EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 October 2014
EMA/CHMP/709396/2014 Rev.1
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

SCENESSE

International non-proprietary name: afamelanotide

Procedure No. EMEA/H/C/002548/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Administrative information

Name of the medicinal product:	Scenesse
Applicant:	Clinuvel (UK) Limited c/o Reed Smith Broadgate Tower, Third Floor 20 Primrose Street London EC2A 2RS United Kingdom
Active substance:	afamelanotide
International Nonproprietary Name/Common Name:	afamelanotide
Pharmaco-therapeutic group (ATC Code):	Emollients and protectives (D02BB02)
Therapeutic indication:	prevention of phototoxicity in adult patients with erythropoietic protoporphyria (EPP)
Pharmaceutical form:	Implant
Strength:	16 mg
Route of administration:	Subcutaneous use
Packaging:	vial (glass)
Package size:	1 vial

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List of abbreviations

ACTH	adrenocorticotrophic hormone
AGRP	agouti-related protein
ASMF	active substance master file
ASP	agouti signalling protein
α-MSH	alpha-melanocyte stimulating hormone (melanotropin)
cAMP	3'-5'-cyclic adenosine monophosphate
CNS	central nervous system
EEG	electroencephalogram
EPP	erythropoietic protoporphyria
ERA	environmental risk assessment
F	female
FFA	free fatty acids
FTIR	Fourier transform infrared spectroscopy
GC	gas chromatography
GD	gestation day
GPC	gel permeation chromatography
HPA	Hypothalamic-Pituitary-Adrenal axis
HPLC	high performance liquid chromatography
ICH	International Conference of Harmonization
IL	intermediary lobe
ip	intraperitoneal
KF	Karl Fischer
LH	Lister Hooded (rat strain)
M	male
MC1-R	melanocortin 1 receptor
MCV	mean cell volume
MED	minimal erythema dose
MTD	maximum tolerated dose
MS/MS	tandem mass spectrometry
MPCE	micronucleated polychromatic erythrocytes
NCE	normochromatic erythrocytes

NMR nuclear magnetic resonance

NZW New Zealand White

PEC predicted environmental concentration

PCE polychromatic erythrocytes

Ph. Eur. European Pharmacopoeia

PK pharmacokinetics

PLG poly(DL-lactide-co-glycolide)

POMC pro-opiomelanocortin

po *per os*

RH relative humidity

sc subcutaneous

SD Sprague Dawley (rat strain)

SmPC summary of product characteristics

TK toxicokinetics

UVR ultra violet radiation

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Clinuvel (UK) Limited submitted on 3 February 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for SCENESSE, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 14 April 2011.

Scenesse, was designated as an orphan medicinal product EU/3/08/541 on 8 May 2008 in the following indication: Treatment of erythropoietic protoporphyria.

The applicant applied for the following indication: prevention of phototoxicity in adult patients with erythropoietic protoporphyria (EPP).

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Scenesse as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website: ema.europa.eu/Find medicine/Rare disease designations.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that afamelanotide was to be considered as a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/292/2011 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/292/2011 was not yet completed as some measures were deferred. A waiver was granted for all subsets of the paediatric population from birth to less than 2 years of age and a deferral for the completion of the paediatric investigational plan by June 2022 for paediatric patients from 2 years to less than 18 years of age (EMEA-000737-PIP01-09).

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's requests for consideration

Marketing Authorisation under exceptional circumstances

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 ;

The applicant proposed two specific obligations in relation with article 14(8) of Regulation (EC) No 726/2004 by establishing a disease registry and a long-term safety study.

New active Substance status

The applicant requested the active substance afamelanotide contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Protocol Assistance

The applicant received Protocol Assistance from the CHMP on 22 October 2009. The Protocol Assistance pertained to quality, non-clinical and clinical aspects of the dossier. With respect to the pharmaceutical and preclinical development the recommendations given in the advice were in principle followed.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer responsible for batch release

Penn Pharmaceutical Services Ltd
23-24 Tafarnaubach Industrial Estate
Tredegar, Gwent NP22 3AA
United Kingdom

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Harald Enzmann Co-Rapporteur: Robert James Hemmings

- The application was received by the EMA on 3 February 2012.
- The procedure started on 21 March 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 June 2012. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 8 June 2012.
- During the meeting on 19 July 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 20 July 2012.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 January 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 25 February 2013.
- During the meeting on 5 March 2013 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC RMP advice and assessment overview.
- During the CHMP meeting on 21 March 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The two inspection reports of the inspections carried out at the following site(s): Clinuvel AG between 27 and 30 May 2013 for the first inspection, and at two clinical investigator sites and the CRO CPR Pharma between February and March 2014 for the second inspection, were issued on 14 June 2013 and 20 May 2014, respectively.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 3 January 2014, including data from an additional clinical study.
- During the CHMP meeting on 23 January 2014, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- During a meeting of an ad-hoc expert group on 29 April 2014, experts were convened to address questions raised by the CHMP.
- The applicant submitted the responses to the CHMP list of outstanding issues on 4 July 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of outstanding issues to all CHMP members on 2 September 2014.
- During the meeting on 11 September 2014 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC RMP advice and assessment overview.
- During the CHMP meeting on 23 September 2014, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the CHMP meeting on 25 September 2014, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.

- The applicant submitted the responses to the CHMP list of outstanding issues on 6 October 2014.
- During the meeting on 9 October 2014 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC RMP advice and assessment overview.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of outstanding issues to all CHMP members on 15 October 2014.
- During the meeting on 23 October 2014, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation under exceptional circumstances to Scenesse.

2. Scientific discussion

2.1. Introduction

Problem statement

Porphyrias are acquired or genetic disorders of the haem biosynthetic pathway. The result of impairment in enzyme function is the accumulation of haem precursors in liver and bone marrow. Haem, an iron-containing pigment, is an essential cofactor of numerous haemoproteins. Virtually all cells of the human body require and synthesize haem. However, most haem is synthesized in the bone marrow (by erythroblasts and reticulocytes) and is incorporated into haemoglobin. The liver is the second most active site of haem synthesis, most of which is incorporated into cytochrome P-450 enzymes. Haem synthesis requires 8 enzymes. These enzymes produce and transform molecular species called porphyrins (and their precursors); accumulation of these substances causes the clinical manifestations of the porphyrias.

Eight porphyrias are described in the medical literature, each associated with a deficiency along the enzymatic pathway of the haem biosynthesis (see Figure 1). The main clinical manifestations of the accumulation of porphyrins are cutaneous photosensitivity, neurological dysfunction and hepatobiliary disease. Photosensitivity may be one or the predominant clinical manifestation in the cutaneous porphyrias.

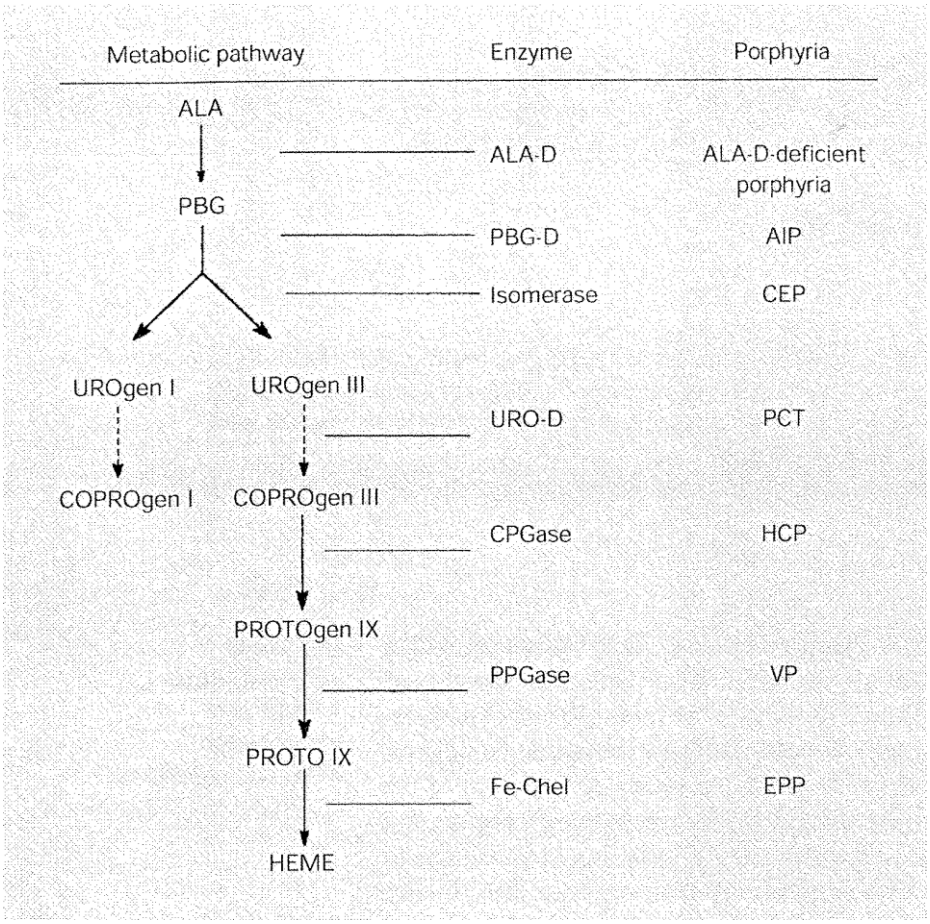


Figure 1: Haem biosynthetic pathway and list of porphyrias associated with each enzymatic deficiency (from (Afonso et al., 1999))

Erythropoietic protoporphyria (EPP) is a rare autosomal cutaneous porphyria that results from a partial deficiency of ferrochelatase, an enzyme of the terminal haem biosynthetic pathway.

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. (Allo et al., 2013).

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.

Its predominant characteristics include cutaneous phototoxicity to visible light from early infancy. Repeated phototoxic episodes may result in thickening and scarring of the skin, especially on the back of the hands, nose and forehead.

EPP is a multisystem disease; cutaneous, also contribute to disease severity and impact on quality of life, in addition to the haematological signs.

Diagnosis

The clinical diagnosis of EPP is established by abnormally high levels of free erythrocyte protoporphyrin (FEP), accompanied by detection of protoporphyrin in stool, and plasma porphyrin fluorescence. No increased porphyrins are found in the urine of EPP patients (Murphy, 2003).

EPP presents with prodromal symptoms of itching and tingling. With prolonged exposure with acute photosensitivity with erythema, oedema, and a painful burning sensation, very similar to sunburn. In some individuals it only requires between 1 and 30 minutes of exposure to sunlight.

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).* Males and females are equally affected. The estimated number of persons affected by the condition in the Community when the application was made was less than 5 in 10000 and is estimated to be less than 0.2 in 10,000.

The rarity of the disease can lead to delayed diagnosis. Behavioural patterns, such as avoidance of light sources, sunlight and the pain resulting from exposure to sunlight, are usually the first indicators for a clinical diagnosis, especially in children (Murphy, 2003). Due to the rarity of the disease, many patients are only diagnosed correctly as adults after having experienced symptoms for many years (Holme et al., 2006).

Pathophysiology and management of the condition

Photoreactive symptoms usually first present in early childhood, often with the clinically relevant, season-dependent, light-induced pain. In the most severe cases an absolute intolerance to sun-exposure is observed, with intolerable burning pain on exposed skin. Effects include:

(i) tingling, pruritus;

(ii) painful burning (immediate or delayed);

(iii) loco-regional edema and erythema;

Pain typically lasts for about three days, but symptoms may persist for up to four weeks (Holme et al., 2006).

Management of EPP is life-long and based mainly on the avoidance of bright light and sun exposure and wearing sun protective clothing. Current supportive care involves the use of analgesics, anti-histamines, topical corticosteroids and cold compress.

The lack of consistent genotype-phenotype correlation in EPP suggests a contribution to clinical phenotype from other factors, such as environment, patients' photoprotective behaviour and genes. EPP patients are severely limited in their outdoor activities, and develop a photoprotective behaviour with a marked negative impact on quality of life. The resulting limitation of social activities frequently has psychosocial consequences for patients (Thunell et al., 2000). A study conducted in the United Kingdom reported that – for instance – two thirds of EPP patients suffered from sleeping problems and irritability.

Patients' reported photosensitivity can depend apart from the visible light intensity, also on environmental factors such as temperature and wind.

Furthermore, the low exposure to sunlight is often related to vitamin D deficiency (Faurschou et al., 2012). Low bone mass and vitamin insufficiency and deficiency are a frequent finding in EPP patients (Allo e al., 2013).

Approximately 5%-20% of patients with EPP develop liver manifestations. Retention of protoporphyrin in the liver is associated with cholestatic phenomena and oxidative stress that predisposes to hepatobiliary

disease of varying degrees of severity, such as cholelithiasis, mild parenchymal liver disease, and in less than 5% of the EPP-patients progressive hepatocellular disease with end-stage liver disease and acute liver failure. Liver damage is the major disease-associated risk in EPP patients, so surveillance and frequent clinical and biochemical liver follow-up is mandatory (Casanova-Gonzalez et al., 2010).

Currently, the main treatment measure is photoprotection with mineral sunscreens containing zinc oxide or titanium dioxide and with protective clothes and sunglasses, and, of course, avoidance of exposure to bright light.

Medical treatment options with limited efficacy include oral beta-carotene and cysteine. Narrow-band UVB is also effective in attenuating symptoms of EPP in patients who can stand exposure to sunlight. In addition, improvement after red cell exchange/transfusions has been reported.

As EPP is connected with uniquely 'painful' socially disabling and in the long run for some patients potentially life-threatening phenotypic manifestations and no authorised medicinal products exists for EPP, there is currently a clear unmet medical need for treatment of patients with EPP.

About the product

Afamelanotide is a synthetic analogue of the physiologically occurring α-melanocyte stimulating hormone (α-MSH or melanotropin), which stimulates tyrosinase, the rate-limiting enzyme in eumelanin biosynthesis (Abdel Malek et al., 1985). Afamelanotide is considered a first-in-class 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 skin and its intended action is to protect against phototoxic reactions caused by sunlight.

Afamelanotide is a tridecapeptide that differs from α-MSH by substitution of the amino acids methionine and L-phenylalanine at positions 4 and 7 with norleucine and D-phenylalanine, respectively. These amino acid substitutions result in a significantly increased half-life and a 10-1000 times greater potency than the natural hormone, depending upon the bioassay employed (Abdel Malek et al., 1985; Hadley and Haskell-Luevano, 1999). Afamelanotide is formulated in a biodegradable implant for subcutaneous administration.

Afamelanotide stimulates melanogenesis. In healthy subjects α-MSH is produced on exposure to sunlight and mediates the synthesis of eumelanin, the natural black-brown pigment in the skin[1] (Abdel-Malek et al., 1999). α-MSH binds to the G-protein coupled melanocortin-1 receptor (MC1R) on melanocytes and activates cellular targets through the cAMP signalling pathway (Figure 2). As a result of this activation, melanin synthesis and formation of eumelanosomes is increased. Additionally, formation of dendritic cellular processes is increased in melanocytes; these cellular processes transfer melanin-containing granules to epidermal keratinocytes. The organelles eumelanosomes form supranuclear caps in melanocytes and keratinocytes that shield nuclei from irradiation and DNA damage. Melanogenesis is further enhanced by the mitogenic effect of α-MSH on melanocytes (Abdel-Malek et al., 1999).

[1] Note: any reference to melanin within this document is a reference to eumelanin, the black-brown pigment.

