Assessment

Afamelanotide (Scenesse) for the treatment of erythropoietic protoporphyria (EPP)

17-12-2018

Norwegian Medicines Agency

PREFACE

Implementation of the National System for the introduction of new technologies in the specialist healthcare system will help ensure that assessment of appropriate new technologies happens in a systematic manner with respect to efficacy and safety, as well as impacts on health and society. The main aim of the new system is described in the National Health and Care Plan 2011-2015 and the White Paper 10 (2012-2013), Good quality - safe services. The regional health authorities, the Norwegian Knowledge Centre for Health Services, the Norwegian Medicines Agency and the Directorate of Health collaborate on tasks related to the establishment and implementation of the new system. Eventually, the National System for the introduction of new technologies in the specialist healthcare system will assist in the rational use of health care resources.

The Norwegian Medicines Agency has been assigned the responsibility to evaluate Single Technology Assessments of individual pharmaceuticals. A Single Technology Assessment is a systematic summary of evidence based on research on efficacy, safety and impact assessment. For pharmaceuticals, this will usually revolve around budgetary consequences or resource allocation. The burden of proof relating to the documentation of efficacy, safety and cost-effectiveness is borne by the MA-holder for the pharmaceutical under review. NoMA can, when necessary, provide guidance to pharmaceutical companies.

NoMA assesses the submitted evidence for all important clinical outcomes, resource use as well as the assumptions made in the analysis presented by the MA-holder and the presented results. NoMA does not perform its own health economic analyses. If required, NoMA may request additional information and perform additional calculations of the costs and cost effectiveness using the submitted model.

NoMA evaluates the relative efficacy and incremental costs in relation to a relevant comparator. NoMA does not assess the benefit risk balance already assessed under the market-authorization procedure. Information about this is provided by EMA.

Single Technology Assessment of pharmaceuticals is intended to support sound decision making on potential introductions of new technologies, and prioritization made at the Health Authority level. NoMA has no decision-making authority in this system.

All assessments are published and available to the public (www.legemiddelverket.no).

EXECUTIVE SUMMARY

Rationale

NoMA has performed a simplified assessment of the clinical efficacy, safety and cost-effectiveness of Scenesse according to the request specifications from Ordering Forum (request number ID2016_048). The request from Ordering Forum can be found at www.nyemetoder.no. NoMA's assessment is mainly, but not exclusively, based on the documentation presented by Clinuvel.

Background

Scenesse is an implant for the treatment of erythropoietic protoporphyria (EPP). There are no recommended treatment options for EPP today. About 40 patients (37-42) may be eligible for treatment with afamelanotide in Norway each year. Normally, the general clinical efficacy for medicinal products is demonstrated through the granting of marketing authorisation. In this case the marketing authorisation was granted under exceptional circumstances, as it was accepted by the EMA that the "applicant can show that he is unable to provide comprehensive data on the efficacy and safety under normal conditions of use".

Clinical efficacy in the Norwegian setting

The clinical efficacy of afamelanotide was demonstrated mainly in the pivotal study CUV039, where afamelanotide was compared to placebo. The primary end point was "total daily duration of time (hrs) spent in direct sunlight 10:00-18:00 hrs on days when no pain was experienced". In the afamelanotide arm a median of 69.4 h was achieved, compared to median 40.8 h in the placebo arm over a period of 180 days, i.e 13.6 min/day in placebo arm and 23.1 minutes in the afamelanotide arm. This translates into 9.5 minutes prolonged exposure per day. If mean duration is used, the difference between the afamelanotide and placebo arms is 18 minutes.

Severity and shortfall

Based on a qualitative evaluation, NoMA considers erythropoietic protoporphyria a severe disease with substantial consequences for the quality of life for the patients with this condition. According to the EPAR (1), the patients avoid sunlight/daylight (which will cause pain) and have to live a very restricted life and are severely limited in their outdoor activities. They develop a photoprotective behaviour with a negative impact on their quality of life and limitation of social activities. The model provided by Clinuvel cannot be used to measure health benefit in the form quality adjusted life-years (QALYs) of afamelanotide or the comparator. This is because the benefit is not given as utilities in the documentation, and hence, the model cannot be used to measure the absolute shortfall. However, by using an approximation of utility based on mapping from DLQI to EQ-5D by NICE, the NoMA has estimated the absolute shortfall of EPP to be approximately 11 QALYs.

Cost effectiveness

The cost of Scenesse, based on list price (max PSP ex VAT), three implants and administration costs per year is 415 000 NOK per patient per year.

The willingness to pay for prolonged exposure to light and sunlight for patients with EPP is unknown. It has not been possible to establish an incremental cost-effectiveness ratio (ICER), since the health-related quality of life gain of afamelanotide is given on a scale based on a non validated disease specific questionnaire which was developed for the purpose of the afamelanotide studies. The SF-36 results from the study CUV017 were not reported. Utility weights by EQ-5D is preferred by NoMA, but SF-36 is another generic instrument, and can be mapped into EQ-5D values.

In the pivotal study CUV039, the validated disease specific questionnaire Dermatology Quality of Life Index (DLQI) was used. HRQoL measured by this questionnaire did not demonstrate any significant difference between the afamelanotide and placebo arms.

Budget impact

The budget impact of recommending adoption will be approximately [redacted] in year 5.

NoMA's overall appraisal

The limited clinical documentation indicates that treatment with afamelanotide has a small effect on duration of exposure to sunlight. However, it has not been possible to establish whether the treatment improves the quality of life. The severity calculations are also subject to high uncertainty.

The Market Authorisation Holder and the clinician NoMA has been in contact with, suggest that the treatment with afamelanotide may have benefits that are not easily demonstrated in clinical trials. They are referring to long term adherence to the treatment in compassionate use and expanded access programmes. Reference to adherence in these programmes is not sufficient to estimate an effect size of the treatment. Therefore, it is not possible for NoMA to assess the potential benefits the patients could acquire with afamelanotide.

NoMA does not consider that cost effectiveness is documented for afamelanotide.

OPPSUMMERING

Formål

Legemiddelverket har gjennomført en forenklet hurtig metodevurdering av klinisk effekt, sikkerhet og kostnadseffektivitet av Scenesse i henhold til bestilling (ID2016_048). Bestillingen finnes på www.nyemetoder.no. Legemiddelverkets vurdering er hovedsakelig basert på dokumentasjon innlevert av Clinuvel.

Bakgrunn

Scenesse er et implantat for behandling av erytropoietisk protoporfyri (EPP). Det finnes ingen anbefalte behandlingsalternativer for EPP i dag. Om lag 40 pasienter (37-42) kan være aktuelle for behandling med afamelanotid hvert år i Norge. Vanligvis vil den generelle kliniske effekten av et legemiddel være dokumentert gjennom utstedelse av markedsføringstillatelse. I dette tilfellet er imidlertid markedsføringstillatelse innvilget «under exceptional circumstances», og EMA har akseptert at søkeren ikke er i stand til å frembringe fullstendige data for effekt og sikkerhet fra normal bruk av legemidlet.

