, som er relevant, og som indeholder en direkte sammenligning mellem afamelanotid og placebo:

- Langendonk et al. Afamelanotide for Erythropoietic Protoporphyria. N Engl J Med. 2015 July 2; 373(1): 48–59. NCT01605136 og NCT00979745

Fagudvalget er interesseret i at inddrage opfølgende data på effekten af lægemidlet eller anden upubliceret data, hvis dette findes og kan bidrage til at belyse effekten af afamelanotid. Derudover ønsker fagudvalget også at modtage data på effektmålene fra tidligere studier i lægemidlets studieprogram. Fagudvalget ønsker endvidere, at firmaet indsender opfølgende data for langtidsbivirkninger, såfremt dette findes. Indsendes upubliceret data, skal firmaet acceptere, at Medicinrådet offentliggør dem i ansøgningsskemaet og i rapporten vedr. lægemidlets værdi. Firmaet bedes også konsultere Det Europæiske Lægemiddelagenturs (EMA) European public assessment report (EPAR) for det aktuelle lægemiddel.

5 Databehandling og -analyse

Clinuvel, som markedsfører afamelanotid, har tilkendegivet, at de ønsker at indsende en ansøgning til Medicinrådet, selvom Medicinrådet har taget vurderingen af afamelanotid op af egen drift. Firmaet skal bruge Medicinrådets ansøgningsskema til sin endelige ansøgning. Vær opmærksom på følgende:

Studier og resultater

- Beskriv det inkluderede studie og baselinekarakteristikken af studiepopulationerne.
- Angiv hvilke studier/referencer der er benyttet til at besvare det kliniske spørgsmål.
- Brug som udgangspunkt ansøgningsskemaet til ekstraktion af al relevant data.
- Krydstjek de ekstraherede data med de resultater, der fremgår af relevante EPAR.
- Angiv årsager, hvis der er uoverensstemmelser mellem resultaterne fra artikler og EPAR.
- Angiv årsager, hvis der er uoverensstemmelser i forhold til PICO mellem protokollen og studiet.
- 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 firmaet 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 (jævnfør 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.

Narrative analyser

- Begrund valget af syntesemetode (metaanalyse eller narrativ beskrivelse), og lad specifikke analysevalg fremgå tydeligt.
- Syntetisér data narrativt, hvis det ikke er en mulighed at udarbejde komparative analyser baseret på statistiske metoder.
- Beskriv studie- og patientkarakteristika samt resultater fra de inkluderede studier narrativt og i tabelform med angivelse af resultater pr. effektmål for både intervention og komparator(er).
- Beskriv forskelle mellem studier og vurdér, hvorvidt resultaterne er sammenlignelige.

Vær opmærksom på, at Medicinrådets sekretariat forbeholder sig retten til at foretage sensitivitets- og subgruppeanalyser på baggrund af studiernes validitet og relevans, uanset valg af analysemetode.

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 vi kan have tiltro til den evidens, vi baserer vurderingen af lægemidlets værdi på.

7 Andre overvejelser

Fagudvalget bemærker, at der vil være behov for monitorering af effekt og bivirkninger ved behandling med afamelanotid. Fagudvalget vil i vurderingsrapporten definere kriterier for opstart, monitorering og seponering. Endvidere bør det overvejes, om der skal være krav om graviditetstest af fertile kvinder umiddelbart inden indsættelse af nyt implantat.

Fagudvalget ønsker, at firmaet giver en beskrivelse af teratogeniciteten (risikoen for fosterskade). Denne risiko ønskes belyst, da der med langvarige behandlinger er sandsynlighed for, at nogle vil blive gravide under et behandlingsforløb. Derudover ønsker fagudvalget også, at firmaet beskriver risiko for udvikling af hudkræft, eftersom lægemidlet bevirker, at hudens pigmentproduktion stimuleres.

Fagudvalget bemærker en stor variation i effektmålet *"antal timer i direkte sollys mellem 10-15 uden smerte"* mellem det europæiske (NCT00979745) og det amerikanske (NCT01605136) fase III-studie. Fagudvalget ønsker derfor, at firmaet redegør for, hvordan effektmålet i hhv. det europæiske forsøg og det amerikanske forsøg er opgjort.

8 Relation til behandlingsvejledning

Der findes ikke en behandlingsvejledning på området.

9 Referencer

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10 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende atopisk eksem

Formand	**Indstillet af**
Gabrielle Randskov Vinding Afdelingslæge	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
Evy Poulsen Overlæge	Region Syddanmark
Kati Hannele Kainu Afdelingslæge	Region Hovedstaden
Rasmus Huan Olsen Afdelingslæge	Dansk Selskab for klinisk Farmakologi
Cathrine Nørgaard Peulicke Klinisk farmaceut	Dansk Selskab for Sygehusapoteksledelse
Charlotte Gotthard Mørtz* Professor, overlæge	Inviteret af formanden
Patient/patientrepræsentant*	Danske Patienter
Line Muller Tribler* Patient/patientrepræsentant	Danske Patienter

*Har ikke deltaget i udarbejdelsen

Andre der har bidraget
Kristine Pallesen Afdelingslæge/dermatolog
Tre patientrepræsentanter med sygdommen *De udpegede patientrepræsentanter, der er medlemmer af fagudvalget, har ikke deltaget i vurderingen af lægemidlet*

Medicinrådets sekretariat

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11 Versionslog

Version	Dato	Ændring
1.0	17. august 2020	Godkendt af Medicinrådet.