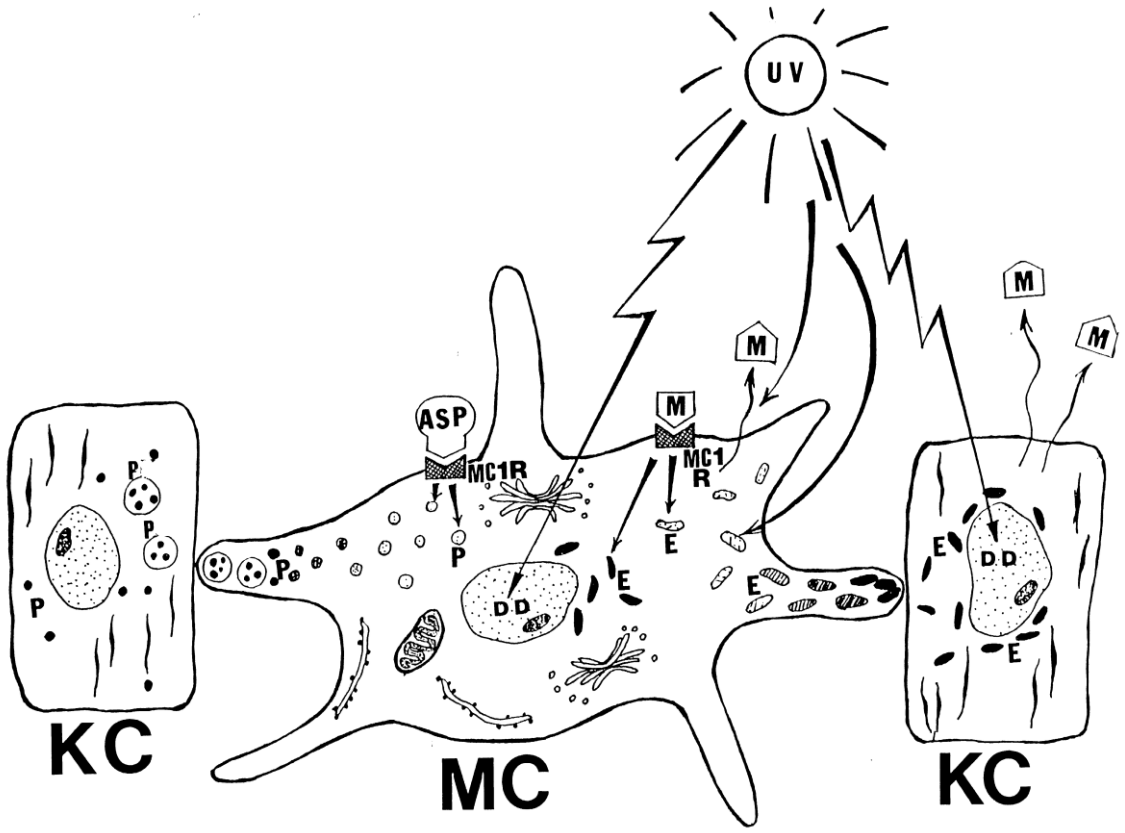


Figure 2: Melanogenesis (taken from (Abdel-Malek et al., 1999)

MC1R expressed on normal human epidermal melanocytes is the binding site for α-MSH, adrenocorticotrophic hormone (ACTH), and Agouti signaling protein (ASP). Activation of MC1R by α-MSH (M) or ACTH binding results in stimulation of eumelanin synthesis, increased eumelanosome (E) formation in melanocytes (MC), and enhanced transfer of eumelanosomes to keratinocytes (KC). Binding of ASP to MC1R inhibits eumelanin synthesis and induces pheomelanin synthesis in pheomelanosomes (P). Irradiation with UVR results in DNA damage (DD) and in increased synthesis of α-MSH and ACTH by melanocytes and keratinocytes. These hormones upregulate the expression of MC1R mRNA and possibly enhance the responsiveness to melanocortins

The pharmacological action of afamelanotide is more prolonged than that of α-MSH as demonstrated by sustained maximal tyrosinase stimulation in a cultured mouse cell line assay (Abdel Malek et al., 1985). This results in part from afamelanotide's resistance to degradation by serum or proteolytic enzymes.

Administration of afamelanotide to humans results in increased production of eumelanin in the skin (Barnetson et al., 2006; Dorr et al., 2004; Levine et al., 1999; Levine et al., 1991; study report CUV010), independently of exposure to sunlight or UV light.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a sterile controlled release implant for subcutaneous administration containing 16 mg of afamelanotide as active substance.

Other ingredients are: poly(DL-lactide-co-glycolide).

The implants are solid white to off-white sterile rods of approximately 1.7 cm in length and 1.5 mm in diameter. The implant core comprises the drug substance admixed with a poly(DL-lactide-co-glycolide) bioresorbable copolymer (PLG).

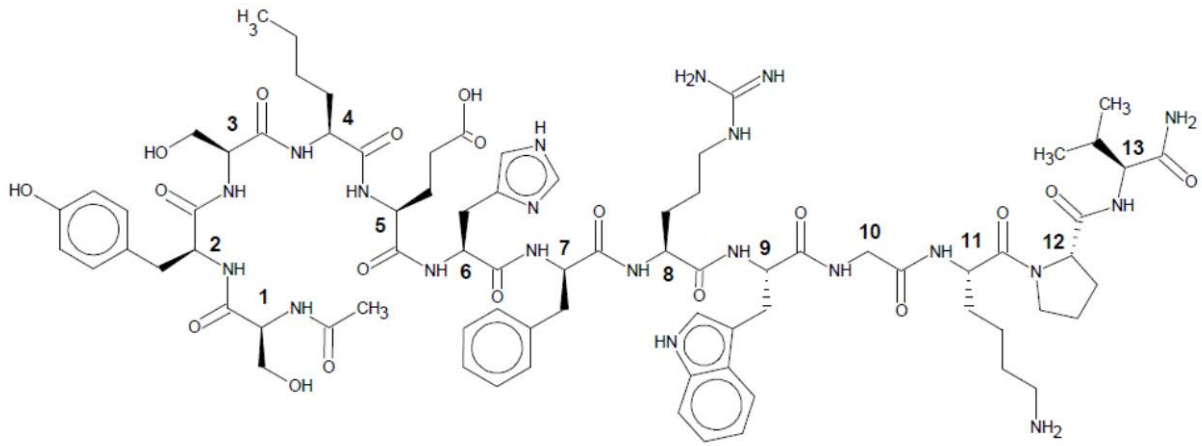
The product is available in type I amber glass vial sealed with a rubber stopper.

2.2.2. Active substance

Afamelanotide is a synthetic structural analogue of α-melanocyte stimulating hormone (α-MSH or melanotropin).

The chemical name of afamelanotide is N-acetyl-L-serinyl-L-tyrosyl-L-seryl-L-norleucyl-L-glutamyl-L-histidinyl-D-phenylalanyl-L-arginyl-L-tryptophanyl-glycyl- L-lysyl-L-prolyl-L-valinamide and has the following structure:

Ac-Ser	Tyr	Ser	Nle	Glu	His	D-Phe	Arg	Trp	Gly	Lys	Pro	Val-NH_2
1	2	3	4	5	6	7	8	9	10	11	12	13



Afamelanotide is also called [Nle4, D-Phe7]-α-melanocyte stimulating hormone (NDP-MSH).

The chemical structure of afamelanotide has been adequately demonstrated by amino acid analysis by GC-MS, sequencing by MS/MS, enantiomeric purity by chiral GC-MS and nuclear magnetic resonance (NMR) spectroscopy: 1D ^{1}H NMR, two-dimensional Correlation Spectroscopy proton Nuclear Magnetic Resonance (2D-COSY ^{1}H NMR), 2D Heteronuclear Single Quantum Correlation (HSQC) ^{1}H-^{13}C NMR and 2D Heteronuclear Multiple Bond Correlation (HMBC) ^{1}H-^{13}C NMR.

The active substance is a white to off-white hygroscopic amorphous powder. It is freely soluble in water, 1% acetic acid and methanol, slightly to very slightly soluble in ethanol, and practically insoluble in acetonitrile and 1-octanol.

Afamelanotide drug substance is a peptide which contains 11-L amino acids, one D-phenylalanine and one glycine. The theoretical stereochemistry of afamelanotide has been confirmed by chiral gas chromatography-mass spectrometry.

The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure.

Manufacture

Afamelanotide is synthesized as an acetate salt by one manufacturer via a solution phase peptide synthesis using commercially available well-defined starting materials with acceptable specifications.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The enantiomeric purity of afamelanotide is controlled by the synthetic strategy which has been optimised by selection of the fragments' coupling and protective groups least likely to racemise, and the selection of coupling reagents and conditions which minimise the chance to form a racemic mixture.

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Specification

The active substance specification includes tests for appearance, identity (MS, HPLC), purity (HPLC), related substances (HPLC), assay (HPLC), mass balance, water content (KF), acetate content (IC-HPLC), optical rotation (polarimetry), residual organic solvents (GC), palladium content (ICP-MS), bacterial endotoxins (Ph. Eur.) and bioburden (Ph. Eur.).

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Batch analysis data on five pilot scale and five commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on six production scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 60 months under long term conditions at -25 ±7 ºC and for up to 12 months under accelerated conditions at 2-8 ºC. Further studies were conducted under the storage conditions of 25 ºC / 60% RH and 40 ºC / 75% RH for up to 12 months in order to obtain information on the stability and degradation patterns of the drug substance under stress conditions.

The following parameters were tested: appearance, assay, peptide purity, related substances, water content, acetate content. The analytical methods used were the same as for release testing and were stability indicating.

In addition, supportive stability data on two pilot scale batches stored for 36 months at -25 ±7 ºC has been provided. These batches were manufactured with a slightly different process than the one proposed for marketing, but the differences are not expected to impact the quality of the drug substance.

The drug substance was shown to be stable at -25 ºC during the period tested. At +5 ºC a slight increase in water content was observed without major degradation of the peptide. The observed changes under further stress conditions were a change in appearance at 40 ºC; a decrease in peptide content, purity and acetate content, and an increase in water content at 25 ºC and 40 ºC.

Photostability testing following the ICH guideline Q1B was performed on one batch showing that afamelanotide is susceptible to light at 25±2 ºC and 60 ± 5% RH. However, the drug substance storage conditions at - 25 ±7 ºC in darkness preclude an impact on afamelanotide quality.

The stability results indicate that the drug substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.2.3. Finished medicinal product

Pharmaceutical development

The aim of the pharmaceutical development was to obtain an afamelanotide formulation for parenteral administration in order to overcome the limited oral bioavailability of peptides. Different dosage forms were investigated. An aqueous injectable formulation (16 mg /mL afamelanotide in 0.9% phosphate buffered saline) was used in the first clinical studies. However, this formulation was not considered to be commercially viable and the development of a biodegradable and biocompatible subcutaneous implant capable to modulate the release of afamelanotide over a defined number of days was further investigated.

Polylactide (PLA) and poly(lactide-co-glycolide) (PLG) were selected as excipients of choice for formulating afamelanotide implants because they are well characterised biodegradable polymers which are used in other commercially available implants and sustained delivery products approved in the EU. After injection in the body PLG degrades by hydrolysis into the monomers glycolic and lactic acid, which are metabolized mostly as carbon dioxide and water and to a lesser extent excreted by the kidney. Thus, these polymers are fully resorbable and the implant core does not need to be surgically removed once the drug supply is depleted.

Early formulation studies were based on laboratory scale implant batches complemented by a series of pharmacokinetic studies with pharmacodynamics endpoints (melanin density measurements) in order to investigate how the in vivo release of the implant (plasma levels and duration of exposure) correlates to its pharmacodynamic effect.

Particle size distribution and density studies of the drug substance and the polymers were performed during process validation. The results from these studies suggest that no control of these parameters will be needed in the future. However, due to the limited data available at the time of opinion, the applicant will continue to monitor these parameters post-approval at least on five additional batches of drug substance and polymer, and then re-assess the need to continue monitoring these parameters.

Different amounts of drug to polymer ratios were investigated and different implant strengths were used until a drug product which achieved the desired pharmacodynamic properties was obtained. Development studies also focused on the reduction of the implant diameter to enable delivery through a needle.

In order to optimize the rate of release of the drug substance from the implant on the basis of pharmacokinetic modelling, the following parameters were evaluated: polymer type, polymer length (MW) or inherent viscosity, and implant surface treatment. The polymer was selected since it enabled the desired afamelanotide release profile and provided acceptable biodegradation characteristic for the final implant, compatible with the proposed dosing regimen (one implant every 60 days). Several surface treatment options were studied during formulation development to avoid dose-dumping while ensuring prolonged release of the drug substance over the required time period. From these studies, the optimal method of implant manufacture to avoid dose dumping while still enabling quantitative release within the desired period was selected.

All excipients are well known pharmaceutical ingredients. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

Ethyl acetate, used during the implant manufacturing process, meets the requirements of the corresponding Ph. Eur. monograph.

The proposed specifications for the non-compendial excipients, poly(DL-lactide-co-glycolide) polymers, used for the implant manufacture are considered acceptable. However, due to the limited data available at the time of opinion, the applicant has committed to add a specification for glass transition temperature (Ph. Eur.) for each polymer post-approval on the basis of data from the next five batches of each polymer.

The compatibility of afamelanotide and the excipients selected for the manufacture of the implant have been investigated. The drug substance decomposes above 167°C and is therefore compatible with the temperatures used during extrusion.

The test for content uniformity of the bulk blend was removed during pharmaceutical development and replaced by bulk density. However, homogeneity has been re-established as in-process control.

The primary packaging is Type I amber glass vial sealed with a rubber stopper. The material complies with Ph.Eur. requirements. The method of administration as described in the SmPC would allow the use of an unspecified 14G catheter and a suitable device for administration of the implant. The proposed container closure system initially represented a major objection since it could hinder the maintenance of the aseptic conditions in clinical practice and the risk of damage of the implants during the proposed administration cannot be excluded. However, this risk is adequately managed since it is intended that the drug product will be administered in certified centres only by expert physicians having successfully completed a Clinuvel mediated education and training program. This is further addressed by appropriate statements that have been included in the SmPC and the package leaflet. Furthermore, appropriate training will be provided to the user, as described in the risk management plan. Nevertheless the applicant is recommended to develop a custom-made device for use with Scenesse which would enable direct injection of the implant at the site of administration.

The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Adventitious agents

No excipients derived from animal or human origin have been used.

Manufacture of the product

The manufacturing process is considered to be a non-standard manufacturing process. It comprises bulk mixing of the drug substance and the polymer, melt extrusion, surface treatment of extruded rods, drying, cutting of coated rods into individual implants, drying, packaging and terminal sterilisation (electron-Beam irradiation).

In general the extrusion process is considered state of the art. An on-line control of the diameter of the rods leaving the die by laser has been implemented.

Terminal sterilisation by e-beam irradiation (minimum dose of 25 kGy) was selected since according to the data presented it had a minor effect on the content of afamelanotide in the drug product than gamma irradiation. This was attributed to a shorter process cycle and lower heat.

Operational parameters and set points are provided for the critical manufacturing steps.

Major steps of the manufacturing process have been validated by a number of studies.

Overall it has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance, dimensions, assay (HPLC), identification (FTIR, HPLC), related substances (HPLC), content uniformity (Ph. Eur.), visual inspection of vials/crimps, *in vitro* release (HPLC), residual water (KF), molecular weight (GPC), residual solvents (GC), sterility (Ph. Eur.) and bacterial endotoxin (Ph. Eur.).

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Batch analysis results are provided for four production scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from five commercial batches of finished product stored for 36 months (two batches), 24 months (two batches) and 18 months (1 batch) under long term conditions at 2 - 8°C, and stability data of two commercial scale batches stored for up to 6 months under accelerated conditions at 25±2ºC/60%RH according to the ICH guidelines were provided. The batches of Scenesse are representative of those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, dimensions, container closure integrity, assay, related substances, water content, dissolution, residual solvents, molecular weight, bacterial endotoxins and sterility. The analytical procedures used are stability indicating.

All the stability data complied with the proposed specification and therefore support the proposed long term storage conditions.

Additionally, a short term stability study was conducted on one commercial scale batch to confirm that the drug product's stability is not affected by short term temperature excursions that could, for example, be encountered during transport. The results from this study confirm the stability of Scenesse for up to 7 days in the freezer (-20°C) and at room temperature (+25°C/60%RH).

In addition, one commercial batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The results demonstrated that the implants are stable to light in the proposed container closure system.

Based on available stability data, the shelf-life and storage conditions as stated in the SmPC are acceptable.

2.2.4. Discussion on chemical, and pharmaceutical aspects

The drug substance, the synthetic peptide afamelanotide, is a structural analogue of α-melanocyte stimulating hormone (α-MSH or melanotropin).

The finished product is a sterile biodegradable controlled release implant for subcutaneous administration. The implant is composed of afamelanotide homogenously dispersed in poly (DL-lactide-co-glycolide) polymer and the implant core is surface-treated to further control the drug release rate. It is extruded as a filament (1.5 mm diameter/1.7 cm length) that releases afamelanotide over a defined period allowing sustained drug levels to the target area and does not need to be removed since the copolymer dissolves and biodegrades mainly into carbon dioxide and water over time. The rate of release bears no relation to the duration of the pharmacodynamic activity which lasts 60 days.