Effektdokumentasjon i henhold til norsk klinisk praksis

Den kliniske effekten av Scenesse ble vist hovedsakelig i den pivotale studien CUV039, der Scenesse ble sammenlignet med placebo. Det primære endepunktet var «total daglig tid (timer) med opphold i direkte sollys mellom kl 10:00 og 18:00 på dager uten opplevd smerte». I Scenesse-armen ble median 69,4 timer oppnådd, sammenlignet med median 40,8 timer i placeboarmen over en periode på 180 dager, dvs. 13,6 min/dag i placeboarmen og 23,1 min/dag i afamelanotidarmen. Dette tilsvarer (median) 9,5 minutter forlenget eksponering per dag. Dersom gjennomsnitt benyttes i stedet for median, er forskjellen mellom armene 18 minutter per dag.

Alvorlighet og helsetap

Basert på en kvalitativ vurdering anser Legemiddelverket EPP som en alvorlig sykdom med store konsekvenser for pasientenes livskvalitet. I henhold til EPAR (1) unngår pasientene sollys/lys (som forårsaker smerte) og må leve et liv som er svært begrenset I forhold til utendørsaktiviteter. Pasientene unngår eksponering for lys, noe som har negativ innvirkning på livskvaliteten og begrenser muligheten for å delta i sosiale aktiviteter. Modellen som er sendt inn av Clinuvel er ikke egnet til å måle helsenytte I form av kvalitetsjusterte leveår (QALYs) av afamelanotid og komparator. Det skyldes at neytten ikke er angitt som utilities i dokumentasjonen, og modellen kan derfor heller ikke benyttes til å gi et mål på absolutt prognosetap (APT). Imidlertid er det mulig å benytte et grovt anslag av helsenytte basert på mapping fra DLQI til EQ-5D (utført av NICE). Legemiddelverket har på dette grunnlag estimert APT for EPP til om lag 11 QALYs.

Kostnadseffektivitet

Den totale kostnaden for Scenesse, basert på pris for Scenesse (maks AUP eks. MVA), tre implantater per år og administrasjonskostnader, er 415 000 NOK per pasient per år.

Betalingsvilligheten for økt varighet av opphold i lys eller sollys for pasienter med EPP er ukjent. Det har ikke vært mulig å etablere en IKER siden gevinsten i helserelatert livskvalitet for Scenesse ble målt med et ikke-validert sykdomsspesifikt instrument som ble utviklet spesielt for Scenesse-studiene. Resultatene fra SF-36 for studie CUV017 ble ikke rapportert. Nytte estimert ved EQ-5D foretrekkes av Legemiddelverket, men SF-36 er et annet generisk instrument som kan mappes til EQ-5D.

I den pivotale studien CUV039 ble det validerte sykdomsspesifikke instrumentet DLQI benyttet. Helserelatert livskvalitet målt med dette spørreskjemaet viste ingen signifikant forskjell mellom Scenesse- og placeboarmen.

Budsjettkonsekvenser

Budsjettkonsekvensene ved å ta i bruk Scenesse vil være om lag [redacted] kroner i år 5.

Legemiddelverkets vurdering

Den begrensede kliniske dokumentasjonen indikerer at behandling med afamelanotide har liten effekt på hvor lenge pasientene kan oppholde seg i sollys. Det har ikke vært mulig ved hjelp av kliniske studier å vise om behandlingen bedrer livskvaliteten. Alvorlighetsberegningene er også beheftet med stor usikkerhet.

Både firmaet som har markedsføringstillatelse for afamelanotide og en klinisk ekspert som Legemiddelverket har vært i kontakt med, anfører at behandling med legemiddelet kan ha fordeler som ikke så lett lar seg påvise i kliniske studier, og viser blant annet til lang tids etterlevelse i compassionate use og expanded access programmer. Henvisning til «lang tids etterlevelse i compassionate use og expanded access programmer» er ikke tilstrekkelig til å anslå effektenstørrelsen av behandlingen, og det er derfor ikke mulig for Legemiddelverket å vurdere størrelsen på den nytten pasientene eventuelt skulle kunne oppnå.

Legemiddelverket vurderer at kostnadseffektivitet ikke er dokumentert for afamelanotide.

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LOG

Order:	*ID-nr 2016_048: Afamelanotide (Scenesse). Treatment of adult patients with erythropoietic protoporphyria (EPP)*
Proposer:	Nasjonalt kompetansesenter for porfyrisykdommer (NAPOS)
Pharmaceutical company:	Clinuvel
Product:	Scenesse
Active substance:	Afamelanotide
Indication:	Scenesse is indicated for prevention of phototoxicity in adult patients with erythropoietic protoporphyria (EPP).
ATC-No:	D02BB02

Process

Documentation requested from NoMA	13-06-2017
Complete documentation received by NoMA	13-11-2017 (incomplete documentation received 10-08-2017)
First clinician contact by NoMA	14-02-2018
First LIS contact by NoMA	26-06-2018
Further documentation requested by NoMA	31-10-2017, 31-01-2018
Further documentation received by NoMA	n.a. requested documentation not received
Report completed:	17-12-2018
Processing time:	399 days whereof 68 days waiting for further documentation from Company.
Assessors:	Einar Andreassen Christina Kvalheim
Clinical experts:	Atle Brun, Helse Vest RHF

Clinical experts have provided clarifications of central assumptions in the analysis (e.g. choice of comparator, patient population, relevance of the clinical studies for Norwegian clinical practice). The NoMA is responsible for the content of the report. The clinical experts have not been involved in any consensus process or had any «peer-review» role during preparation of the report.

GLOSSARY

DLQI	Dermatology Life Quality Index
EMA	European Medicines Agency
EPP	Erythropoietic protoporphyria
EPP-QoL	EPP-specific quality of life questionnaire
MA	Market Authorisation
MAH	Market Authorisation Holder
NAPOS	Nasjonalt kompetansesenter for porfyrisykdommer (ved Helse Bergen Haukeland universitetssjukehus)
NoMA	Norwegian Medicines Agency
SF-36	Short Form 36
STA	Single Technology Assessment

1 BACKGROUND

1.1 SCOPE

Single technology assessments are used to assess whether the three prioritisation criteria are fulfilled. The three criteria are: benefit for the patient, severity of the disease and resource use.

In order for the Norwegian Medicines Agency (NoMA) to assess a new pharmaceutical with the methodology of a single technology assessment (STA), the marketing authorisation holder (MAH) is obligated to provide the necessary documentation of treatment effect. In our guidelines on how to conduct pharmacoeconomic analyses NoMA guides the company on preferred and necessary documentation for submission: a cost-utility model model with the possibility of measuring the severity of the disease, treatment effectiveness, utility for the patients and related costs for intervention and comparator. The technology appraisal guidelines are available on NoMA webpage (2).

Afamelanotide (Scenesse) is an orphan medicinal product in the treatment of erythropoietic protoporphyria and was granted market autorisation by EMA under *exceptional circumstances*. This implies that the EMA (3) has accepted that the "applicant can show that he is unable to provide comprehensive data on the efficacy and safety under normal conditions of use", because:

- The indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, or
- In the present state of scientific knowledge, comprehensive information cannot be provided, or
- It would be contrary to generally accepted principles of medical ethics to collect such information

EMA considers the second bulletpoint to be the key argument (1): "specifically the limitations of randomised controlled trials (the absence of clear measures for exposure and efficacy and the conditioned behaviour severely impacting the sensitivity of the study to detect drug effects) also the absence of clear epidemiology, it is argued that comprehensive information cannot be provided to the standards usually expected for MAAs."

1.2 SEVERITY AND SHORTFALL

Based on a qualitative evaluation, NoMA considers erythropoietic protoporphyria a severe disease with substantial consequences for the quality of life for the patients with this condition.