The implant is packaged in Type I amber glass vials sealed with a rubber stopper. The proposed container closure system is acceptable for use under the conditions specified i.e. in certified centres by expert physicians having successfully completed a Clinuvel mediated education and training program. However, the applicant is recommended to develop a custom-made device for use with Scenesse which would enable direct injection of the implant at the site of administration.

The description and composition of the product have been properly documented. The pharmaceutical development of the drug product has been adequately and sufficiently described. The final sterilization by e-beam radiation has been adequately justified.

The method of manufacture is non-standard. Description of the manufacturing process, in-process controls, critical steps and their controls and methods applied are satisfactory. All critical in-process controls parameters are well established and justified.

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

-The applicant is recommended to develop a custom-made device for use with afamelanotide implant that would enable direct injection of the implant at the site of administration.

-The applicant is recommended to continue measuring the particle size distribution and density of both the polymer and the drug substance on at least five additional batches in order to further evaluate their impact on blend uniformity or other manufacturing parameters.

-The applicant is recommended to add a specification for glass transition temperature for the polymers on the basis of data from the next five batches of each polymer.

2.3. Non-clinical aspects

2.3.1. Introduction

2.3.2. Pharmacology

Afamelanotide is a synthetic analogue of the physiologically occurring α-melanocyte stimulating hormone (α-MSH or melanotropin). It is an agonist of the melanocortin 1 receptor (MC1-R) and mimics the pharmacological activity of des-acetyl-α-MSH by activating, via cyclic AMP (cAMP) production, the tyrosinase-mediated pathway stimulating the synthesis of eumelanin (melanogenesis).

There are many published studies relating to the potential secondary pharmacology of afamelanotide, which may be elicited by binding to the melanocortin receptors other than MC1-R. Possible neuroprotective, cardiovascular, anti-inflammatory and immunomodulatory properties have been described in the literature as well as effects on food intake and energy homeostasis. No dedicated safety pharmacology studies were conducted by the applicant, but relevant end points in the CNS, cardiovascular and respiratory systems were incorporated into the single and repeated-dose toxicity studies in mice, rats and dogs.

Primary pharmacodynamic studies

Afamelanotide has been developed to provide photoprotection to individuals with erythropoietic protoporphyria (EPP).

Afamelanotide is a synthetic analogue of α-melanocyte stimulating hormone (α-MSH or melanotropin) and has been developed to provide photoprotection to individuals with erythropoietic protoporphyria (EPP). It is a linear tridecapeptide that differs from α-MSH by substitution of the amino acids methionine and L-phenylalanine at positions 4 and 7 with norleucine and D-phenylalanine, respectively ([Nle4, D-Phe7]-α-MSH). It is an agonist of the melanocortin 1 receptor (MC1-R).

Background information on melanocortins and afamelanotide is available in published literature and was reviewed in detail. Some of this information is summarised below.

Alpha-melanocyte stimulating hormone is one of a family of biologically active peptides known as melanocortins, which are derived from a 31- to 36 kDa precursor peptide, pro-opiomelanocortin (POMC). The melanocortins also include β- and γ-MSH, lipotropins, endorphins and adreno-corticotrophic hormone (ACTH), and have been highly conserved through evolutionary development.

In most mammalian species, α-MSH originates from POMC in the pars intermedia of the anterior pituitary gland. In humans, the production of α-MSH appears to have a different mechanism that does not involve the central pathway along the Hypothalamic-Pituitary-Adrenal (HPA) axis, but a loco-regional effect involving melanocytes and adjacent keratinocytes in the skin.

Following UV and light irradiation of exposed skin, the melanocyte (autocrine) and keratinocyte (paracrine) release exclusively des-acetyl α-MSH in the affected dermal region. Des-acetyl α-MSH is the predominant form found in human skin and it binds to the melanocortin 1 receptor (MC1-R) expressed on the plasma membrane of the melanocyte. Subsequently, the melanocyte starts the cAMP-mediated process of loco-regional melanin pigment production (melanogenesis). Des-acetyl α-MSH is a relatively weak agonist at the human MC1-R receptor compared to the acetylated form.

Afamelanotide is an agonist of the MC1-R and exhibits its primary pharmacology by binding to this receptor and mimicking the activity of des-acetyl-α-MSH by activating the tyrosinase-mediated pathway stimulating melanogenesis (the synthesis of eumelanin).

Afamelanotide is more stable than α-MSH and has the capacity to stimulate tyrosinase for longer than the endogenous compound. Both the binding affinity for the MC1-R and the activity of adenylate cyclase (coupled to the MC1-R receptor) were greater for afamelanotide than for α-MSH.

Afamelanotide induces activation of follicular melanocytes when injected or applied topically to the skin of mice and also results in increased pigmentation when injected subcutaneously in humans. The melanogenic activity of afamelanotide has also been demonstrated in the skin of frogs, lizards, guinea pigs, dogs and miniature pigs.

Melanocortins act by the activation of G-protein coupled receptors and production of cyclic AMP (cAMP) via adenylate cyclase. Five melanocortin receptors have been identified (MC1-R, MC2-R, MC3-R, MC4-R and MC5-R), which differ in their tissue distribution and in their ability to recognise the various melanocortins and the physiological antagonists, agouti signalling protein (ASP) and agouti-related protein (AGRP).

MC1-R is the receptor for α-MSH on melanocytes and is predominantly present in the skin and has a key role in determining skin and hair pigmentation. It is also present in keratinocytes, fibroblasts and microvascular endothelial cells; it has the highest affinity for α-MSH (Gantz and Fong 2003). MC1-R has also been found in adrenals, leucocytes, lung, lymph node, ovary, testis, pituitary, placenta, spleen and uterus.

Whilst α-MSH originates from and is synthesised in the pars intermedia of the anterior pituitary gland in most mammalian species, findings in human experiments have demonstrated a significantly different POMC mechanism in man. For example, although the POMC is cleaved to both ACTH and α-MSH in the rat pituitary, POMC is processed to ACTH but not to α-MSH in the human pituitary. In humans, it appears that the physiological tanning response is elicited by a loco-regional mechanism involving melanocytes and adjacent keratinocytes and not by the central pathway along the Hypothalamic-Pituitary-Adrenal (HPA) axis. Nor is there any feedback mechanism that might lead to a positive increase of α-MSH at the hypothalamic or pituitary level. Following UV and light irradiation of exposed skin, the melanocyte (autocrine) and keratinocyte (paracrine) release exclusively des-acetyl α-MSH in the affected dermal region. Des-acetyl α-MSH is the predominant form found in human skin and it binds to the MC1-R expressed on the plasma membrane of the melanocyte. Subsequently, the melanocyte starts the cAMP mediated process of loco-regional melanogenesis (melanin pigment production). In clinical terms, the human skin melanises (tones, bronzes or tans) exclusively at the irradiated site while other un-irradiated parts of the dermis remain unaffected by melanin, hence the physiological dermal response is restricted to the loco-regional effect of emitted radiation (λ ranges from 280-650 nm).

The primary pharmacology of afamelanotide is expressed by binding to MC1-R (that is expressed predominantly in the skin in humans) and mimicking the activity of des-acetyl-α-MSH by activating the tyrosinase-mediated pathway stimulating the synthesis of eumelanin (melanogenesis).

Afamelanotide induces activation of follicular melanocytes when injected or applied topically to the skin of mice and also results in increased pigmentation when injected subcutaneously in humans. The melanogenic activity of afamelanotide has also been demonstrated in the skin of frogs, lizards, guinea pigs, dogs and miniature pigs. Increased pigmentation affecting both the epidermis and hair follicles is associated with preferential increases in photoprotective eumelanin versus inefficient epidermal phaeomelanin.

The pharmacological activity of afamelanotide was first investigated in the 1980s. It was shown to have a higher (10-1000 times) physiological activity and stability than α-MSH and to have the capacity to stimulate tyrosinase for longer than the endogenous compound. The activity of adenylate cyclase (coupled to the MC1-R receptor) was also considerably increased (Sawyer *et al*., 1980). Haskell-Luevano *et al*. (1994) also demonstrated that, whereas α-MSH has a binding IC_{50} value of 6.5 x 10^{-9} M for the human MC1 receptor and cAMP EC_{50} value of 2.0 x 10^{-9} M, afamelanotide possesses a binding IC_{50} of 1.2 x 10^{-9} M and a cAMP EC_{50} of 0.5 x 10^{-9} M, therefore the latter is more potent than the endogenous hormone.

Under physiological conditions, human epidermal melanocytes express a relatively low number of MC1-R but α-MSH and afamelanotide binding to human MC1-R results in prolonged stimulation of c-AMP signal transduction continuing for more than 24 hours. With afamelanotide the dissociation rate from the human epidermal MC1-R is two times slower than for physiological α-MSH (Haskell-Luevano *et al*., 1996) contributing to the prolonged PD activity of afamelanotide. Increased pigmentation affecting both the epidermis and hair follicles is associated with preferential increases in photoprotective eumelanin versus inefficient epidermal phaeomelanin.

In addition to the literature review, the applicant included some study reports on the pharmacodynamics of afamelanotide. These included a series of studies in hairless mice to investigate their suitability as a model (ept-0002, ept-0003, ept-0005) and a long-term study (43 weeks) in beagle dogs to evaluate the effects of afamelanotide implants on pigmentation and the reversibility, progression or delayed appearance of any observed afamelanotide-induced changes (Study 1822-002). The applicant also conducted a 26-week toxicity study with a 4-week recovery period in Lister Hooded (LH) Rats (Study 10/070-218P), which included measurement of the melanin content of the skin from one white and one pigmented area in animals at the end of treatment and at the end of recovery.

The series of studies in hairless mice to investigate their suitability as a model for tanning with afamelanotide are mentioned below.

Two strains of pigmented hairless mice, IP/PA and IB/BT were given daily subcutaneous (sc) injections of 40-50 µg of afamelanotide solution, approximately equivalent to a dose of 1.6-2.0mg/kg/day (Study **ept-0002**). During this period animals were also subjected to twice daily exposure for 3.5min to UV radiation (UVR). The IP/PA strain were given 12 injections of afamelanotide prior to 14 days of UVR exposure, whilst the IB/BT strain was exposed from Day 1 to 26 days of UVR, combined with 20 afamelanotide injections. The development of a tan was only observed in animals that received UVR, with or without afamelanotide. The IB/BT group developed erythema or 'sunburn', and developed more of a tan than IP/PA animals, according to the percentage change in luminosity (L) value and melanin density. Differences between the strains could be due to a number of factors, from genetics to experimental differences, but both strains produced melanin in response to UV radiation and the IP/PA strain may have been protected from the effects of UVR by pretreatment with afamelanotide.

Study **ept-0003** showed that subcutaneously implanted micro-osmotic pumps were an effective means of delivering afamelanotide to produce a tan that was deeper than that caused by UVR alone in pigmented hairless mice when delivered at a dose of ≥ 5.0µg/day + UVR.

In the third study (**ept-0005**), groups of IB/BT and IP/PA hairless pigmented mice and IP/PA albino mice were used to establish minimal erythema dose (MED) and investigate skin damage caused by UVR above the MED (thickening and peeling, and at higher levels [1080 mJ/cm2], mice were severely burnt with later scab formation).

Study **1822-002** was conducted in response to CHMP scientific advice and was carried out to investigate the long term effects of afamelanotide implant on skin pigmentation in dogs after 43 weeks and to evaluate the reversibility, progression or delayed appearance of any observed changes during a 120 day

post-treatment period. Beagle dogs (4/sex/group) were implanted with either placebo (D,L-lactide-co-glycolide, one implant) or afamelanotide (32mg, i.e. two implants) on days 0, 30, 60, 90, 120, 150, 180, 210, 240, 270 and 300 by subcutaneous injection in the lower abdomen, alternating left and right sides between dosing days.

Measured parameters were morbidity, mortality, injury, food and water consumption, clinical observations and body weight. Photographs were taken weekly to document changes in skin and hair colour. Biopsy samples were collected prior to dosing on Days 0, 60, 120, 180, 240, and 300, and during the recovery period on Days 330, 362, 390, and 420, and evaluated for pigmentation within melanocytes and keratinocytes. Animals were necropsied after the end of the recovery period. No test article-related macroscopic findings were noted.

There were no treatment-related changes in body weight during the study. Clinical signs were within normal variation and not considered to be treatment-related, with the exception of coat colour. Changes in hair colour were found in an increasing number of treated animals beginning at Week 6 (appeared in males first) and persisted until the end of the recovery period.

Regions that were originally populated with brown hair gradually turned to black or a brown black mix of hair. Regions that were originally populated with white and black hair maintained their original colour. Observations of an unkempt appearance were found in some treated animals beginning at Week 32 (appeared in females first). The unkempt hair was mainly in the brown and black hair regions, although also was noted to some extent in the white hair in the torso and neck. Excessive shedding appeared in the treated animals beginning at Week 26; this may have been a result of the roughened hair making the shedding more noticeable, compounded by seasonal coat shedding.

Histomorphometric measures of pigmentation in skin biopsies taken from white, brown, and black hair did not show substantial increases in pigment in treated animals, but did indicate a delay and/or attenuation in the cessation of melanin production due to seasonal coat shedding. Mean proportional pigment showed bimodal peaks for all three hair colours, with a decline beginning at Day 240 for both placebo and treated groups. The pigment reduction in both groups is likely related to seasonal rhythms of coat shedding. Seasonal shedding in canines generally corresponds with the telogen phase, or the resting phase, of the hair growth cycle. Melanogenesis ceases during catagen, the resting phase between anagen (active growth phase) and telogen, and is absent through telogen. The initiation of a decline in pigment with the clinical observations of excessive shedding and photographic documentation of shedding of many animals in the same time frame indicate that a seasonal rhythm may be responsible for the pigment decline. The animals' hair growth cycle is estimated to have entered telogen around or following the Day 180 biopsy (July 2010) and begun anagen just prior to or following the Day 240 biopsy (September 2010) (or later in the treatment group animals). Increasing proportional pigment areas following the decline may indicate an increasing number of hair follicles entering anagen, supporting the supposition of a seasonal rhythm.

While the placebo group animals did not present clinical observations of shedding, they underwent the same cyclical decline in pigment. As the study animals were all born in the same month, it is expected that they would all enter seasonal coat shed around the same time. The decline in pigment in the treated group appears to be attenuated and/or delayed over the placebo group, not reaching a nadir until Day 300 or Day 330. For both treatment and placebo groups, pigment mean proportional areas were generally higher in black hair than in either brown or white hair (exceptions were at Day 60, 240, and 330 for 32 mg), which was not unexpected.

In a 26-week toxicity study in Lister Hooded rats, an increased colour intensity was seen in pigmented skin areas in high dose animals (given 2 x 16 mg implants every month) compared with the placebo

group at the end of treatment, but was no longer apparent in the recovery animals. No pigmentation was present in white skin in either control or high dose animals at the end of treatment or recovery periods.

In addition to a literature review, four studies were reported, three of which used hairless mice to investigate their usefulness as a model for tanning effects of afamelanotide, establish a dosing regimen via a subcutaneously implanted micro-osmotic pump and to investigate a minimal erythema dose (MED). However this model was not developed further.

Study 1822-002 in dogs provided the main support for the use of afamelanotide in the requested indication. This was a chronic study in which dogs were administered subcutaneous implants of either placebo or afamelanotide (2 x 16 mg implants) every 30 days for 10 months. The only notable finding was that of a change in pigmentation at the hair follicle resulting in profound changes in hair colour hair from brown to black or brown/black in all treated animals, as well as roughening of the coat knap beginning 6 weeks after the start of dosing. These changes did not reverse over a 120-day recovery period.

Secondary pharmacodynamic studies

There are many published studies relating to the potential secondary pharmacology of afamelanotide, which may be elicited by binding to the melanocortin receptors other than MC1-R.

Five melanocortin receptors have been identified differing in their tissue distribution and in their ability to recognise the various melanocortins and physiological antagonists. MC1-R has been discussed above as it is the primary target for afamelanotide, but the other receptors, MC2-R, MC3-R, MC4-R and MC5-R, could give rise to secondary pharmacology and have been discussed in the applicant's written summaries and overviews.

MC2-R is the ACTH receptor and is mainly expressed in the zona fasciculata, the site of glucocorticoid production, and in the zona glomerulosa, the site of mineralocorticoid production in the adrenal cortex. MC2-R is expressed in adipocytes of various mammals, and mediates most of the lipolytic activity of ACTH. It differs from the other MCRs in that it is thought to bind only ACTH and has no affinity for α-, β-, and γ-MSH.

MC3-R is highly expressed in the hypothalamus, thalamus, hippocampus, anterior amygdala, and cortex. Its distribution sites suggest a role in regulating cardiovascular functions and thermoregulation, as well as in control of feeding behaviour. MC3-R is also expressed in the placenta, stomach, duodenum, and pancreas, and is detectable in the testis, ovary, mammary gland, skeletal muscle, and kidney.

MC4-R is widely expressed in the central nervous system, including the cortex, thalamus, hypothalamus and brain stem. The distribution of the receptor suggests its involvement in autonomic and neuroendocrine functions (energy homeostasis and sexual function).

The MC5-R gene has the most sequence homology to MC4-R and the least homology to MC2-R. It is similar to MC1-R and MC4-R in its ability to respond to all melanocortins, except γ-MSH. The order of potency of the melanocortins in activating MC5-R is α-MSH > ACTH = β-MSH > γ-MSH. MC5-R mRNA is expressed at high levels in the exocrine glands, such as lacrimal and Harderian glands. It is also expressed in skin tissues, particularly in sebaceous glands, and in skeletal muscles. Expression of MC5-R mRNA has been detected in mouse adipocytes but at a lower level than MC2-R mRNA (Abdel-Malek 2001).

Possible neuroprotective, cardiovascular, anti-inflammatory and immunomodulatory properties have been described in the literature as well as effects on food intake and energy homeostasis. For example, melanocortins and MSH analogues have effects on the sympathetic nervous system (Li 1996; Dunbar 2000) via MC3 and MC4 receptors, as antagonists of the receptors block the cardiovascular and

sympathetic responses. In addition, possible involvement of α-MSH and afamelanotide in oncogenesis has been discussed in some detail but no increased risk has been found.

Safety pharmacology programme

No dedicated safety pharmacology studies were conducted by the applicant. This is acceptable as relevant end points in the CNS, cardiovascular and respiratory systems were incorporated into the single and repeated dose toxicity studies in mice, rats and dogs. The results suggest that no adverse effects on these systems are likely at the proposed clinical dose.

Stand-alone safety pharmacology studies have not been conducted with afamelanotide along the lines of the ICH S7A – S7B guidelines. However, evaluation of the effects of afamelanotide on vital function of the central nervous, cardiovascular (including ECG and effects on the QT interval) and respiratory systems has been incorporated within the single and repeated-dose toxicology studies conducted throughout development. A functional battery of neurobehavioural screens was built into the repeated-dose toxicity studies in rats and dogs whilst blood pressure and ECG measurements formed part of the repeated-dose studies in dogs. Visual assessment of respiration was common to all single and repeated-dose toxicity studies.

Central nervous system (CNS)

Signs of reaction to treatment were monitored in rats, mice and rabbits given single subcutaneous doses of afamelanotide as high as 2000 mg/kg (for rats and mice, studies **1564/001** and, **1564/002** respectively) and 20 mg/kg (for rabbits, study **IMVS 12Nov2004**). Observations in mice included hunched posture, lethargy/ataxia and ptosis at 500 and 2000 mg/kg; lower doses were not examined in single dose toxicity studies. In rats, signs of reaction to treatment at 2000 mg/kg included hunched posture, lethargy, ataxia, decreased respiratory rate, laboured breathing, ptosis, and tip toe gait, all resolving within a few days of treatment. Additional signs included continuous excessive grooming, resolving within 60 minutes of dosing. At 500 mg/kg, there was no indication of systemic toxicity. Many of the signs described above in rats and mice may have been due to effects on the CNS at high doses but there was no indication of CNS toxicity at lower doses in these species.

Rabbits received α-MSH or afamelanotide at up to 20 mg/kg subcutaneously and all either died or were euthanased on humane grounds within 24 hours of treatment. The symptoms appeared to show evidence of a CNS-response (rapid increases in heart rate and respiration, evidence of vasodilatation and the appearance of being heavily sedated) and were generally noted within 0-60 minutes post-dose. Further investigation suggested rapid metabolic acidosis following MSH or afamelanotide had occurred. The study is discussed further under single dose toxicity. The rabbit appears to be an unsuitable animal model for evaluation of melanocortins.

Animal studies have confirmed that that there is minimal and limited ability of afamelanotide to cross the blood-brain barrier (Vaidyanathan and Zalutsky 1997), and the repeated dose studies, using lower doses than the 2000 mg/kg in the single dose studies, do not suggest a CNS effect.

In the 28 day subcutaneous toxicity study in rats, afamelanotide was given at up to 1.6 mg/kg/day (Study **ICPQN 283**). No untoward effects were observed in a functional observational test battery approach where the respiratory, circulatory, autonomic and central nervous systems were monitored with particular attention being paid to observation of tremor, convulsion, salivation, diarrhoea, lethargy, sleep and coma.

In the 90 day subcutaneous study in rats, afamelanotide was given at up to 80 mg/kg/day (Study **1564/003**). Functional observations and behavioural assessments consisting of detailed individual clinical observations performed approximately 2 hours post-dosing, and including the following

behavioural assessments: gait, tremors, twitches, convulsions, bizarre/abnormal/stereotypic behaviour, salivation, piloerection, exophthalmia, lacrimation, hypo/hyperthermia, skin colour, respiration, palpebral closure, urination, defecation, transfer arousal, and tail elevation, were made at monthly intervals. No abnormalities were detected.

A modified Irwin test consisting of a qualitative assessment of the grip strength and measurements of the landing foot splay and fore/hind grip strength was incorporated into a 26-week subcutaneous toxicity study in rats at 1, 3 and 6 months after the first implantation and, for the treatment-free animals, at the end of the recovery period (Study **10/070-218P**). No treatment-related effects were detected.

No abnormalities were detected in a neurological assessment (including mental status, posture, movement, erectogenesis, proprioceptive positioning, withdrawal reflex, muscle symmetry, pupil symmetry, eye movement, light reflex, blink reflex, menace reflex, jaw tone, and gag reflex) conducted weekly in dogs in a 28-day subcutaneous toxicity study at 15 mg/kg/day (Study **506609**).

In the 10-month subcutaneous toxicity study in dogs (Study **1822-001**), neurobehavioral examinations were conducted pretest and on Days 1, 61, 121, 181, 241, and 301. The observations included assessment of signs of autonomic function, general motor activity, gait, posture, neuromuscular function, response to handling, the presence of tonic and clonic movements, stereotypy, and bizarre behaviour. No abnormalities were detected.

Cardiovascular system

There was no effect on systolic, diastolic and mean arterial blood pressure in dogs given subcutaneous doses of 15 mg/kg/day for 28 days (Study **506609**).

In the 90 day dog study (**507361**), electrocardiogram tracings were taken from all animals on one occasion during the pre-trial period and then on Day 1 and during Week 13 of the study. Measurements were taken at the same time on each dosing occasion, equivalent to the pretrial time. ECGs were recorded for the standard limb lead (II). Recordings from the other standard limb leads (I and III) and the 3 augmented limb leads (aVL, aVR and aVF) were not obtained as no abnormalities were observed. The signals obtained from Lead II were evaluated and the interval data (P-R, QRS and Q-T waves), and heart rate derived. In addition, the R-R interval was determined from the heart rate to calculate the Q-Tc interval (corrected QT interval) as calculated using Fridericia's formula. There was no effect of treatment upon the electrocardiograms.

In the 10-month subcutaneous toxicity study in dogs (**1822-001**), ECG was monitored in the same manner pre-dose and 1 day post implant re-administration on Days 90, 180, and 270. Blood pressure was also monitored at the same time. There were no effects on ECG (particularly QT interval) or on systolic, diastolic or mean arterial blood pressure.

Respiratory system

Breathing was monitored visually in rats and mice in the single dose toxicity studies (**1564/001** and **1564/002**) following single subcutaneous doses of afamelanotide as high as 2000 mg/kg. No effects on breathing were seen in mice. In rats given 2000 mg/kg but not 500 mg/kg, decreased respiratory rate and laboured breathing were recorded. There were no signs of respiratory distress or other signs of compromised respiration during the 28 day and 90 day repeat-dose toxicity studies in rats and dogs or in the long-term studies in rats and dogs of 6 and 10 months duration respectively.

Pharmacodynamic drug interactions

The applicant has not conducted any non-clinical pharmacodynamic drug interaction studies, justifying

their absence because there are no particular groups of compounds that are likely to be commonly co-administered with afamelanotide to patients who are otherwise stated to be healthy. From a non-clinical perspective, this is acceptable.

2.3.3. Pharmacokinetics

Only absorption studies have been included in the dossier. These comprise single dose studies in rats and guinea pigs and repeated dose studies in rats and dogs using subcutaneous administration by injection, infusion or implant. A justification has been provided for the absence of studies on distribution, metabolism, excretion and pharmacokinetic drug interactions, this was accepted by the CHMP.

Analytical methods: The analytical methods used (Liquid Chromatography-Mass Spectrometry [LC-MS] or High Performance Liquid Chromatography [HPLC]/MS/MS) appear appropriate for measurement of afamelanotide in plasma from Sprague Dawley rats and Beagle dogs. The calibration range was from 2.00 to 500 ng/mL for rats and 2.50 to 500 ng/mL for dogs. The accuracy of the method was between 94 to 112% for SD rat plasma and between 97 to 107% for Beagle dogs with a precision of 101.2 to 109.7% for rats and 102.0 to 108.0% for dogs.

In a 26-week rat study in Lister Hooded rats (10/070-218p), the assay failed and further investigation revealed that afamelanotide is unstable in Lister Hooded rat plasma under the conditions tested (thawed at room temperature for 24 hours (RT 24 hr), thawed and stored at 4°C for 24 hours (4C 24hr) and put through 3 freeze thaw cycles), whilst it is stable in Sprague Dawley rat plasma under each of these conditions. The rate of instability was similar between male and female Lister Hooded plasma and was independent of concentration. Results were therefore reported as either “detected” or “not detected”.

Afamelanotide appeared to be stable in dog plasma under similar conditions as tested for rat plasma (RT 24 hr, RT 24 hr then 4°C for 5 days and put through 3 freeze thaw cycles).

Absorption: Initial pharmacokinetic studies used aqueous solutions of afamelanotide but to avoid repeated daily dosing, subcutaneous implants were developed. Most of the absorption studies submitted were carried out to investigate the suitability of the implant characteristics and different formulations were used. These studies did not always provide useful pharmacokinetic data.

A preliminary study of afamelanotide implants in Sprague Dawley rats showed release of afamelanotide appeared to follow first-order kinetics, with peak plasma concentrations measured at the first post-dose time point (Day 2). The mean plasma concentrations decreased to below 50% and 10% of their maximum values by Days 5 and 11, respectively, but afamelanotide was still quantifiable in a number of samples after 3 weeks. Other studies investigated the effects of different implant dimensions and formulations on release characteristics. Later studies in rats using implants closer to the final formulation showed a bimodal release pattern in some animals. Initial mean plasma peak concentrations were seen at 24h post-implantation, declining to generally below LOQ after a few days. In those rats showing bimodal release, the second peaks occurred after several weeks. An additional study was carried out to characterise the second peak but there were insufficient time points to do so fully. A further study using more time points in the initial phase showed rapid release, with levels no longer quantifiable by day 7.

A series of investigations with different implant formulations in hairless guinea pigs showed peak afamelanotide levels within a few days of implantation with levels unquantifiable 1 to 3 weeks after implantation, depending on the study.

In a 14-day PK study in guinea pigs, peak concentrations were seen 24 hours after a 16mg implant was administered, with levels undetectable by day 7 in most animals. The AUC values in this study were 481

and 377 ng.mL/day for the 16mg and 2x10mg implant groups, respectively, according to the study report (PC0106).

Following daily sc injection of afamelanotide at 0.16mg/kg/day for 10 days to dogs, peak concentrations were similar on days 1 and 10 (50-60 ng/mL) and were seen at the first time point (0.5 hours). Plasma levels were not detectable by 4 hours post-dose, showing rapid absorption and elimination following sc injection in this species.

Distribution: The applicant has not conducted any distribution studies with afamelanotide, but distribution studies in mice and rats have been published. In CD1 mice, the highest levels of radioactivity one hour after a subcutaneous dose of radiolabelled afamelanotide were found in urine, small intestine, liver and kidney. Levels in the brain ranged from 0.2 to 0.4% and only 0.05 to 0.07% was distributed into the eye.

In another study, afamelanotide labelled with ^{18}F or ^{125}I was administered intravenously to BALB/c (albino) mice and animals were killed at 1 and 4 hours post-dose. High levels of both labels were found in the urine obtained at necropsy. The kidney also had the highest level after 1 hour.

In pigmented mice administered intravenous[^{125}I]-afamelanotide, specific binding was seen in the Harderian and lacrimal glands, bladder, brown adipose tissue, preputial glands, duodenum and submandibular glands, with relatively low, but specific, uptake also observed in the skin, spleen, adrenal glands, pancreas, hypothalamus and white adipose tissue. A similar pattern was generally seen in albino (SD) rats, with specific uptake observed in preputial, clitoral, thyroid, Harderian and lacrimal glands and in pancreas, duodenum, spleen, hypothalamus and white adipose tissue. However, in contrast to results obtained in pigmented mice, specific uptake of tracer was not observed in the skin, brown adipose tissue or bladder of the albino rat. Uterus and retina did not exhibit specific uptake of tracer.

From these studies it would appear that radioactivity is eliminated rapidly via the urine in albino mice and that afamelanotide (or its metabolites) is distributed the tissues in which melanocortin receptors have been reported (for example, Harderian and lacrimal glands and adipose tissue). However, distribution to the brain was very low in these studies.

Metabolism: The absence of metabolism studies was justified by reference to ICH guidance S6, the principles of which may also be applicable to chemically synthesised peptides. This justification can be accepted as afamelanotide would be expected to be hydrolysed to individual amino acids as for other peptides.

Excretion: Renal excretion appears to be a major elimination route in both mice and rats. There may also be some biliary elimination in mice, but similar information does not appear to be available for rats.

Pharmacokinetic interactions: No nonclinical studies of PK drug interactions have been conducted by the applicant.

2.3.4. Toxicology

Single dose toxicity

Afamelanotide appeared to be of relatively low acute toxicity in mice, rats and guinea pigs when administered subcutaneously. A subcutaneous dose of 2000 mg/kg in both mice and rats did not cause any deaths; clinical signs were noted and lasted for several days. Irritation, scabbing and swelling at the injection site also at the lower dose of 500mg/kg prevented a NOAEL being established. Male hairless guinea pigs tolerated a 20 mg subcutaneous implant well, with only mild inflammation evident by changes

in white blood cells. These guinea pigs also showed a darkening in colour, reflecting the intended pharmacological effect of afamelanotide.

In contrast to the findings in mice, rats and guinea pigs, the rabbit is extremely sensitive to the effects of afamelanotide and α-MSH, with single doses as low as 0.05 mg/kg resulting in death or euthanasia. Previous work in this area and a study conducted with afamelanotide and α-MSH in NZW and Semi-Lop rabbits suggested that the physiology of the rabbit is uniquely responsive to melanocortins, possibly via effects on the sympathetic nervous system, pituitary and pancreas, resulting in major biochemical, respiratory and haemodynamic effects. This therefore has implications for the conduct of reproductive toxicity studies in rabbits.

Repeat dose toxicity

Studies of appropriate duration have been conducted in rats and dogs to support the proposed use of afamelanotide in the requested indication. In all the rat studies, findings in the Harderian gland (not fully reversible in those studies in which recovery groups were included) were observed and injection site reactions were seen with daily sc injection for 90 days. Liver weight was increased in females, along with an increase in AST, at the high dose of 20mg/kg/day in the 90-day study. In the 26-week study in Lister Hooded rats, a reversible increase in colour was noted in the pigmented skin areas.