EPP is characterized biochemically by high levels of protoporphyrin IX (PPIX) in red blood cells, plasma and tissues, especially the skin. It is caused by a deficiency of ferrochelatase (FECH), the final enzyme in the haem biosynthetic pathway. As a result of this deficiency, the substrate for this enzyme, protoporphyrin IX (PPIX), accumulates. This leads to excessive formation of protoporphyrin IX in bone marrow cells, resulting in its accumulation in erythrocytes, plasma, liver, and other tissues. In these patients, protoporhyrins accumulated in the skin can produce free radicals upon exposure to light, strong artificial light or sunlight, causing painful cutaneous damage (1).

EPP presents with prodromal symptoms of itching and tingling with exposure to light. With prolonged exposure acute photosensitivity can occur, with erythema, oedema, and a painful burning sensation. The patients avoid sunlight/daylight and have to live a very restricted life and are severely limited in their outdoor activities, and develop a photoprotective behaviour with a marked negative impact on their quality of life and limitation of social activities (1).

According to NoMA guidelines severity of the disease should be measured as Absolute Shortfall. This is measured as the utility and life years lost (measured in Quality Adjusted Life Years, QALYs) due to disease. Absolute Shortfall is estimated to be 11 QALYs lost. The QALY-estimates used in this calculation should be interpreted with caution. However, the absolute shortfall measure indicates that EPP is a severe disease that greatly affect quality of life for the patients. See chapter 3.4.3 for a discussion of using these QALY-estimates for this specific population.

See Appendix 1 Severity and shortfall for calculations.

1.3 TREATMENT OF ERYTHROPOIETIC PROTOPORPHYRIA (EPP)

1.3.1 Treatment with afamelanotide (4)

- Therapeutic indication

Scenesse is indicated for prevention of phototoxicity in adult patients with erythropoietic protoporphyria (EPP).

- Mechanism of action

Afamelanotide is a melanocortin-1 receptor agonist and is indicated for the prevention of phototoxicity in adult patients with erythropoietic protoporphyria (EPP). It acts by directly stimulating melanocytes to produce eumelanin, which pigments the epidermis and therefore protects against phototoxic reactions caused by light.

- Posology

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.

- *Undesirable effects*

The most commonly reported adverse reactions are nausea, experienced by approximately 19% of subjects who received treatment with this medicinal product, headache (20%), and implant site reactions (21%; mainly discolouration, pain, haematoma, erythema). In most cases these adverse reactions are reported to be mild in severity (4).

- *Restricted medical prescription*

Scenesse should only be prescribed by specialist physicians in recognised porphyria centers and administration should be performed by a physician trained and accredited by the marketing authorisation

holder to administer the implant (4). In Norway, Scenesse is intended to be available through Nasjonalt kompetansesenter for porfyrisykdommer (NAPOS) initially (5).

1.3.2 Treatment guidelines

There is no recommended treatment for EPP. The only way to avoid symptoms is to keep the skin protected from direct sunlight, by dressing up, stay in the shade or use special sunscreens (6).

1.3.3 Treatment with comparator

As there is no recommended treatment for EPP, there is no active comparator. The comparator is therefore placebo.

2 SUBMITTED DOCUMENTATION TO DEMONSTRATE THE RELATIVE EFFECTIVENESS

Clinuvel has not submitted clinical documentation according to our guidelines (7, 8). Clinuvel has not performed systematic literature search in relevant databases. In their pricing application it is mentioned that the clinical benefit of Scenesse has been demonstrated in four placebo controlled studies: CUV017, CUV 029, CUV 030 and CUV 039.The clinical data and outcomes from these studies are described in the EPAR of Scenesse (1). NoMA has relied on the outcomes reported in the EPAR. As there is no treatment of the condition today, placebo can be regarded as a relevant comparator in the current evaluation.

In the initial submission from Clinuvel, the company has highlighted the difficulty related to conduct of the clinical trials in this population.

2.1 OVERVIEW OF RELEVANT CLINICAL STUDIES

The following studies are considered relevant for the assessment (Study CUV039 is considered the main study by CHMP):

Study (acronym, ID)	Population	Intervention/Control	Primary outcome	Secondary outcomes	Adverse events
CUV017 (very sparse information in EPAR)	Phase III, RCT double-blind crossover study, patients with EPP (n=100) Duration 360 days	I: Afamelanotide 16 mg/implant on days 0, 120, 240 C: placebo implant on days 60, 180 or 300 Or treatment sequence vice versa	Number and severity of phototoxic reactions		Nausea, flushing
CUV029* Europe	Phase III, RCT, double-blind, patients with EPP. Duration 270 days	I: Afamelanotide 16 mg/implant every 2 months, 5 doses in total C: placebo implant	Number and severity of phototoxic reactions, **post hoc** changed to time of sun exposure		
CUV030* (US)	Phase II, RCT, double-blind, patients with EPP. Duration 180 days	I: Afamelanotide 16 mg/implant every 2 months, 3 doses in total C: placebo implant	Severity of phototoxic reactions, safety and tolerability, **post hoc** changed to time of sun exposure		
CUV039 Main study	Adults with biochemically-confirmed diagnosis of EPP who experience phototoxic reactions (n=89) Duration 180 days	I: Afamelanotide 16 mg/implant for 6 months, delivered at days 0, 60 and 120 (safety follow-up at 12 months) C: placebo implant	Number of pain-free hours that patients exposed themselves to direct sunlight between 10:00-18:00 hours (on days without pain, Likert score: 0)	-Duration of sun exposure between 10 and 18 on days with no pain or mild pain. -Duration of sunexposure between 10 and 18 during the study -QoL assessment according to DQLI and EPP-QoL -etc.	Fatigue, implant site reactions/pain, arthralgia, myalgia, headache

***** Due to GCP-noncompliance of studies CUV029 and CUV030, the main efficacy data were not considered to be robust, and they could not be relied upon by CHMP for the benefit-risk assessment.

Ongoing studies

PASS study: EEDR: European EPP Disease Registry Study

Annual reports from the study will be submitted to EMA.

NoMA's assessment of the submitted evidence

The relevant clinical studies are described in the EPAR of afamelanotide (1). The documentation is weak, which is reflected in the fact that MA has been granted "under exceptional circumstances".

3 PICO[1]

3.1 Patient Population

The patient population in the Norwegian setting

According to Norwegian clinicians symptoms usually appear from age 6/7 up to adult age. They argue that Norway is quicker to diagnose new patients compared to other countries. However, there may be individuals with EPP yet to be diagnosed. According to Clinuvel, the median delay in diagnosis is 12 years in the UK, but 16 and 18 years respectively in Sweden and Switzerland.

Clinuvel estimate 68 individuals in Norway, 37 of whom have been identified by the Norwegian Porphyria Centre (NAPOS), as eligible for treatment. The Norwegian clinicians NoMA has contacted, reports that there are 46 patients, of which four are children.

The patient population in the submitted clinical studies related to Norwegian setting.

The main study is conducted on adult patients. The mean age in CUV039 was approximately 40 years (1).

The patient population in the HE-model related to the Norwegian setting and clinical studies

The mean age used in the model is 38 years.

NoMA's evaluation of the patient population

Although the main study is not conducted in children, NoMA considers this acceptable, given that few patients under 18 are diagnosed with EPP.

3.2 Intervention

Intervention in the Norwegian setting

The afamelanotide implant is assumed to be used according to the SmPC in the Norwegian setting. Three implants per year are recommended, depending on the length of protection required. The recommended maximum number of implants is four per year (4).

Intervention in the submitted clinical studies related to Norwegian setting.

In the pivotal clinical study (CUV039), afamelanotide is used as described in the SmPC (4).

Intervention in the HE-model related to the Norwegian setting and clinical studies

Clinuvel assumes that there will be on average [redacted] implants per patient per year in Norway, with reference to observational follow up studies: "Clinical experience to date suggests that the average patient receives between 2.2 and 4 implants per annum long-term. The base case is formulated based on experience of use of the product in expanded access programs in Italy and Switzerland."

[1] Patients, Intervention, Comparator, Outcome.

NoMA's evaluation of the intervention

NoMA considers the use of afamelanotide as reasonable in clinical setting and studies.

According to EMA (1) the mean number of implants in the studied populations of the trials are 231 individuals with a mean of 3.6 implants each year.

A long term observational study by Biolcati et al (9) in Swiss and Italian patients collected patients from the first phase II trial (CUV 010) in 2006 until 14 June 2014. Biolcati et al (9) reports an average implant per patient to be 2.6 in Italy (60% of population) and 4.4 in Switzerland (40% of population). The weighted mean would be 3.3 implants each year.

Thus, NoMA assumes that 3 implants per year may be used in clinical practice (e.g. April, June and August), which is in agreement with the posology in the SmPC.

3.3 COMPARATOR

Comparator in the Norwegian setting

There is no available treatment for this patient group.

Comparator in the submitted clinical studies related to Norwegian setting.

Placebo (dummy implant) is used in the clinical studies.

Comparator in the HE-model related to the Norwegian setting and clinical studies

Placebo with best supportive care is used as comparator in the model.

NoMA's evaluation of the Comparator

NoMA considers the use of placebo in the studies as reasonable, given that there is no available treatment in the clinical setting.

3.4 OUTCOMES

3.4.1 Efficacy

Submitted clinical documentation

CUV039

The pivotal study CUV039 reports the primary outcome: "total daily duration of time (hrs) spent in direct sunlight 10:00-18:00 hrs on days when no pain was experienced". In the afamelanotide arm a median of 69.4 h was achieved, compared to median 40.8 h in the placebo arm over a period of 180 days.

Table 1 Outcomes - primary endpoint CUV039 (1)

	Afamelanotide	Placebo	Result
Total daily duration of time (hrs) spent in direct sunlight – painfree days (Likert pain score of 0)			
Mean (SD)	115.6 (140.6)	60.6 (60.6)	
Median	69.4	40.8	
Range	0-650.5	0-224.0	
Kiskali-Wallis p-value			0.044
Mean daily minutes in direct sunlight – painfree days (Likert pain score of 0)			
Mean (SD)	43.3 (52.0)	23.7 (22.5)	
Median	25.9	18.1	
Range	0-260.2	0-83.5	
Kiskali-Wallis p-value			0.075

The difference in duration (hours over the time period of 180 days) was 28.63 hours (median), which translates into 9.5 minutes prolonged exposure per day. If the mean difference rather than median is taken into account, the corresponding duration is 55 hours (18 minutes per day). Presented as "mean daily minutes in direct sunlight", the result is no longer statistically significant.

Other studies: CUV017, CUV029 and CUV030

Upon GCP inspection of the clinical studies CUV029 and CUV030, four critical and four major findings were identified. These were related to data handling, data management, and improper statistical planning (including change of the statistical analysis plan after data analysis). NoMA therefore considers these studies only as supportive, and hesitate to use data from these studies in determination of the relative efficacy of afamelanotide.

CUV017 is only sparsely described in the EPAR, and NoMA has not seen (quantitative) efficacy data.

Submitted model

The primary or secondary outcomes from study CUV039 is not used as efficacy input in the model. Instead, Clinuvel has estimated shares of patients in the three EPP-QoL categories; mild, moderate and severe for either active treatment or placebo. The data are pooled from three studies (whereof two of them were excluded from assessment by the CHMP due to non-compliance with GCP).

NoMA's evaluation of efficacy

According to the EPAR, study CUV039 did not unequivocally show efficacy, but studies CUV039, as well as CUV029 and CUV030 show a positive trend favouring the efficacy of Scenesse. The effect size in CUV039 appears to be small. NICE remarks that "Testimonies from patients and clinical experts suggest that the benefits may be greater than those seen in trials, and that even small improvements would be of great importance to them. The true benefit of afamelanotide has, however, not been quantified" (10).

As pointed out in the EPAR, the randomised controlled trial appears to be a less effective tool for determining treatment effects, as the patients tend to avoid exposure to light sources. The ad-hoc expert group [consulted by EMA] confirmed two important points; firstly that these [EPP] patients have a 'learnt'

or 'conditioned' behaviour to avoid potentially painful exposure to sunlight, hence if a trial is based on endpoints that require patients to expose themselves to light in order to show a protection from pain, failure to expose to light will result in an insensitive comparison wherein treatment effects will not be demonstrated; second the ad-hoc group could not clearly define other measures of light exposure, clinical efficacy or QoL endpoints that would result in a sensitive comparison.

Owing to the conditioned behaviour and disease characteristic prodromal phase, patients are reluctant to expose themselves to light sources during clinical trials. The lack of available scientific instruments to capture and measure the impact of light along the visible part of the electromagnetic spectrum and tools to measure the prodromal symptom poses a repetitive challenge to generate comprehensive and meaningful data under normal conditions of use. In all 5 clinical trials of various designs it has proven impossible to accurately record the increased clinical freedom and loss of risk aversion reported by the majority of patients and physicians.

The efficacy of afamelanotide is modelled as the fraction of individuals with mild, moderate or severe symptoms after treatment with afamelanotide for 120 days. Pooled data from CUV039, CUV029 and CUV030 is used in the model. The classification is performed by Clinuvel and it is not possible for NoMA to validate based on the submitted documentation.

3.4.2 Safety

Submitted clinical documentation

The most common adverse events seen in clinical trials were headache, nausea, nasopharyngitis, fatigue, ephelides, migraine, back pain, upper respiratory tract infection, influenza and dizziness.

Submitted model

Adverse events are not included in the model analysis.

NoMA's evaluation of safety

The MA is granted under "exeptional circumstances" and comprehensive data on the safety under normal conditions is not available. There is a lack of long-term data. Additional pharmacovigilance studies and activities are defined in the Risk Mangement Plan.

3.4.3 Health related quality of life (HRQoL)

Submitted documentation

Three different HRQoL instruments have been employed by Clinuvel in the various clinical trials. These were the Short Form 36 (SF-36) in studies CUV010 and CUV017, the Dermatology Life Quality Index (DLQI) and an EPP-specific questionnaire (EPP-QoL) in studies CUV029, CUV030 and CUV039.

HRQoL, measured by the questionnaires DLQI and EPP-QoL, was a secondary endpoint in study CUV039. These were completed on day 0, 60, 120 and 180. In addition, EPP-QoL was completed at baseline and at safety follow-up at 360 days. Table 2 summarises the effect of afamelanotide on patients EPP-QoL.