In the dog studies, the pharmacological effect of afamelanotide was seen, with darkening of skin beneath pigmented areas, darkening of brown hair to black or brown/black and follicular hyperpigmentation /hyperplasia at the implant site. Decreased body weight or decreased body weight gain were noted in 28-day and 13-week studies, respectively, and in the 10-month study urinary changes (decreased specific gravity and increased pH) were observed at the 6-month time point.

Inflammation seen at sites implanted with afamelanotide or placebo implants were similar and therefore was related to the implant polymer rather than afamelanotide. The more severe reactions seen in the 90-day rat study using daily subcutaneous injections are not relevant to the clinical dosage form.

The applicant discussed in some detail the changes in skin/hair colouring in pigmented species, liver changes in the rat, transient changes in urine parameters in the 10-month dog study that may be indicative of possible effects on renal function, reduced bodyweight in dogs and degeneration of the Harderian gland in the rat. These findings are also discussed below.

In the repeated-dose toxicity studies, afamelanotide-induced **changes in skin / hair colouring** were seen in pigmented species (the Lister Hooded rat and the Beagle dog).

In the LH rat, a mild increase in colour intensity in the pigmented skin areas was seen in high dose animals (32 mg implant per rat) when compared with controls, but this difference was not seen at the end of a 28-day recovery period. No pigmentation based on the melanin content was noted in the white skin area either in control or high dose animals at any time. No changes were seen in the studies involving albino SD rats.

In dogs, darkening of the skin was noted from Day 19 onwards below the non-white coloured areas of fur in a 28-day study at sc doses of 15 mg/kg/day. There was hyperpigmentation in the epidermal layer of the skin of the scrotum and vulva and/or ears of all animals. In the 13-week dog study, skin from the implant sites and ear of treated animals (20 and 100 mg implants) showed increased incidences of follicular pigmentation when compared with controls. Increased incidences of follicular hyperplasia of minimal to moderate severity were also observed at the implant sites of treated animals when compared with controls. The follicular pigmentation and hyperplasia, correlated with soft, dense, dark fur observed at necropsy. In the 10-month dog study involving treatment with implants at 16 and 32 mg per animal, changes in hair colour and coat appearance were seen in all afamelanotide treated groups. Regions that

were originally populated with brown hair gradually turned to black or a brown/black mix of hair. Regions that were originally populated with white and black hair maintained their original colour. After a 28-day recovery period, mild black hair discoloration was still present at 32 mg afamelanotide (the only treated group retained for the treatment-free period).

These findings can be attributed to the pharmacological activity of afamelanotide and are not considered a toxic effect.

Possible **hepatic effects** were suggested by a significant increase in AST in high dose (20 mg/kg/day) females in a 90-day study, which was accompanied by an increased liver weight. However there were no accompanying histopathological changes in the liver. In the 28-day rat toxicity using continuous sc administration, liver weights were lower in males at the high dose of approximately 1.6mg/kg/day than controls, but there were no other indications of an hepatic effect

In the dog 10-month study, there was a decrease in **urine specific gravity** and concurrent increases in **urine pH** in the mid and high dose groups (2 x 16 mg implants either bimonthly or monthly, respectively) at the 6 month interval relative to controls. These findings were not present at the end of the 10-month study, and there were no gross or histopathological changes in the kidney at necropsy. The toxicological significance of the findings at 6 months was therefore not clear. At the NOAEL (low dose, 1 x 16 mg implant bi-monthly), the Cmax in males was 5.3 ng/mL at day 300, and in females at this dose and time point was 6.8 ng/mL. This is about 1.5 to 2-fold the human Cmax.

Reductions in **bodyweight** were seen only in dog studies. For rats, if there was any effect it was generally increased weight gain rather than loss, but this was not consistent and only seen in the shorter-term studies.

Body weight loss was seen in the 28-day repeated dose dog study at a dose of 15 mg/kg/day. The male dogs lost between 0.5 and 0.7 kg, and the females lost between 0.6 and 1.1 kg. In the 13-week repeated-dose study in dogs, weight gain was unaffected in the group given 20 mg implants every 15 or 30 days and in the females given 100 mg implants every 15 days. The males in this latter group, however, showed a significant reduction in weight gain from Week 4 and, overall, weight gain was lower than the controls by 27%. In both of these studies food consumption was unaffected. In the 10-month study, however, there were no effects on bodyweight in either sex even at the highest dose of 32 mg monthly. The effects on body weight could well be due to secondary pharmacology of afamelanotide via stimulation of MC3-R and MC4-R subtypes, which have been shown to be involved in regulation of ingestion and energy expenditure. In rats, stimulation of MC3-R and MC4-R receptor subtypes has been shown to cause a reduction in food intake, whereas antagonism of MC3-R and MC4-R increases food intake. In macaques, infusion of afamelanotide into the lateral cerebral ventricle suppressed food intake without affecting other behaviours (Koegler *et al.*, 2001). The body weight reductions in dogs were seen at the highest doses used, although Cmax in males in the 13-week study at the dose at which the weight loss was seen (100mg) was 18.0ng/mL, which was 4.9-fold that in man (3.65 ng/mL, study CUV038). At the high dose in the 10-month study, at which no effect on weight was seen, the Cmax ratio compared with humans was 2.7- to 4.5-fold.

Findings in the **Harderian gland** were observed in all rat studies. In the 28-day study, inflammation of the epithelial lining of the acini in the Harderian glands was seen in two high dose females (0.4 mg afamelanotide/day by continuous diffusion from an osmotic mini-pump, an exposure totalling 11.2 mg per rat over the 28 day period, approximating to 1.6 mg/kg/day). In the 90-day rat toxicity study, again the only histopathological changes noted were increased numbers of animals with chronic inflammatory cell foci in the Harderian glands at the high dose in both sexes with reduced secretory activity in both sexes at all dose levels (0.2, 2 or 20 mg/kg/day administered by SC injection). In the 26-week study, minimal to mild tubular degeneration/atrophy and/or mononuclear cell infiltrate of the Harderian gland

was seen in 13/20 males and 18/20 females of the high dose group at the end of the treatment period. Minimal focal unilateral mononuclear cell infiltrate in the Harderian gland without signs of degeneration/atrophy was present in one control female. The low and mid dose groups were apparently not examined in this study. Tubular degeneration/atrophy of the Harderian gland was still evident in most of the high dose animals after a 28-day recovery period, but was classed as minimal rather than mild to minimal suggesting some small degree of reversibility. The high dose group were given 32 (2x16) mg implants each month for 6 months, averaging 64mg/kg. No effects were seen in the Harderian glands in the 10-month dog study, the only dog study in which they were examined, which could be a result of the dose used (about 3.2 mg/kg at the high dose) and lower exposure achieved compared with the rat studies.

MC5-R is found in Harderian glands and α-MSH is the most potent of the melanocortins at this receptor, therefore it is not unexpected that this gland would be targeted by afamelanotide. Specific binding of [^{125}I]-afamelanotide was noted in the Harderian glands of mice and rats in a published distribution study (Tatro and Reichlin, 1987). As the Harderian gland is not present in primates, this finding may not be of clinical relevance**.** The MC5R is found in skeletal muscle, adipose tissues, cerebrum, adrenal and stomach (Labbe O *et al.,* 1994). It is unclear whether MC5R is distributed evenly in all tissues and what the clinical relevance is of MC5R binding. As Chen et al reported that very little melanocortin crosses the blood-brain barrier (BBB), most effects if any are expected to take place outside the BBB.

Thody *et al* demonstrated that MC5R expression in skin indicating that α-MSH may influence hair lipid synthesis/secretion by its direct action in the skin in mice. It is unclear whether sebum production is regulated by MC5R in man. It is known that MC5R plays a role by the exocrine stimulation of the Harderian gland in rodents however.

It has also been hypothesized that non-selective melanocortins may increase the efficiency at the neuromuscular junction via a presynaptic receptor possibly the MC5R. This hypothesis is only tested in mice (Hughes S, 1994).

Overall, however, the repeated dose toxicity studies in rats and dogs are considered to cover adequately the intended clinical use of afamelanotide implants; the duration of the chronic studies (26 weeks in rats and 10 months in dogs) are in line with ICH M3 (R2) guidance (non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals, CPMP/ICH/286/95) and acceptable. The frequency of dosing (daily sc injections, continuous sc infusion or one or more implants changed every 15, 30 or 60 days) exceeds the recommended clinical frequency of 1 implant every 2 months. The findings from the toxicity studies have generally been discussed adequately by the applicant with reference to published literature, although further discussion of potential (human) secondary pharmacology is required.

Genotoxicity

Afamelanotide did not show genotoxic potential in a standard battery of genotoxicity studies.

Carcinogenicity

Carcinogenicity studies have not been conducted and the applicant has justified their omission by reference to appropriate guidance (ICH S1A [Guideline on the Need for Carcinogenicity Studies of Pharmaceuticals, 1995]). The negative genotoxicity studies, proposed pattern of use of the implants and nature of the active substance (synthetic peptide analogue of an endogenous compound) do not indicate a risk of carcinogenicity. In addition, information available in the literature also suggests a lack of carcinogenic potential and the absence of carcinogenicity studies can be accepted.

Reproduction Toxicity

Fertility: There were no effects on fertility or reproductive performance in Sprague Dawley rats at subcutaneous doses of up to 20mg/kg/day.

Embryo-foetal development: Afamelanotide showed no adverse effects on embryo-foetal development in a preliminary study in Sprague Dawley rats at sc doses up to 20 mg/kg/day when administered throughout the period of organogenesis. The pivotal study used the same doses as the preliminary study and similarly showed no effects on embryo-foetal development at doses up to 20 mg/kg/day. The possibility of using higher doses did not seem to be considered. No toxicokinetic data are available from pregnant Sprague Dawley rats, as samples taken in the preliminary study in this strain thawed out between shipment and receipt and were not analysed until a year after the termination of the study. There was no information on sample stability under these circumstances therefore the toxicokinetics for the study were not valid. Exposure (Cmax) at the high dose of 20 mg/kg/day was therefore extrapolated from the 90-day repeated dose study in SD rats (1564/003), which gave an exposure margin of 135-fold compared to that in man, based on mean Cmax in (non-pregnant) females on day 1. However, it is not known whether the kinetics would be different in pregnant compared with non-pregnant females.

A preliminary embryo-foetal development study in NZW rabbits was terminated early as the first animals to be dosed had to be killed in extremis within 4 to 5 hours of the first dose. This led to the non-GLP investigation into the effects of afamelanotide and of α-MSH in rabbits (imvs 12Nov2004). Rabbits were found to be extremely sensitive to the effects of afamelanotide and α-MSH and therefore were an unsuitable species for further study.

Following CHMP protocol assistance, a study in Lister Hooded rats was carried out to enable assessment of effects of the product on organogenesis at the dermal level in pigmented animals. Subcutaneous doses up to 20 mg/kg/day were administered during the period of organogenesis. There were no effects on the dams or on embryo-foetal parameters measured except a higher (2.78%) late embryonic death in the high dose group (compared with 0 in the control group. Values in the low- and mid-dose groups were 1.0 and 0%, respectively. This was considered by the applicant to be due to biological variability. Toxicokinetic analysis could not be conducted in this study as afamelanotide was found to be unstable in plasma from this strain of rat. Exposure of the dams was confirmed only by the detection of afamelanotide in plasma from the treated groups. It was not detected in plasma from the control group.

Although there were no findings of concern in the embryo-foetal developmental toxicity studies in SD or LH rats, it is possible that sufficiently high doses were not used. In addition, there are no TK data available for LH rats, nor for pregnant SD rats, and a second species (rabbit) could not be used due to the severe effects of afamelanotide in this species.

Pre- and post-natal development: There were no remarkable effects of treatment with afamelanotide when administered subcutaneously at doses up to 20 mg/kg/day to Sprague Dawley rats from day 6 of gestation, to the weaning of the pups. A pre-weaning lower body weight gain in the pups from dams dosed at the high dose of 20 mg/kg/day was no longer evident post-weaning and development of the F1 generation was no different from that of the control animals. The NOAEL was therefore 20 mg/kg/day for both the F0 and F1 generations.

Toxicokinetic data

Toxicokinetics: Exposure margins (based on Cmax) at the NOAELs in the 28-day and 90-day rat studies were 295- and 25-fold that in man (3.65 ng/mL in volunteers, from study CUV038).

In the 90-day study in rats, all dose groups showed substantially higher Cmax and AUC at Day 90 than had been seen at Day 1, so elimination appeared to be more prolonged at the end of the study. In view of the

rapid plasma clearance of afamelanotide, the applicant suggests that this change cannot be explained as a consequence of bioaccumulation, but that the difference is sufficiently marked to suggest some difference in the mechanism by which afamelanotide is handled, in rats, following single or repeated administration.

In the 26-week study in Lister Hooded rats (10/070-218p), no TK data were obtained as afamelanotide was found to be unstable in plasma from this strain. Consequently, afamelanotide was reported as 'detected' or 'not detected' rather than specific values and thus exposure margins cannot be calculated on the basis of systemic exposure in this study. At the high dose (2x16mg implants/month, averaging a dose of 64mg/kg/month to rats weighing 500g), the administered dose is 280-fold that in man on a mg/kg basis (1x16 mg implant for a 70kg human).

Exposure margins (based on Cmax) at the NOAELs in the 21-day, 13-week and 10-month dog studies were about 7.6-fold, 1.5-fold and 1.5- to 2-fold, respectively, that in man (3.65 ng/mL in volunteers, from study CUV038).

As limited time points were used in a number of these studies, the stated Cmax values may not be the true Cmax values and thus margins between human Cmax and the animal species may be greater.

However the studies showed that afamelanotide was released rapidly from the implants, beginning within 8 hours of administration, and that the release was controlled over a number of days, with a similar release profile following repeated doses.

Local Tolerance

Local tolerance has been addressed in the single and repeated dose toxicity studies. Single subcutaneous injections of afamelanotide at doses of 500 and 2000 mg/kg in mice and rats produced local irritation at the injection site (persistent hardened scabbing and swollen or blue/black coloured injection site). However, there were generally few signs of irritancy when afamelanotide was administered by subcutaneous infusion or implant, as opposed to subcutaneous injection. Inflammation was seen around the afamelanotide implant site but was also seen with placebo implants and therefore was associated with the polymer used for the implant rather than afamelanotide. The afamelanotide implant shows acceptable local tolerance.

Other toxicity studies

Antigenicity, immunotoxicity and dependence: There were no indications from the toxicity studies conducted that afamelanotide would be antigenic, immunotoxic or induce dependence and therefore it is acceptable that these aspects have not been studied specifically.

Impurities: A change in analytical methodology with improved detection was largely responsible for the 'identification' of a number of impurities that prompted the conduct of the four qualification studies.

A lyophilised extract of afamelanotide implants (batch FL351, containing a total of 4.21% impurities) was negative in bacterial reverse mutation and *in vivo* mouse micronucleus studies.

A 28-day rat study did not reveal additional toxicity to that seen in other repeated dose rat studies, although it is noted that the Harderian gland was not examined in this study. The certificate of analysis of the batch used (FL320) states results for total impurities as RRT 1.06=0.5%, which seems particularly pure for use in a study to qualify impurities.

As for the rat study, the 21-day dog study did not reveal additional toxicity to that seen in other repeated-dose dog studies. The implant batch used in this study contained 15 individual impurities, identified only by relative retention time (RRT), with a total impurity content of 5.28%.

The drug product specification for total impurities is ≤ 5.0% and only one qualification study used a batch with higher total impurities than this. However, it was reported that further investigations revealed that the impurities were found retrospectively in previous batches used in non-clinical and clinical studies and as such did not represent new impurities. The qualification studies showed similar results to those conducted previously. In addition, the chronic toxicity studies that were subsequently performed in rats and dogs were stated to use the new drug product formulation and therefore supersede these short-term studies. Again, the findings were similar to those in the shorter studies. Therefore although the qualification studies did not clearly qualify individual impurities at specific levels, the overall package of non-clinical studies can be considered satisfactory to support the total impurity limit of ≤5.0%.

2.3.5. Ecotoxicity / environmental risk assessment

The applicant provided an ERA according to the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00, June 2006). In Phase I the action limit is not exceeded and no detailed assessment in phase II is necessary.

In response to the request on a study on log K_{OW} for the PBT-screening, the Applicant provided experimentally determined values of log Kow at different pH ranges of afamelanotide (OECD 107) that are below the PBT screening value of log Kow 4.5.