Table 2 Quality of life - EPP-QoL, Study CUV039 (1)

Visit		Afamelanotide (n=47)	Placebo (n=43)
EPP-QoL Day 0	Mean (SD) Median (min, max)	21.7 (8.3) 23.0 (-1, 35)	22.0 (8.2) 24.0 (-1, 34)
EPP-QoL Day 60	Mean (SD) Median (min, max)	3.0 (10.2) 1.0 (-10, 33)	12.0 (12.5) 9.0 (-7, 31)
EPP-QoL Day 120	Mean (SD) Median (min, max)	0.4 (9.6) -2.0 (-10, 27)	9.4 (12.5) 8.0 (-8, 32)
EPP-QoL Day 180	Mean (SD) Median (min, max)	0.5 (10.4) -2.5 (-10, 28)	6.9 (10.6) 5.0 (-7, 27)
Follow-up (360)	Mean (SD) Median (min, max)	17.0 (11.2) 19.5 (-7, 33)	14.2 (11.9) 14.0 (-6, 34)

From day 0 to day 180 the median EPP-QoL score improved (as shown by decreases) in both groups. The improvement was more pronounced in afamelanotide (from 23 to -2,5) as compared to placebo (from 24 to 5). The results for the two groups differed significantly with regard to the change in median total scores (calculated by Kruskal-Wallis test statistics and Hodges-Lehmann shift estimates for inter-group comparisons). Six months after treatment was discontinued, the EPP-QoL score had increased dramatically in both groups (corresponding to lower HRQoL).

Health economic model

In order to quantify the QoL of EPP patients, Clinuvel has used the WHO Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) that aims to quantify health losses from a wide range of diseases and injuries. Premature mortality and the time spent in these reduced states of health are expressed in units of DALYs. A DALY can be thought of as 1 lost year of 'healthy' life. The most recent disability weights were published in 2012 and did not include disability weightings for EPP or what was considered by Clinuvel as the most applicable proxy, hereditary angioedema (HAE) (11).

Clinuvel suggests that behaviour adopted by individuals with EPP can be likened to that of individuals who suffer from agoraphobia due to a fear of certain environmental factors. Agoraphobia is clinically considered as a DSM-IV anxiety disorder which is defined as 'Clinically significant distress or impairment in social, occupational or other important areas of functioning'. The GBD categorises anxiety disorders into three groups; mild, moderate and severe with the respective DALY weights being 0.030, 0.149 and 0.523 respectively.

In research conducted by Clinuvel, people with EPP were likened to people suffering with haemophilia (data on file). A study by Henrard et al (2014) (12) was recently conducted in Belgium to determine the health and economic burden of disease for haemophilia. The health burden for haemophilia was expressed in DALYs, with disability weights for mild, moderate and severe haemophilia provided. The respective weights in each of these categories are 0.054, 0.151 and 0.197.

Table 3 Global burden of disease disability weightings for proxy disorders

Global burden of disease (GBD) disability weightings / Severity	Anxiety disorders	Haemophilia
Mild	0.030	0.054
Moderate	0.149	0.151
Severe	0.523	0.197

To use these proxies, Clinuvel analysed the EPP-QoL data from three afamelanotide clinical trials (CUV029, CUV030, and CUV039; NCT00979745, NCT01097044, and NCT01605136, respectively). According to Clinuvel, the longest follow-up interval available in all trials was 120 days. The individual patient data for EPP-QoL scores was provided and the baseline/ 120-day data were used to group the results into three EPP-QOL groups:

- severe – 0 to 33.3
- moderate – 33.4 to 66.6
- mild – 66.7 to 100.

A division of three was used in order to utilise the three groups in each of the disability weight proxies identified.

Table 4 EPP-QoL: groupings by EPP-QoL score from studies CUV029/30/39 (5)

	Baseline		120 days	
Severity category	**Afamelanotide**	**Placebo**	**Afamelanotide**	**Placebo**
66.7 to 100 (mild)	[redacted]	[redacted]	[redacted]	[redacted]
33.4 to 66.6 (moderate)	[redacted]	[redacted]	[redacted]	[redacted]
0 to 33.3 (severe)	[redacted]	[redacted]	[redacted]	[redacted]

In addition, Clinuvel has performed a scenario analysis with the use of HAE as proxy for EPP patients' quality of life. Anaphylactic reactions that characterise EPP, according to clinical experts' opinion, are similar to those suffered by patients with HAE. In a study conducted by Aygören-Pürsün et al. (2013) (13) health state utility weights for different levels of pain during HAE attacks and in between attacks were estimated (Table 8 in the submission).

Table 5 Health state utilities for hereditary angioedema

Health state utilities for hereditary angioedema	Utilities
In between attacks	0.722
Mild attack	0.558
Moderate attack	0.467
Severe attack	0.080

The study by Aygören-Pürsün et al. (2013) were based on a survey that contained items overlapping with dimensions in the EQ-5D. Utility weights were obtained by mapping to EQ-5D. The disutility obtained was then subtracted from the utilities for the general population. In the base case the utility value for "mild attack" was used for patients in the mild group.

NoMA's evaluation of Health related quality of life

Even though HRQoL data exist from the clinical trials of afamelanotide, which could have been converted to QALYs with validated methods (SF-36 and DLQI), Clinuvel has developed their own disease specific questionnaire (EPP-QoL), converted this to DALYs based on proxy diseases, and these data are used in their base case. Some other methods are also discussed in the documentation which is submitted to NoMA.

DALYs vs. QALYs

For STA assessments NoMA requests HRQoL measured as QALYs by a generic instrument. This is the accepted method of measurement expressed in the government White paper "Principles for priority setting in health care" (14). NoMA prefer utility weights which are estimated by using the EQ-5D instrument with preferences from the British population (2).

Clinuvel states in their application that the QALY methodology does not capture the specific characteristics of EPP, and that QALY should not be a part of the decision tool for afamelanotide. Instead, Clinuvel has used utility from proxy diseases - measured in DALYs. Mathematically, DALYs are the inverse of QALYs. Hence, a utility gain measured in QALYs could have been used equivalently to disutilty lost measured in DALYs. The reason QALYs are preferred by NoMA is the method used to measure the utility weights by population wide preference studies.

Use of proxy diseases and severity categories

The choice of anxiety disorders and haemophilia as diseases that are comparable to EPP is not convinving. Clinuvel states that HAE is their preferred proxy. In NoMA's opinion, the use of HAE as a proxy disease also lacks documentation. The division of EPP scores into three even groups (mild, moderate, severe), and equating them to the corresponding groups in the proxy diseases (anxiety and haemophilia) is not well justified or validated.

According to Clinuvel HAE is the preferred proxy disease for EPP patients. It seems that Clinuvel has chosen anxiety disorders and haemophilia because DALY weights exist for these diseases. NoMA does not follow this argument, as QALY weights are available for HAE in a study referred to by Clinuvel (13). In NoMA's opinion, the use of HAE as a proxy disease lacks documentation, but it would still be better to use the preferred disease proxy to capture incremental utility of treatment combined with the preferred method to capture utility, than to use DALYs from even less related condition.

SF-36 and DLQI

Clinuvel has conducted HRQoL measurements using **the generic instrument SF-36** in study CUV017. By applying preference weights from SF-6D index, it is possible to use the data obtained from SF-36 to generate QALYs to be used in a cost-utility analysis. It is also possible to map to EQ-5D. However, this conversion has not been performed by Clinuvel.

The SF-36 consists of eight scaled scores including the dimensions of emotional functioning, social functioning, bodily pain and vitality. These dimensions correspond to what seems to be important for EPP patients, as stated by Clinuvel in the application. Data from CUV017, however, showed no improvement in HRQoL measured by SF-36 during and after treatment with afamelanotide (1).

DLQI is a disease specific instrument to measure HRQoL of skin diseases (i.e. psoriasis and hand eczema) and consists of 10 dimensions including the dimensions of pain, leisure and social activities, work and everyday life. NoMA expects these dimensions to be important for measuring HRQoL for EPP patients. Holme et al (5) used DLQI in a large, British study of HRQoL in EPP patients. A high DLQI score represents a large impact on HRQoL. Clinuvel has used the Holme study to justify the burden of disease for EPP patients.

The Holme study found that DLQI scores of EPP patients was "unexpectedly high by comparison with those for other skin diseases generally regarded as more severe, with levels of pain comparable with severe eczema and epidermolysis bullosa". The mean DLQI score reported in this study was 14, which is somewhat higher than the mean DLQI score from CUV039, cf. *Table 6* shows that both afamelanotide and placebo seems to equally improve HRQoL measured by DLQI. There were no clinically relevant or statistically significant differences between groups in quality of life at any time point when assessed by the DLQI questionnaire (1).

Both Holme et al, and CUV039 show that EPP considerably impairs the HRQoL of the patients. DLQI does not measure HRQoL in terms of QALYs, as requested by NoMA guidelines. However, is possible to map DLQI-scores to the preferred EQ-5D-intrument and in terms of QALYs. NICE has performed a mapping exercise from the DLQI measurements to the EQ-5D. The results are presented in the HRQoL-measurements in

Table 6 Quality of life, DLQI questionnaire, Study CUV039

Visit		Afamelanotide (n=47)	Placebo (n=43)
DLQI Day 0	Mean (SD) Median (min, max)	10.7 (6.3) 10.0 (0.26)	10.4 (5.7) 11.0 (0.22)
DLQI Day 60	Mean (SD) Median (min, max)	4.7 (5.7) 2.0 (0.21)	6.4 (6.0) 4.0 (0.21)
DLQI Day 120	Mean (SD) Median (min, max)	2.8 (4.2) 0.5 (0.16)	4.1 (4.8) 2.5 (0.19)
DLQI Day 180	Mean (SD) Median (min, max)	2.4 (4.2) 1.0 (0.16)	3.1 (4.1) 1.0 (0.14)

0: no effect on subject's life, >20: extremely large effect on subject's life. Estimates of the minimal clinically important difference in DLQI in inflammatory skin diseases varies from 3 to 4 or 5 (15).

Table 7 NICE HRQoL results from mapping DLQI to EQ-5D

Severity	N[1]	Proportion [a]	Score (assume centre)	EQ-5D[b]	EQ-5D[c]
No effect (DLQI ≤ 1)	6	3.41%	0.5	0.8679	0.9433
Small (DLQI 2-5)	15	8.52%	3.5	0.8091	0.8668
Moderate (DLQI 6-10)	32	18.18%	8.0	0.7209	0.7522
Very large effect (DLQI 11-20)	92	52.27%	15.5	0.5739	0.5611
Severe (DLQI 21-30)	31	17.61%	25.5	0.3779	0.3063
Total	176	100.00%	14.4	0.5962	0.5900
Mean			14.0	0.6033	0.5993
Best possible			0	0.8777	0.9560
Worst possible			30	0.2897	0.1916

[a] N and proportions are derived from Holme et al. (2006), the assumed central points of each severity and the mapping are the work of the ERG[17]

[b] Norlin 2012 (whole population), EQ-5D = 0·8777 – 0·0196 DLQI[37]

[c] Currie & Conway 2006 EQ-5D = 0.956–0.0255 DLQI[43]

A study by Blome et al (16) discusses the validity of mapping DLQI scores to EQ 5D. They do not recommend mapping DLQI to EQ-5D and argues that "skin-specific quality of life as measured with the DLQI and generic health states as measured with the EQ-5D seems to be too different constructs to be equivalent to each other, because the two instruments assess largely different aspects of patient impairment". This suggests carefulness of interpreting the utilities mapped from DLQI to EQ-5D, as shown in Table 7.

The DLQI is established as a quality of life instrument in other dermatological diseases. It does not include, however, any questions that specifically measure the impact of light on the skin.

EPP-QoL

The **EPP-QoL is a disease specific instrument** to measure the HRQoL of EPP patients. It has 15 (12) questions about the impact of EPP over the last two months on symptoms, daily activities, social and leisure activities, on a similar four point scale. The wording of several EPP-QoL questions relates specifically to effects on a sunny day and on outdoor activities. Unlike the DLQI, the EPP-QoL includes a direct question on well-being ("much better" to "worse") and one on improvement in the quality of life ("very much" to "not at all"). EPP-QoL does not measure HRQoL in terms of QALYs.

Whether EPP-QoL-data could have been mapped to EQ-5D or not could have been explored by Clinuvel. EQ-5D captures dimensions for depression, anxiety and anger of psychological health, and dimensions for pain, and of ability of doing usual activities or work for physical health (17). However, the 12 item EPP-QoL questionnaire used in Langendonk et al (18) does not contain any questions explicitly directed at psychological health or pain. It is a paradox that two of the most important dimensions to explain burdens of the disease were not included in the instrument designed to measure quality of life in EPP.

Further, NoMA considers that the EPP-QoL questions used to measure the quality of life are not mutually exclusive. Hence, it is likely that the patients' answers are correlated. This again may affect the scoring of EPP-QoL for the patients, however, as the EPP-QoL is not validated, we have no information on how the different questions are weighted in the EPP-QoL score. Of the 12 questions:

- 2 are general questions about quality of life or well being
- 2 are general questions about EPP symptoms/complaints
- 4 are questions about outdoor activites
- 4 are questions about planning/clothing

Following afamelanotide treatment, the EPP-QoL improved significantly from baseline, and compared to placebo recipients, both for the revised and the original version.

Since neither of the two EPP-QoL versions are validated, the NoMA cannot valuate the clinical meaning of the results from these questionnaires.

Clinuvel has not used EPP-QoL data to estimate utility/disutility weights. EPP-QoL has been used to measure the effect in terms of share of patients which are defined as mild, moderate and severe. See Table 4. The classification into severity groups was based on division into three EPP-QoL groups (0-33.3, 33.4-66.6, 66.7-100). These EPP-QoL data was pooled from three studies, whereof two (CUV029 and CUV030) were non-compliant to GCP. The cut off used in the pooled data is 120 days, which is shorter than the trials of 180-270 days. Table 2 shows gradually better results of placebo towards day 180 in CUV039.

EPP-QoL scores are not used directly in the model to indicate level of QoL. The resulting pooled EPP-QoL score at 120 days is used as an effect parameter in the model.

Conclusion for HRQoL

In NoMA's opinion the DALYs used in the health economic model is not appropriate to model the impact of quality of life.

In NoMAs opinion the QALY calculations by NICE should also be considered with caution. First, the DLQI measure may not capture all the specific characteristics of EPP patients' HRQoL. Secondly, the study by Blome et al shows strong arguments against mapping from DLQI to EQ-5D. As a result of these two considerations, NoMA have decided not to use the QALY data from the NICE mapping exercise for further analysis. However, we have used the NICE data for severity calculations only, as an indicator of the severity of EPP measured in absolute shortfall.

The validated instruments for measuring HRQoL, the SF-36 and DLQI, have not shown statistically significant differences in HRQoL between the treatment of afamelanotide and placebo in study CUV017 and CUV039 respectively, nevertheless, the DLQI shows an increase in HRQoL in both afamelanotide and placebo arms after treatment.