Afamelanotide is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

Afamelanotide is a synthetic analogue of α-melanocyte stimulating hormone (α-MSH or melanotropin), which is one of a family of melanocortins that are derived from a precursor peptide, pro-opiomelanocortin (POMC). Binding of des-acetyl α-MSH (the predominant form of α-MSH found in human skin) at the melanocortin 1 receptor (MC1-R), which is mainly expressed on the plasma membrane of the melanocyte, starts the cAMP-mediated process of melanin pigment production (melanogenesis). Afamelanotide is an agonist of the melanocortin 1 receptor (MC1-R), but is more potent at the receptor and is more stable than the endogenous peptide. The desired effect in the requested indication is the production of protective eumelanin.

The intended primary pharmacology of afamelanotide has been outlined based on a discussion of published literature and supported by a 43-week study in dogs.

Afamelanotide induces activation of follicular melanocytes when injected or applied topically to the skin of mice and also results in increased pigmentation when injected subcutaneously in humans. The melanogenic activity of afamelanotide has also been demonstrated in the skin of frogs, lizards, guinea pigs, dogs and miniature pigs.

Published studies as well as those conducted by the applicant demonstrate that afamelanotide is active at the level of epidermal pigmentation although the findings vary between species.

In the 43-week dog study, afamelanotide produced a change in pigmentation at the hair follicle resulting in profound changes in hair colour from brown to black or brown/black in all treated animals, as well as roughening of the coat knap. Afamelanotide implants also caused an increased colour intensity in pigmented skin areas of Lister hooded rats. No pigmentation was present in white skin in either control or high dose animals at the end of treatment or recovery periods.

Potential secondary pharmacology of afamelanotide may be elicited by binding to the melanocortin receptors other than MC1-R. These differ in their tissue distribution and in their ability to recognise the various melanocortins.

Possible neuroprotective, cardiovascular, anti-inflammatory and immunomodulatory properties have been described in the literature as well as effects on food intake and energy homeostasis. The potential effects are therefore wide ranging. The published studies have used various routes of administration and ranges of doses. The applicant has argued that the route of administration, formulation, dose and dosing frequency should be considered when interpreting the results of these published studies and that their relevance to the current formulation is minimal given the low, intermittent dose of the afamelanotide implant.

This does seem a pertinent argument given that, for example, studies eliciting CNS effects have sometimes used intracerebroventricular administration, thus avoiding the blood:brain barrier.

Thus potential unspecific secondary pharmacological effects and/or clinical adverse effects of afamelanotide cannot to be linked to unspecific receptor binding and/or interference of affinity to specific functional molecules.

However, the applicant has discussed the findings from the toxicity studies adequately in the application dossier, and thus the lack of conventional secondary *in vitro* (human) molecular pharmacological data are not considered absolutely essential with respect to the safety assessment.

The absence of dedicated safety pharmacology studies is acceptable as relevant end points in the CNS, cardiovascular and respiratory systems have been incorporated into the single and repeated dose toxicity studies in mice, rats and dogs. The results suggest that no adverse effects on these systems are likely at the proposed clinical dose.

Regarding pharmacokinetics, only absorption studies were submitted, comprising single dose studies in rats and guinea pigs and repeated dose studies in rats and dogs using subcutaneous administration by injection, infusion or implant. The release characteristics of afamelanotide from different implant formulations were investigated in these studies. Justification was provided for the absence of studies on distribution, metabolism, excretion and pharmacokinetic drug interactions, this was accepted by the CHMP.

Pharmacokinetic data are not available for Lister Hooded rats as afamelanotide was found to be unstable in plasma from this rat strain. The instability of afamelanotide in the plasma of LH rats was clearly confirmed, but no conclusive explanation for the noted instability and observed inter-strain differences in Sprague Dawley, Lister Hooded and Long Evans rats is possible.

Afamelanotide appeared to be of relatively low acute toxicity in mice, rats and guinea pigs when administered subcutaneously. Male hairless guinea pigs tolerated a 20 mg subcutaneous implant well, and also showed a darkening in colour, reflecting the intended pharmacological effect of afamelanotide. In contrast, the rabbit is extremely sensitive to the effects of afamelanotide and α-MSH, possibly via effects on the sympathetic nervous system, pituitary and pancreas, resulting in major biochemical, respiratory and haemodynamic effects.

Repeated-dose studies of appropriate duration have been conducted in rats and dogs to support the proposed use of afamelanotide in the requested indication. In all the rat studies, there were findings in the Harderian gland. The Labbe paper (Labbe O *et al.,* 1994) mentions the presence of MC5R in skin, adrenal gland, skeletal muscle, bone marrow, spleen, thymus, gonads, uterus and brain, but refers to mouse tissue rather than human tissues. It also states that organs where no expression of HGMP01B (mouse genomic clone coding for MC5R) could be found included the pituitary, lung, heart muscle, kidney, oesophagus, stomach, duodenum, jejunum, ileum, caecum, colon, pancreas, placenta, prostate and

seminal vesicle. Therefore, Labbe et al did not find MC5R in the stomach. If a similar distribution of MC5R occurs in man, it would be unlikely that some of the digestive tract reactions seen following administration of afamelanotide could be attributed to MC5R binding, as the receptor appears to be absent from the tissues of the GI tract. However Abdel-Malek did report in 2001 that although the functions of MC5R are not well understood, they were thought to include neuro/myotropic, gastric and anti-inflammatory effects and regulation of aldosterone secretion; therefore a possible gastric effect was reported subsequent to the publication of the Labbe paper. The animal data do not explain distribution of MC5R in man (there is more information published on melanocortin receptors in rodents), nor the possible consequences of afamelanotide binding to these receptors in man (which has not been formally studied). The findings in the Harderian gland are also likely to be related to the secondary pharmacology of afamelanotide as the MC5-R receptor is present in this organ and specific binding of [^{125}I]-afamelanotide was noted in the Harderian glands of mice and rats in a distribution study. The Harderian gland is not present in primates so this finding may not be of clinical relevance, but potential binding of afamelanotide to MC5-R in man has not been discussed (secondary pharmacology) and this omission should be addressed.

Increased liver weight and AST were seen in high dose female rats at the high dose in a 90-day study. In the absence of consistent findings throughout the toxicity studies (no hepatic findings in the 26-week rat study or in any dog studies), the applicant considered the findings were fortuitous and without bearing on the safety evaluation of afamelanotide. The CHMP agrees, given the high dose at which it was seen, is probably not of clinical significance; the systemic exposure (AUC and Cmax) in females at the NOAEL of 2mg/kg/day in the 90-day study was 61 ng.h/mL and 78.7 ng/mL, respectively. At the high dose at which the effect was seen, the AUC in females was 2549 ng.h/mL and the Cmax was 1098.9 ng/mL. There is consequently a large exposure margin compared with clinical exposure (AUC was 138.9 ng.h/mL and Cmax 3.65 ng/mL in study CUV038).

In the dog studies, the pharmacological effect of afamelanotide was seen, with darkening of skin beneath pigmented areas, darkening of brown hair to black or brown/black and follicular hyperpigmentation /hyperplasia at the implant site. Decreased body weight or decreased body weight gain were noted in 28-day and 13-week studies, respectively, and in the 10-month study urinary changes were observed at the 6-month time point.

The applicant discussed these findings in detail and generally none of them are considered likely to be of importance to safety in use of the implant as proposed. Skin darkening is indicative of the intended pharmacological effect of afamelanotide. The liver findings were in one species and sex at high dose and not accompanied by histopathological findings. The urinary findings in dog occurred at only one time point with no gross or histopathological changes in the kidney at necropsy. At the NOAEL in this study, the Cmax in dogs was about 1.5 to 2-fold the human Cmax.

Body weight changes in the dog may have been related to secondary pharmacology of afamelanotide via stimulation of MC3-R and MC4-R subtypes, although similar effects were not seen in the chronic dog study at similar systemic exposures (about 4.5- to 5-fold) to that in man.

The results from study PC0408 (one or two 10 mg implants administered on days 0 and 15) are considered to be more representative of the clinical situation and do not show an increase in the exposure to afamelanotide after the second dose compared with the first. The apparent bioaccumulation in the 90-day rat study is essentially attributed to inter-individual variability and the considerably higher doses given than those anticipated in man. Afamelanotide would be expected to be hydrolysed to smaller peptides and individual amino acids and its pharmacokinetic handling is unlikely to change with increasing dose. The rapid plasma clearance of afamelanotide suggests that the higher levels measured at the end of the 90-day study are more likely a result of variability than genuine bioaccumulation. Therefore,

although the response does not attempt to discuss the mechanism by which the handling of afamelanotide may differ following single or repeated doing in rats in terms of differences in metabolism, excretion, enzyme induction or transporters, the applicant presented a reasonable argument for the apparent increased exposure in the 90-day rat study.

Afamelanotide was not genotoxic, and the absence of carcinogenicity studies has been adequately justified.

The reproductive toxicity studies do not indicate an effect on fertility, embryo-foetal development or pre- and post-natal development in Sprague Dawley rats at sc doses up to 20 mg/kg/day. Rabbits could not be used as a second species due to their extreme sensitivity to afamelanotide and α-MSH An embryo-foetal study in Lister hooded rats also revealed no adverse effects on embryo-foetal development. It is possible that sufficiently high doses were not used in these studies**.** Reproductive toxicity studies performed have not shown any evidence of pre- or post-natal toxicity. The data are not considered sufficient at present to support the use of Scenesse during pregnancy this is reflected in section 4.6 of the SmPC.

The addition of protease inhibitors limited degradation of afamelanotide to some extent and the effect was more marked at refrigerated temperatures, however, considerable degradation was also noted in the presence of two different protease inhibitors in LH rat plasma samples.

The afamelanotide implant shows acceptable local tolerance. Qualification studies (*in vitro* genotoxicity and repeated-dose rat and dog studies) did not clearly qualify individual impurities at specific levels, but the overall package of non-clinical studies can be considered satisfactory to support the total impurity limit of ≤5.0%.

Afamelanotide is not expected to pose a risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

From a non-clinical point of view, despite the identified deficiencies in the preclinical afamelanotide development program, such as missing non-melanocortin receptor binding properties of afamelanotide, incomplete ADME in animals, and unresolved drug instability in a specific rat strain (LH rat), there are no major safety concerns from toxicological findings.

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, toxicity to reproduction and development, Animal studies have not shown any harmful effect on fertility and reproduction; this is highlighted in SmPC 4.6 and 5.3. There are no or limited amounts of data from the use of afamelanotide in pregnant women this is reflected in section 4.6 in the SmPC.

Women of childbearing potential have to use effective contraception during treatment with Scenesse and for a period of three months thereafter (see section 4.6).

Together with the available clinical data and the proposed clinical use only in EPP patients under close surveillance by trained physicians in the treatment of this condition, in specialised treatment centres, the missing information in reproductive toxicity is considered acceptable by the CHMP.

2.4. Clinical aspects

For this marketing authorisation application the Applicant submitted the clinical trials CUV029 and CUV030 as pivotal studies. In the course of the studies' assessment, a number of clinically relevant protocol deviations were observed and the CHMP triggered a GCP inspection that was done in 2013. As a

reply to address CHMP questions, the applicant submitted the clinical trial CUV039. This study then served as the sole pivotal study.

The formulation of the finished product is comprised of afamelanotide in a bioresorbable polylactide-co-glycolide implant core. This polymer is fully resorbed within 50 to 60 days after implantation. The implant core is also surface treated to further control the rate of release of afamelanotide. This formulation was selected from a number of candidate formulations on the basis of its in vivo release profile.

2.4.1. Introduction

(a) GCP inspections

Studies CUV029/CUV030

The triggers for the GCP inspection were based on the changes to the analysis plans of studies CUV029 and CUV030 and the lack of clarity regarding sample size. In study CUV030 the Company has applied post hoc changes to the Statistical Analysis Plan after the data had been analysed, which brought into question the validity of the efficacy results.

In total there were four critical, four major and five minor findings identified during the inspection.

The main areas of concern identified during the inspection were related to data handling by the sponsor, data management, and the statistical planning of the trials (Critical Findings 2 and 3, Major Findings 2, 3 and 4).

The main efficacy data of the trials CUV029 and CUV030 were not considered to be robust and it was recommended not to use them for the evaluation of the MAA by the Assessors for the following reasons:

1. Non-suitable design of the patient diary for capturing the data as needed for the analysis of endpoints related to duration of sun exposure

2. Change of the SAP after analysis of the data in CUV030, i.e. in knowledge of the data

3. Improper statistical planning for both trials

Improper data handling in both trials (by the sponsor and the CRO)

4. No-availability of the databases. Verification of their existence and of relevant events like database lock / unlock was not possible.

5. Storage and collection of the originals of the patient diaries as relevant source documents by the sponsor. Thus there was no proof possible whether the diary data entered into the database were identical with those collected at the sites. The overall conclusion of the GCP inspection was that GCP compliance could not be confirmed for those parts of the two trials which were inspected and that the main efficacy data were not valid and reliable.

Due to the GCP-noncompliance of studies CUV029 and CUV030 these studies could not be relied upon for the benefit-risk assessment of Scenesse. In reply to CHMP questions, the Applicant submitted the data of a third clinical trial (CUV039). A GCP inspection for study CUV039 was triggered by CHMP on 20 January 2014 and the timetable for evaluation was extended accordingly.

Study CUV039

The inspection was held at two clinical sites and at the CRO which was involved in the data handling/management of trial CUV039.

The actual impact of the findings from this inspection (major finding on adverse events reporting) was considered as low by the inspectors. Therefore, it was concluded that study CUV039 was performed in compliance with ICH GCP and that the data can be used for the clinical assessment.

2.4.2. Pharmacokinetics

The Applicant has provided eight studies which cover the development of the formulation (implant) with regards absorption and the plasma afamelanotide level profile.

Study **EP001** examined the absorption of an aqueous formulation of afamelanotide. It showed that as a subcutaneous injection it was rapidly absorbed and did not accumulate with repeated administration over 10 days. Large numbers of adverse events were recorded in the healthy subjects, mainly flushing, nausea and injection site problems and one subject withdrawing because of adverse events.

The aqueous formulation was not considered to be a viable dosage form because of the need for multiple daily subcutaneous injections. Therefore a subcutaneous implant formulation designed to release afamelanotide over a defined number of days was developed.

A dose-escalation study was conducted in 30 volunteers with implant dosages between 5 mg and 40 mg (**EP004**). Increases in melanin density were observed, especially at the 20 mg and 40 mg dose levels. The absolute increases exceeded those seen with the aqueous afamelanotide formulation despite the significantly lower doses used.

An evaluation of the relationship between afamelanotide plasma levels and changes in melanin density was undertaken and the results of this evaluation were used to target the ideal implant release profile and to assess candidate implant formulations.

In study **EP006**, the single dose PK and PD of the first candidate implant capable of being administered via a catheter needle containing 12 mg of afamelanotide in a polylactide core were investigated in six healthy volunteers. Afamelanotide was rapidly absorbed yielding a peak plasma approximately 1 hour after administration. Plasma levels fell to below the level of quantification after a few days.
From this study it has been inferred that the 12 mg implant formulation resulted in a slower, sustained release of afamelanotide than observed following the aqueous formulation. However, the plasma levels decreased quite quickly, indicating that the controlled release formulation was not yet optimised.

In study **CUV006** a new formulation containing afamelanotide in a bioresorbable polyactide-co-gycolide implant core was assessed. The tolerability and PK of two strengths, 16 mg and 20 mg, were evaluated in two study groups of six healthy male volunteers, each subject receiving a single implant.
After administration of the 16 mg implant all subjects had quantifiable plasma levels of afamelanotide until 72 hours, with all falling below the lower limit of quantitation after 216 hours the latest. The shape of the plasma concentration versus time profile suggests an initial burst of afamelanotide release from the implant, followed by a more sustained release phase lasting for several days in most subjects.

The plasma concentration versus time profile for the 20 mg implant was overall similar to that obtained for the 16 mg implant.

A total of 31 adverse events were reported during the conduct of the study, of which 18 were considered to have a causal relationship to the study treatments. All adverse events were mild or moderate in severity and no serious adverse events were reported.

Study **CUV007** was conducted to determine the PK and tolerance of a 10 mg formulation (polylactide-co-glycolide core) of a single afamelanotide implant in six healthy male volunteers. Administration of the 10 mg implant resulted in most subjects not having quantifiable levels of afamelanotide until 12-24 hours after administration.