Patients receiving afamelanotide have significant higher EPP-QoL score than patients treated with placebo in the three trials. However, the EPP-QoL is not mapped to utility weights, and the transition of EPP-QoL score to patient utility by using proxy diseases is weakly substantiated. The EPP-QoL is used as an effect parameter in the model. The health states are derived to fit the DALY weights of mild, moderate and severe. The classification is performed by Clinuvel and it is not possible for NoMA to validate based on the submitted documentation, see chapters 3.4.1 and 4.1.

4 HEALTH ECONOMIC ANALYSES

This section presents a summary of the economic evidence submitted by Clinuvel in support of the use of afamelanotide for the treatment of EPP, and NoMA's assessment of the evidence. A typical health economic model will include the calculation of costs, life-years gained, and quality-adjusted-life-years gained (QALYs).

4.1 THE MODEL, METHODS AND ASSUMPTIONS USED

Model description

Clinuvel has submitted a simple health economic model which summarises the mean costs and the mean health gained for each year, both for placebo and afamelanotide.

The effect of afamelanotide from day one to end of life are modelled as groupings by EPP-QoL score from studies CUV029/30/39 (5). Improvement in effect is demonstrated by a larger share of patients with mild symptoms in the afamelanotide arm and the effect is assumed to be constant over time.

NoMA's appraisal of the model

The model does not include the primary and secondary efficacy outcome of afamelanotide from the pivotal study CUV039. Further, estimation of the quality of life is performed by applying DALYs to the different severity categories, assuming that the strata equal the severity strata for haemophilia or anxiety disorders. This is very weakly substantiated in the submitted documentation, cf. chapter 3.4.

The effect is calculated as the share of patients in each severity group, mild, moderate or severe, for patients receiving either afamelanotide or placebo. The share of patients in each severity group is determined by the EPP-QoL scores at day 120. NoMA cannot validate the clinical meaning of the results from these questionnaires, and does not know how the EPP-QoL scores relates to generic QoL which is a prerequisite for comparison of benefit to other diseases.

The model is simple and transparent. The use of DALYs (disutility weights) instead of QALYs (utility weights) could simply be modified, as DALYs are mathematically the inverse expression of utility. However, this would not have changed our conclusion, since we are not able to validate the input parameter of effectiveness. The model cannot be used to quantify the benefit of afamelanotide for EPP patients.

NoMA considers the model to be useful to quantify the resource use in relation to placebo and afamelanotide arms, but not for quantification of the effect size.

4.1.1 Model perspective

n.a.

NoMA's appraisal of the models perspective

n.a.

4.1.2 Resource use and costs

Direct costs

Submitted documentation

Clinuvel has submitted both drug costs and costs of administration of the use of afamelanotide. This is summarised in the table below.

Table 8 Costs related to afamelanotide treatment AUP

Item		Unit Price		Number each year
Drugs	Afamelanotide implant	[redacted]		[redacted]
	β-carotene (vitamin A)	NOK	6.80	0
	Vitamin D + Calcium	NOK	1.50	365.25
Laboratory tests	Erythrocyte total protoporphyrin	NOK	700.00	2
	Plasma poryphrin	NOK	651.00	2
	Complete blood count	NOK	24.00	2
	Ferritin	NOK	21.00	2
	Liver functioning	NOK	51.00	2
Staffing	Principal physician	NOK	710.00	-
	Consultant	NOK	710.00	-
	Nurse	NOK	410.00	-
Dermatological screening		NOK	1 120.00	2
	Physician	NOK	710.00	-
	Nurse	NOK	410.00	-
Photoprovocation test	Photoprovocation test	NOK	710.00	1
Implant injection visits		NOK	1 297.50	[redacted]
	Principal physician	NOK	355.00	-
	Consultant	NOK	355.00	-
	Consultant	NOK	177.50	-
	Nurse	NOK	410.00	-
Final visit of the year visit		NOK	942.50	1
	Principal physician	NOK	177.50	-
	Consultant	NOK	177.50	-
	Consultant	NOK	177.50	-
	Nurse	NOK	410.00	-

NoMA's assessment

The model lacks reference to some of the input data, so it is difficult for NoMA to validate both the unit prices used and the number of units needed to treat patients each year. However, this being said, the most important input data in the model is the price of afamelanotide and the number of implants each year. NoMA has therefore not validated, but accepts the unit costs used in the model.

The price used in the model does not correspond to the maximum selling price in Norway, which is NOK 135 633 exc. VAT (19).

An implant may be given every 60 days. NoMA expects that Norwegian patients will need 3 implants each year, with dosing in April, June and August, cf. chapter 3.2.

The yearly price of treating EPP patients in the placebo-arm is approx. NOK 3 500.

4.2 RESULTS

4.2.1 Clinuvel main analysis

Using Clinuvel's estimate of [redacted] implants each year, the yearly cost of afamelanotide amounts to approx. [redacted] (based on PSP exl VAT) each year per patient.

In Clinuvel's base case scenario the incremental cost of approximately NOK 5.3 million is largely driven by the additional cost incurred by the afamelanotide implant as additional treatment; visit costs for treated patients have a small impact on total costs.

Clinuvel estimates an incremental benefit (measured in DALYs averted) for patients with afamelanotide compared to those who are untreated is close to 2 DALYs.

The base case incremental cost effectiveness ratio (ICER) is NOK 2.9 million per DALY averted. This is calculated as the ratio between the incremental costs and the incremental DALYs averted.

4.2.2 NoMA main analysis

With 3 implants each year on average, the yearly cost of afamelanotide including administration costs increases to approx. NOK 415 000 each year per patient excluding VAT, and 520 000 NOK including VAT (based on PSP). The average cost per day with treatment is approx. 2 300 NOK excluding VAT, and 2 900 NOK including VAT.

5 BUDGET IMPACT ANALYSIS

5.1 APPROXIMATION OF THE NUMBER OF PATIENTS POTENTIALLY SUITABLE FOR THE TREATMENT

According to Clinuvel EPP is an ultra-rare metabolic disorder affecting an estimated 68 individuals in Norway, 37 of whom have been identified by the Norwegian Porphyria Centre (NAPOS), as eligible for treatment. Clinicians NoMA has been in contact with states that there are 46 patients in Norway of which 4 are children. This implies that there are about 37-42 patients in Norway that may be eligible for treatment with afamelanotide. NoMA has used the mean of 39.5 for further calculations.

Its prevalence in Europe ranges between 1:75,000 in The Netherlands, Northern Ireland and Slovenia (Went & Klasen, 1984, Todd et al., 1990, Marko et al., 2007) and 1:150,000 in Great Britain (Holme et al, 2006). Prevalence in Norway corresponds to a ratio of 1:75 000. This suggests that less than one new incident per year in Norway (approx 60 000 births each year). NoMA has assumed 0.5 new patients each year in further calculations.

5.2 COST ESTIMATION

For budget impact calculation, NoMA has assumed 3 implants each year, cf Chapter 3.2. Thus, the yearly cost associated with afamelanotide treatment is approx. 520 000 NOK including VAT (based on PSP public prices).

5.3 BUDGET IMPACT

Clinuvel expects that the uptake the first year will be [redacted] of the population, and [redacted] of the population in subsequent years. The expected budget impact of adopting afamelanotide, estimated from Clinuvel, is presented in the table below.

Table 9 Expected budget impact in MNOK

	2019	2020	2021	2022	2023
Total drug costs if afamelanotide is adopted (Clinuvel's market share assumptions) (if 100% uptake)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total drug costs without adoption of afamelanotide (current situation)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
The budget impact of recommending adoption (Clinuvel's market share assumptions) (if 100% uptake)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6 DISCUSSION

Afamelanotide (Scenesse) is an orphan medicinal product in the treatment of EPP and was approved for market authorisation by EMA under *exceptional circumstances*. This implies that the EMA (3) has accepted that the "applicant can show that he is unable to provide comprehensive data on the efficacy and safety under normal conditions of use".

While the objective of the EMA assessment is to assess whether the benefit exceeds the risk of the treatment, the objective of the NoMA HTA assessment is to assess the benefit of the treatment in relation to the costs, considering the severity of the disease. This implies that we need to assess the *relative effect size*, rather than whether or not there exist an effect. In some cases, other data than assessed by EMA might be emphasized.

The pivotal study CUV039, as well as studies CUV029 and CUV030, did not unequivocally show efficacy, but shows a positive trend favouring the efficacy of Scenesse. The effect size appears to be small.

NoMA acknowledges the challenge related to designing suitable clinical trials in EPP. The conditioned behaviour of the patients (avoiding light since childhood) and the disease characteristic prodromal phase, makes the patients reluctant to expose themselves to light sources during clinical trials. In all 5 clinical trials of various designs it has proven impossible to accurately record the increased clinical freedom and loss of risk aversion reported by the majority of patients and physicians.

The testimonies from patients and clinical experts suggest that the benefits may be greater than those seen in trials, and that even small improvements would be of great importance to them. However, the results of the trials also show that placebo has a remarkable effect on the disease. This suggests that one should interpret any argument of incremental effect with caution.

According to the pivotal trial, treatment with afamelanotide brings a median of 9.5 minutes (mean 18 minutes) of prolonged sun exposure per day. Whether this improves the quality of life for the patients is of concern. Measured with validated intruments of health related quality of life, treatment with afamelanotide does not seem to affect the quality of life of patients compared to placebo. Clinuvel has argued that these instruments do not capture the unique characteristics of EPP. The validated instruments include dimensions that Clinuvel argues to be important to describe the burden of EPP on patients, such as questions regarding emotional and social functioning, bodily pain and vitality.

The price of afamelanotide is the major cost of the intervention. The yearly cost of afamelanotide incl administration costs is about 520 000 NOK incl. VAT. This equals approx. 2900 NOK per day for 9.5 incremental minutes exposed in the sun.

7 CONCLUSION

NoMA considers that the submitted documentation insufficient to establish a reliable ICER. NoMA acknowledges the challenge related to designing suitable clinical trials in EPP. The testimonies from patients and clinical experts suggest that the benefits may be greater than those seen in trials. The relative effect size, however, is not transferable to QALYs, but is measured in increased duration of light exposure per day without pain (9 or 18 minutes per day). The HRQoL measured by validated instruments did not show any advantage of afamelanotide over placebo.

NoMA has to evaluate the pharmaceutical against the three prioritisation criteria; the benefit criterion, the resource criterion and the severity criterion. The priority-setting criteria are to be evaluated together and weighed against each other. A cost-effectiveness ratio must be calculated which reflects the use of resources in relation to benefit. This is to be done using a health economic analysis, by means of a health economic evaluation, typically involving decision analytic modelling. The cost-effectiveness ratio will be weighed against the severity of the relevant condition/disease.

In this evaluation, the relative efficacy is unclear, and is not expressed in QALYs. Given the Company's reluctance to describe the QoL of patients with EPP in QALYs, an ICER is not established. Using DALYs, Clinuvel presents an ICER of 2.9 million NOK per DALY averted. NoMA does not consider that cost effectiveness is documented for afamelanotide.

Table 10 Summary of health benefit, costs and severity in this STA

Priority criterion		Result	Comments
Relative efficacy (No. of hours in direct sunlight between 10 a.m. and 3 p.m. without pain after 9 months)	Afamelanotide Placebo	6.0 h (median) – 20.4 h (mean) 0.8 h (median) -5.6 h (mean)	From study CUV029 reported in Langendonk et al (18)
(No. of hours in direct sunlight between 10 a.m. and 6 p.m. without pain after 6 months)	Afamelanotide Placebo	69.4 h (median) – 115.6 h (mean) 40.8 h (mean) – 60.6 h (mean)	From study CUV039 reported in EPAR (1) and Langendonk et al (18)
Incremental cost per patient per year	Afamelanotide	415 000 NOK	Ex. VAT
Severity (absolute shortfall)		11 QALYs lost – high severity	Based on DLQI mapped to EQ-5D performed by NICE

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APPENDIX 1 SEVERITY AND SHORTFALL

NoMA has measured severity of EPP using the absolute shortfall method. The absolute shortfall is the amount of Quality adjusted life years of EPP patients lost due to the disease compared to the general population in Norway. This is measured by subtracting the lifelong prognosis for EPP patients from the number of QALYs for the general population.

NoMA has used the QALY-measures from the NICE assessment of afamelanotide, as presented below.

Proportion of patiens from Holme et al (20)	**EQ-5d[1]**
3.41 %	0.8679
8.52 %	0.8091
18.18 %	0.7209
52.27 %	0.5739
17.61 %	0.3779

[1]mapped by NICE using regression by Currie and Conway(21).

These numbers give a weighted QALY-average for EPP patients of 0,596.

The mean age in the model is 38. The Norwegian population of 38 years olds has approx. 45 expected life years left. This corresponds to 36.3 expected QALYs left. The mean QALY weight for the 38 year old general population is 0.85.

This gives a prognosis in the first year of approx. 0.25 and a proportion shortfall of 29.9%. The lifetime prognosis for a 38 years old person is 25.4 QALYs.

Absolute shortfall calculations

Age	38
QALY general population	36.3
Prognosis	25.3
Absolute shortfall	11

Prognisis calculations		
Age	QALY Weight overall population	QALY Weight EPP
38	0,85	0,596
39	0,85	0,596
40	0,85	0,596
41	0,85	0,596
42	0,85	0,596
43	0,85	0,596
44	0,85	0,596
45	0,82	0,57496471
46	0,82	0,57496471
47	0,82	0,57496471
48	0,82	0,57496471
49	0,82	0,57496471
50	0,82	0,57496471
51	0,82	0,57496471
52	0,82	0,57496471
53	0,82	0,57496471
54	0,82	0,57496471
55	0,80	0,56094118
56	0,80	0,56094118
57	0,80	0,56094118
58	0,80	0,56094118
59	0,80	0,56094118
60	0,80	0,56094118
61	0,80	0,56094118
62	0,80	0,56094118
63	0,80	0,56094118
64	0,80	0,56094118
65	0,80	0,56094118
66	0,80	0,56094118
67	0,80	0,56094118
68	0,80	0,56094118
69	0,80	0,56094118
70	0,80	0,56094118
71	0,80	0,56094118
72	0,80	0,56094118
73	0,80	0,56094118
74	0,76	0,53289412
75	0,76	0,53289412
76	0,76	0,53289412
77	0,76	0,53289412
78	0,76	0,53289412
79	0,76	0,53289412
80	0,76	0,53289412
81	0,76	0,53289412
82	0,76	0,53289412
	Sum Prognosis	25,3755765

ATTACHMENT 1 COMMENTS FROM COMPANY (ATTACHED SEPARATELY)