In study **CUV009** ten healthy male volunteers were administered two doses of 16 mg afamelanotide implant (polylactide-co-glycolide core) given 28 days apart.

There was no significant difference in $AUC_{0\text{-last}}$, Cmax or t_{max} between the first (Day 0) 16 mg implant and the second (Day 28) 16 mg implant. The afamelanotide concentration then decreased to below the LOQ by 96 hours for nine and eight of the ten subjects following the first and second implants, respectively.

A total of 53 adverse events were reported during the conduct of the study. Benign pathology results from four significant visual changes in skin pigmentation were of minimal medical concern. No observable trends were noted in any of the safety assessments including physical examination of any skin abnormalities, and the one serious adverse event was not related to study treatment (football injury).

CUV028 was a single dose, open-label pharmacokinetic and pharmacodynamic study in 24 healthy male and female adult subjects, who were assigned to receive either a 16 mg afamelanotide implant from the earlier manufacturing process (Group 1) or a 16 mg afamelanotide implant from the final manufacturing process (Group 2). Both implant lots used the same formulation (poly-lactide-co-glycolide core). From the PK (and PD) results it was concluded that afamelanotide 16 mg bioresorbable implants produced by the final manufacturing process appear to be comparable to those manufactured using the previous process.

CUV038 was performed to confirm the single dose PK (and PD) of afamelanotide following administration of the final formulation of 16 mg afamelanotide implant to twelve healthy male volunteers.

For most subjects, the last measurable concentration was detected a number of days post dose (LOQ 0.025 ng/mL). There were no measurable levels after approximately 2 weeks post dose in any subjects.

In this study, treatment-emergent AEs (TEAEs) were reported for all 13 subjects (100%) with a total of 44 TEAEs. There were no deaths or other SAEs, and no subjects were withdrawn from the study due to AEs. AEs that were deemed to be (probably or possibly) related were reported by 11 subjects (85%) and included ephelides (sun spots, freckles) and melanocytic nevus (both probably related); lethargy, implant site erythema; implant site pain; hot flush; dizziness, and oral hypoesthesia (all possibly related).

Clearance and half-life values for the final formulation have not been reported but were calculated from estimated AUC values and dose information from studies CUV028 and CUV038
Calculated Clearance values (CL/F) are: 58.7 L/h from study CUV028 and 115.2L/h from CUV038. The blood sampling schedule was optimised following earlier studies and the CUV038 study provides the most representative pharmacokinetic data on the Scenesse implant. The actual derived clearance values for the CUV038 study were 1451 to 1457 mL/hr/kg. In addition the Applicant reported in his responses to the D180 LoOI that the clearance following the administration of the aqueous presentation of afamelanotide was 1650 to 1800 mL/hr/kg. These results are similar to those observed in the CUV038 study.

In summary, data on afamelanotide's clearance and half-life, distribution and metabolism are limited. The available data are mostly confined to healthy individuals. This was regarded acceptable from the CHMP.

Absorption

Bioavailability

Bioavailability of the subcutaneous implant has not been investigated in humans. Across study comparison in terms of AUC between the administration of the aqueous solution and the solid biodegradable implant has not been performed.

Bioequivalence

Investigation of bioequivalence was relevant in study CU028 where the influence of different manufacturing processes should be evaluated.

Distribution

No data or discussion available

Elimination

No data or discussion available

Dose proportionality and time dependencies

Study EP004 (Nov 2003 – Nov 2004) reports a dose escalation study in the dose range of 5 to 40 mg as biodegradable modified release implant using 6 subjects for each dose level. Two different formulations were used containing different amounts of excipients and API content (batch ML123 and ML134). Pharmacokinetic and pharmacodynamic (i.e. skin reflectance) results were generated.

It is reported that the majority of blood samples had afamelanotide plasma levels less than the LLOQ. Concentrations achieved with the revised formulation were lower than with the initial formulation.

Study CUV006 compared the 16 and 20 mg dose.

Mainly due to the limited sample sizes used in the studies but also due to other limitations (e.g. switching of formulations and sampling schedule) a clear conclusion on dose proportionality is not possible. But from the available data, dose proportionality between doses 10, 16 and 20 mg is questionable. The 16 mg dose strength has been chosen based on PD considerations.

Special populations

No studies were performed in special populations, this was regarded acceptable by the CHMP.

Pharmacokinetic interaction studies

The applicant has not conducted interaction studies and this was regarded acceptable from the CHMP.

2.4.3. Pharmacodynamics

Afamelanotide, a melanocortin-1 receptor agonist for which the mechanism of action is to stimulate the melanogenesis, resulting in enhanced levels of eumelanin in the dermis. The enhanced levels of eumelanin provide photoprotection by absorption and scattering of inbound light with eumelanin acting as a filter, and scavenging of free radicals and activated oxygen species.

A relationship between plasma levels of afamelanotide and increases of melanin density was determined. Plasma levels between a defined range and for a defined period was shown to be required for maximal impact on melanin levels. It was presumed that these are the levels at which all melanocortin 1 receptors

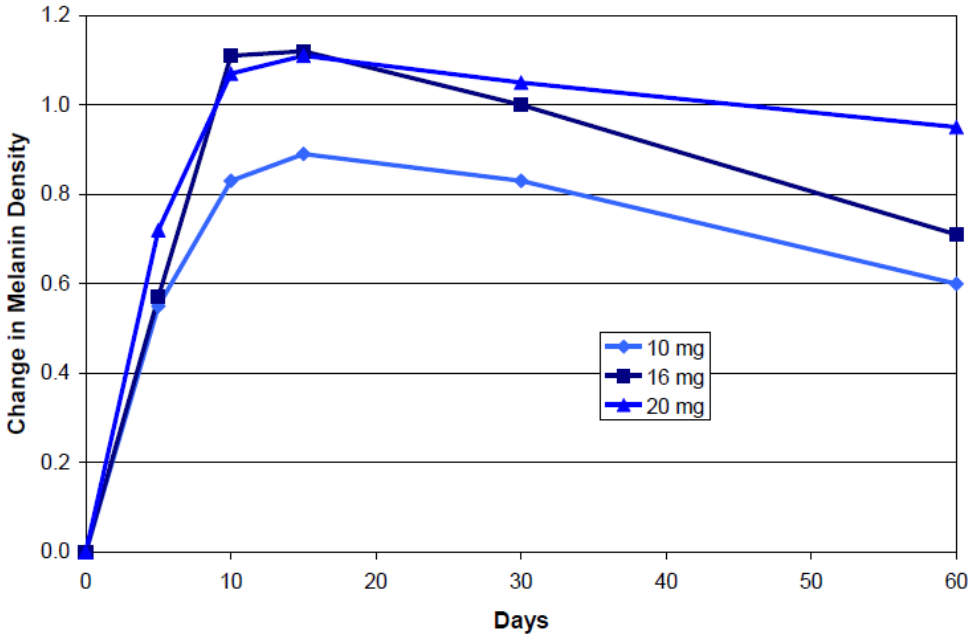
were occupied by afamelanotide molecules. Plasma levels above this range or for longer periods were not be expected to result in any additional increase in melanin density.

Study **EP001, EP002, and EP004** were early studies to assess the pharmacodynamic effect of afamelanotide with EP004 being the first study to use an implant. In this study, the 20 and 40 mg cohorts had significant melanin density (MD) increases at Days 10, 30 and 60 compared to baseline and to the 5 and 10 mg cohorts.

Study **EP008** was a double-blind, randomised, placebo-controlled study to assess the PD effects of afamelanotide in a total of 45 fair skinned healthy Caucasians. A single subcutaneous administration of an implant containing 20 mg afamelanotide or a matching placebo was administered to each subject and subjects were monitored for 12 weeks after implantation. It was found that afamelanotide-treated subjects showed greater increases in MD at all six monitored skin sites when compared to placebo. Twenty-one (91.3%) subjects in the afamelanotide group and 18 (81.8%) subjects in the placebo group experienced at least one AE during the course of the study. In the afamelanotide group the most commonly reported AE was injection site discolouration in 11 (47.8%) subjects with none in the placebo group, followed by upper respiratory tract infection in 5 (21.7%) afamelanotide-treated subjects and 9 (40.9%) in the placebo group.

Study CUV006 and CUV007 investigated the PD of another type of implant with either 16 or 20mg (CUV006) or 10 mg (CUV007) of afamelanotide. This formulation had a longer lasting release than previous formulations and it was shown that while 16 mg and 20 mg doses increased melanin density to similar levels (plus 33%), the increases were lower for the 10 mg implant (plus 27%; across study comparison, see figure 2 below).

Figure 2: Pharmacodynamic response (measured by the change in MD on sun exposed areas) following administration of three different strengths (10, 16, and 20 mg) of afamelanotide implants (a change in melanin density of 1.0 corresponds to an increase by 30%)



Study CUV009 investigated repeat administration of the 16 mg implant, with 2 implants given 28 days apart. A cumulative increase in melanin density, especially in exposed areas, was seen over time.

Study CUV028 was compared the pharmacodynamics of the previous with those of the final formulation of the implant.

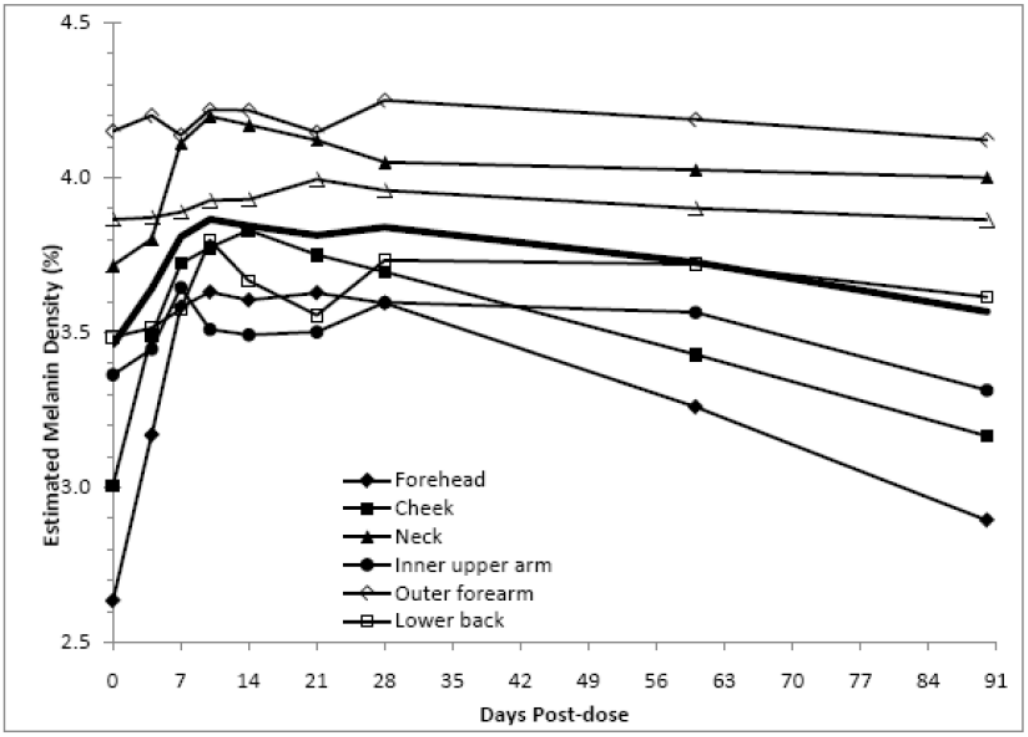
Table 4: Average melanin density at each visit for CUV028 study (a change in melanin density (MD) of 1.0 corresponds to an increase by 30%)

Day	GROUP 1 (Previous Manufacturing Process) (Lot# ML470)			GROUP 2 (Optimized Final Manufacturing Process) (Lot# ML504)		
	n	MD ± SD	Change in MD	N	MD ± SD	Change in MD
1	12	3.84 ± 0.73	0.00	12	3.54 ± 0.68	0.00
3	12	3.92 ± 0.76	0.08	12	3.59 ± 0.72	0.05
5	12	4.08 ± 0.76	0.24	12	3.75 ± 0.64	0.22
7	12	4.15 ± 0.68	0.30	12	3.94 ± 0.56	0.41
15	12	4.17 ± 0.67	0.33	12	4.21 ± 0.59	0.68
30	12	4.16 ± 0.71	0.31	12	4.12 ± 0.59	0.58
60	12	4.20 ± 1.00	0.35	12	3.91 ± 0.56	0.38

It was concluded that the implants produced by the final manufacturing process appear to be comparable in terms of changes in MD to those manufactured using the previous process. The inter-subject variability was greater than the difference in group means. Changes in L* and b* were similar between treatment groups through the Day 30 visit (L*, a*, and b*: skin reflectance parameters in colorimetric measurement with Minolta chromameter). There was a difference between the means at Day 60, this was not considered significant.

Study CUV038 was conducted with the final formulation 16 mg implant and measured the MD on days 0, 4, 7, 10, 14, 21 and 28, 60, and 90 at different sites of the body (see figure 5).

Figure 5: Mean melanin density across all sites over time (CUV038)



Note: n=12, omitting Subject 1007 Source: Table 14.3.3.1

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

The absorption and bioavailability of the different developmental formulations and the final formulation have been characterized in a number of studies in healthy volunteers.

CUV009 study indicated that the administration of two 16 mg afamelanotide implants 28 days apart was safe and tolerable. The superimposability of the first and second dose profiles suggested there were no accumulation of afamelanotide and no effect of the first dose on the second dose pharmacokinetics.

Information submitted regarding clearance (elimination) and half-life of afamelanotide in humans is not considered complete. PK data from EPP patients and in special populations are missing.

Less than 5% of patients incur terminal liver failure due to their porphyria. Annual ultrasonic screening and liver function tests in EPP patients are routine procedures coordinated by hepatologists employed in each centre, and will be continued as part of post-authorization measures as outlined in the RMP.

The SmPC also recommends that patients over the age of 70 years not be treated with Scenesse.

Routine safety monitoring is necessary and routine biochemical parameters which are used to assess hepatic and renal impairment will be monitored in all patients. The physician responsible for the integral care of EPP patients will report as part of the protocol the biochemical, hepatic ultrasonic evaluation and other clinical symptoms. Should patients be assessed as having either hepatic or renal impairment, they

will not be eligible for afamelanotide treatment. Contraindications in hepatic and renal impairment are included in the section 4.3 of SmPC.

Over the past 8 years, 347 EPP patients have been enrolled in clinical trials and 115 have received treatment in Italy and Switzerland. In these patients there has been limited use of concomitant medications. As part of the post-approval safety data collection, the use of concomitant medication will be recorded through the proposed 5 year treatment protocol as described in the RMP. Retrospective analyses will be undertaken to determine if any concomitant medication influences either the effectiveness of afamelanotide or adverse reactions experienced by patients.

In summary, thus far there is no indication or evidence to suggest that afamelanotide interacts with any other pharmaceutical agent that is likely to be taken by an EPP patient. This is reflected in section 4.5.

Study (CUV011) conducted in 82 organ transplant patients in order to assess whether afamelanotide could slow down or arrest the development of actinic damage.

The scientific rationale of the CUV011 study and the use of afamelanotide was to evaluate whether reducing the effect of light and UV radiation on skin by providing photoprotection to patients would have an influence on the development of actinic keratosis and squamous cell carcinoma in immunocompromised patients. It is known from clinical practice that in xenograft or organ transplant recipients after surgical transplantation a higher lifelong incidence of (epi)dermal actinic damage (actinic keratoses, squamous cell and basal cell carcinoma) is observed due to the combination of UV light and immunosuppression.

In the CUV011 study, organ transplant recipients were evaluated after 24 months (12 doses of afamelanotide) of drug administration. Forty three (43) recipients were given active drug, and 42 patients received placebo. All patients in CUV011 used a combination of immunosuppressive drugs such as azathioprine, prednisolone, cyclosporin, sirolimus, mycophenolic acid, tacrolimus, everolimus, dexamethasone, and methylprednisolone.

While the study analyses have not been completed, preliminary analyses of the safety data during 24 months of drug use alone have shown that afamelanotide has no influence on immunosuppression and there is no indication on drug-drug interaction in patients with severe co-morbidity.

Pharmacodynamics

The CHMP is of the view that the Applicant has conclusively shown that afamelanotide increases the melanin density in the skin of healthy volunteers. In EPP patients changes have been measured in study CUV017 and appear to be less pronounced than in healthy individuals (see section on efficacy below).

2.4.5. Conclusions on clinical pharmacology

The pharmacokinetics of the afamelanotide implant have not been fully characterized. While several studies during product development targeted on the absorption characteristics of the drug, information on distribution, metabolism, and excretion remain incomplete. Moreover, information on the PK in special populations (e.g. use in patients with renal/hepatic impairment is contraindicated and special caution is advised if used in older patients in the SmPC) and drug-drug interaction studies is missing as described in section 4.5 of the SmPC. The pharmacodynamic studies relied on the melanin density as a sole marker, or clinical improvement in EPP patients is plausible but has not been shown.

The summary of product characteristics (SmPC) and the patient information leaflet (PIL) will inform physicians and patients about the current limitations in PK knowledge.

In view of the current knowledge of Scenesse's safety profile the long-term safety information will be collected in a retrospective study comparing long term safety data and outcome endpoints in patients receiving and not receiving Scenesse, or having discontinued Scenesse use.

2.5. Clinical efficacy

2.5.1. Dose response study

No dose ranging study has been submitted. The dose regimen investigated in phase II and III studies was based on pharmacokinetic and pharmacodynamic considerations only. As the PK was considered similar for the 16 mg and the 20 mg implant (CUV006) and also the melanin density increases were not different between the groups, the 16 mg implant was taken forward in the further clinical development. The rationale for the selection of the dosing interval of 60 days is less clear from the data submitted. In fact, based on the changes in melanin density a dosing interval of 30 days would have appeared more plausible. This would have been supported also by the findings of study CUV009, indicating a lack of accumulation after repeat administration after 28 days. Indeed, the selection of a 60-day dosing interval might have been based on the sole fact, that this is the interval after which the previous implant has been resorbed, and the findings of study CUV038 in a very limited number of healthy volunteers indicating that the melanin density is still well above the baseline values after 60 days.

2.5.2. Main study

Study Title: "A Phase III, Multicentre, Double-Blind, Randomized, Placebo-Controlled Study to Confirm the Safety and Efficacy of Subcutaneous Bioresorbable Afamelanotide Implants in Patients with Erythropoietic Protoporphyria (EPP)"
Protocol Number: CUV039

IND Number: 103,131
First subject screened: 23 May 2012
First subject implanted: 25 May 2012
Last subject implanted: 21 November 2012
Last subject in visit 4/Day 180: 21 February 2013
Last subject in Follow-up visit = last subject contact: 31 Jul 2013
Study centres: 7 US reference centres for porphyria

Methods

Study Participants
Main inclusion criteria:
Female and male subjects aged 18 or older with biochemically-confirmed diagnosis of erythropoietic protoporphyria (EPP) who experience phototoxic reactions.

Main exclusion criteria:
- Allergy to afamelanotide or the polymer contained in the implant or to lidocaine or other local anaesthetic to be used during the administration of study medication
- EPP patients with significant hepatic involvement

- Current Bowen's disease, basal cell carcinoma, squamous cell carcinoma, or other malignant or premalignant skin lesions
- Personal history of melanoma or dysplastic nevus syndrome or any other photodermatosis.
- 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)
- Not suitable for the study in the opinion of the Principal Investigator or delegate (e.g. noncompliance history),
- Participation in a clinical trial of an investigational agent within 30 days prior to the screening visit.
- Prior and concomitant therapy with medications which could interfere with the objectives of the study, including drugs that cause photosensitivity or skin pigmentation.
- Female who was pregnant or lactating at baseline.
- Female of child-bearing potential not using adequate contraceptive measures

Main discontinuation/withdrawal criteria:
- Informed consent withdrawn by the patient
- Unacceptable level of patient non-compliance with protocol requirements
- Patient experienced an adverse event requiring study discontinuation
- When in the patients best interest according to the Investigator's or nominee.
- Violation of inclusion/exclusion requirements

Any subject(s) withdrawn from the trial prior to their completion for any reason could ("may") be replaced, provided the replacement was able to complete the study before the start of winter.

Treatments

The study consisted of a screening phase of up to 14 days, followed by a treatment phase of 6 months duration and safety follow-up visit was conducted at 12 months.

Study Posology:

Test product (Active): Scenesse: Afamelanotide (16 mg/implant) contained in a poly(D,L-lactide-co-glycolide) implant core

Dose:	Release of 16 mg of afamelanotide over 7 to 10 days
Mode of administration:	Subcutaneous implantation
Lot numbers:	ML638, ML639, and ML660

Reference therapy (Placebo): Poly(D,L-lactide-co-glycolide) implant in size identical with verum

Dose:	Not applicable (placebo)
Mode of administration:	Subcutaneous implantation
Lot numbers:	ML597 and ML739

Both sets of implants were manufactured by Birmingham Laboratories, Evonik Corporation, Birmingham, Alabama, USA.

Patients received implants (active or placebo) on Days 0, 60 and 120

Implants were administered following application of a local anaesthetic, subcutaneously via a 14G catheter with needle into the (subcutaneous) fat above the anterior portion of the iliac crest.

Objectives

Primary objective:
The primary objective of CUV039.

To determine whether afamelanotide can enable EPP patients to expose themselves to sunlight without incurring pain and phototoxic reactions. The primary objective addresses sunlight only, not bright artificial light that also is a reason for phototoxic reactions in EPP patients.

Secondary objectives:

To determine whether administration of afamelanotide implants can:

• improve the quality of life of EPP patients

• reduce the susceptibility to photoprovocation with a standardized 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

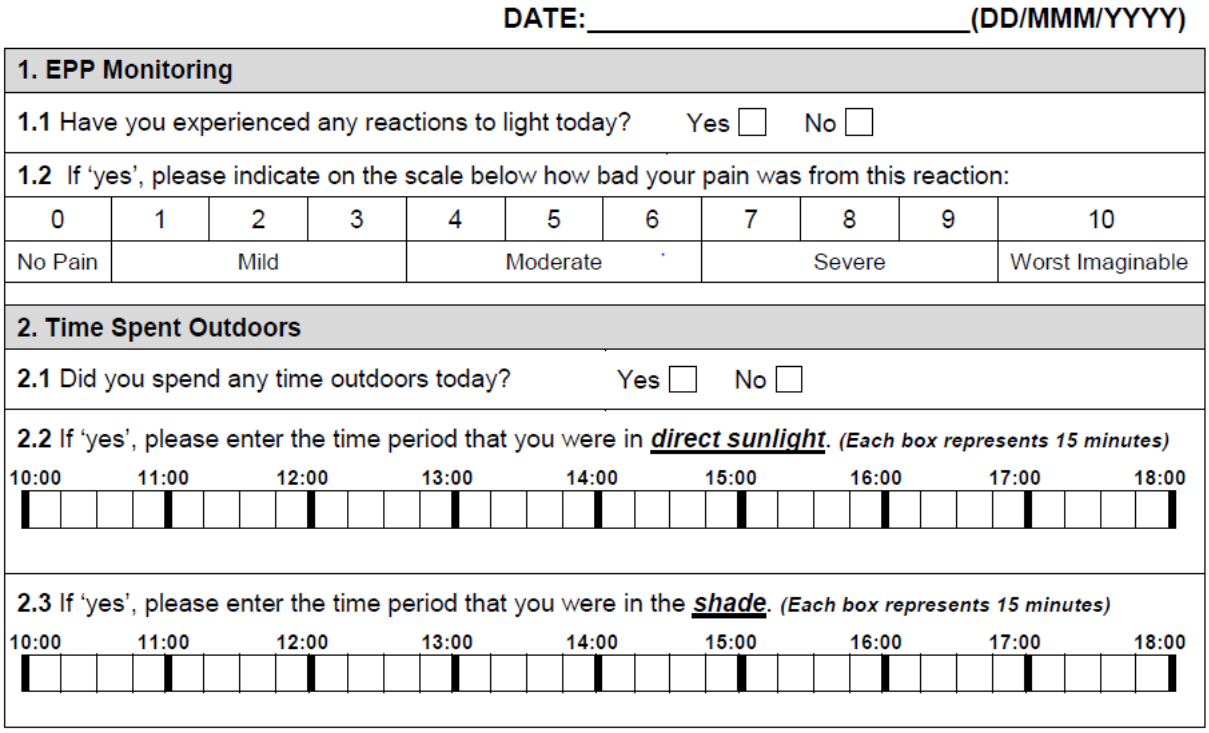
- to investigate the reversibility of afamelanotide-induced increase in dermal pigmentation.

Outcomes/endpoints
Primary endpoint

As per protocol (version 4), the sunlight exposure for days without pain is calculated for each patient as the mean duration of daily direct sunlight exposure between 10:00 and 18:00 hours on study days when patients report not experiencing phototoxicity-associated pain (Likert score of 0).
The mean daily duration in direct sunlight exposure will be calculated for each subject and compared between the treatment groups using a Kruskal-Wallis test with a significance level of $p<0.05$.
H0: there is no difference in the duration of sunlight exposure on days without pain between active and placebo groups

The evaluation of this endpoint is based on a patient diary.
Time outdoors was reported separately as being time in direct sunlight or time in the shade in each 15 minute block from 10:00 to 18:00.
According to the Applicant this study follows a similar design to the CUV029 and CUV030 studies, with a subtle difference in the recording of time spent outdoors. That is, the diaries used in this study more distinctly capture the quantity of time spent in direct sunlight, by having the subjects record time outdoors as direct sunlight exposure or time in shade, for each 15 minute block of time spent outdoors. This distinction between sun and shade was made to approximate both sources of visible light radiation, and direct versus diffuse light. This distinction is in contrast to the previous studies, where subjects recorded in their diaries the quantity of time spent outdoors each day, with each day's exposure classified as mainly in direct sunlight, mainly in shade, or a combination of both.

Figure 04: Patient diary card



According to the Applicant there was ambiguity in the wording of the primary endpoint in the CUV039 study protocol since although the endpoint was stated in terms of duration (hours) the subsequent calculation referred to mean daily duration.

According to the revised CSR, the duration of time (hours) was retained as the primary efficacy endpoint, but "for completeness and transparency", the mean daily duration in direct sunlight exposure between 10:00 and 18:00 hours on days when no pain was experienced was also calculated for each subject by dividing the total duration of time spent in direct sunlight (for the study) by the number of days that each subject was on the study.

According to the original CSR, the primary objective of the study was "to determine whether afamelanotide can enable EPP patients to expose themselves to sunlight without incurring pain and phototoxic reactions". In discussions with the study statistician it was agreed that calculation of mean daily sun exposure on pain-free days does not take into account the number of pain free days. For a totally effective prophylactic treatment it is likely that there would be many more pain-free days than would be expected for a patient receiving placebo treatment. This makes the calculation of mean daily exposure inappropriate because the number of pain-free days is used as the denominator. For this reason the analysis followed the study objective and the definition of the primary endpoint.

Only protocol version 1.0 names one primary safety endpoint:
"Type and incidence of treatment emergent adverse events".
Subsequent protocol versions list safety as secondary endpoints only (see below)

Secondary endpoints

Secondary endpoints related to efficacy:

- Duration of sun exposure (hours in direct sunlight) between 10:00 and 18:00 hours on days when no pain or mild pain was experienced (pain scores of 0-3)
- Duration of sun exposure (hours in direct sunlight) between 10:00 and 18:00 during the study
- Quality of life assessment score according to the DLQI and EPP-QoL (original and revised version) questionnaires
- Photoprovocation (in a subset of patients): The minimum symptom dose following photoprovocation on the lower back and dorsal surface of the hand, determined using the irradiation dose of the light source and the time to first development of symptoms at the site of photoprovocation
- Maximum and total pain severity scores (Likert scale) for phototoxic episodes.
- Number of phototoxic episodes during the study

With protocol version 4.0 (17 June 2013), an additional, eighth secondary efficacy endpoint was introduced:

- "Duration of direct sunlight exposure between 10:00 and 15:00 hours on days when no pain was experienced (Likert score of 0)".

This endpoint was also used in clinical Scenesse trials CUV029 (as the primary efficacy endpoint in the protocol's revised version) and in CUV030 (co-primary efficacy endpoint).

Secondary endpoints related to safety:

- Physical examination changes from Screening
- Changes in blood pressure and heart rate from screening to all subsequent visits
- Changes in clinical chemistry, haematology and urinalysis parameters from Screening to all subsequent visits (days 60, 120, 180, and at early termination visit, if applicable)

With protocol version 2.0 (17 July 2012) an additional secondary safety endpoint was introduced:

- Any significant abnormalities detected in EKG.

Phototoxic Reactions: Patients reported their daily pain due to phototoxic reactions (caused by exposure to natural light) in the study diary (see below). On each day such a reaction occurred, the subject scored the level of pain using an 11 point Likert pain intensity scale.
The ***number*** of phototoxic reactions was determined by counting the number of episodes on which patients report a Likert scale score of 4 or more for one or more consecutive days. 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.

Quality of Life Measurement: The quality of life (QoL) was determined using the EPP-QoL (original, later in combination with a revised version) and the DLQI questionnaires. Both questionnaires were completed at on Days 0, 60, 120 and 180, or at Early Termination Visit, The EPP-QoL (original and revised) was also completed at the day 360 safety follow-up visit.
In addition, a baseline EPP questionnaire and an end of study EPP questionnaire were also completed.

Photoprovocation: In a subset of patients and at one site only (site #01), the minimum irradiation dose of visible light required to provoke symptoms was determined at baseline (Day 0) and on Days 30, 60, 90 and 120. Conventional phototesting equipment was used with a purpose-built filter which removed ultraviolet and infrared radiation.

An area of approximately 33mm in diameter was irradiated with light filtered to transmit radiation between 400nm and 650nm up to a maximum irradiation dose of 300 J/cm2 using a standardized and calibrated light source. The time taken for the patient to first experience symptoms together with the radiation output from the light source was used to calculate the “Minimum Symptom Dose”.

Sample size

Analysis of data from the CUV029 and CUV030 studies demonstrated that a significant difference in the primary endpoint of the study could be detected with approximately 75-100 patients.

Although no formal sample size calculation was performed, the justification of the sample size based on the previous phase III trials is considered acceptable.

Randomisation

The study was conducted at seven sites in the USA. To account for the differences in climatic conditions between the study sites and the potential impact that this may have had on phototoxicity experienced, a computer generated randomization list for each study site was used to assign each subject to a treatment arm. To ensure that treatment was balanced within study sites, the randomization method used a small block size.

Blinding (masking)

In this double-blind study, all personnel involved, i.e. physicians, site staff, and participants were to remain blinded at all times, except in an emergency where knowledge of the code break was required to provide appropriate treatment.

Implants used in the placebo arm were identical in size to those in the active treatment arm but contained only polylactide-co-glycolide polymer.

Statistical methods

According to the revised CSR the main population for all efficacy analyses was the intent-to-treat (ITT) population defined as all treated participants who provided at least one post dose efficacy assessment. There were three separate ITT populations reflecting the availability of post-dose efficacy data for different data types (Diary Card, Photoprovocation Subset, and Quality of Life).

The Study Completers population included subjects who received all three doses of study drug and returned adequately completed patient diary entries (Diary Card population), completed all quality of life assessments (Quality of Life population) or had the required number of photoprovocation tests (Photoprovocation Subset). This population was for supplementary efficacy analyses.

The Safety Population included all enrolled subjects who were randomized and received at least one dose of study medication.

Analyses were performed on the available data. Missing data were imputed for sensitivity analyses: For assessment of the number of phototoxic reactions and exposure to sunlight, analyses based on best and worst case imputations of missing values were performed.

The clinically relevant primary endpoint was the number of pain-free hours that patients exposed themselves to direct sunlight between 10:00-18:00 hours (on days with a recorded Likert pain score of 0). The total duration in direct sunlight exposure was calculated for each patient and compared between the treatment arms using a Kruskal-Wallis test with a significance level of $p<0.05$. Post-hoc, it was specified that the difference between treatments was also to be characterized using Hodges-Lehmann estimates with a 95% confidence interval. This followed a suggestion by the Rapporteurs at a clarification

meeting.

The mean daily duration in direct sunlight exposure between 10:00 and 18:00 hours on days when no pain was experienced (see Outcomes/Endpoints) was also calculated for each subject by dividing the total duration of time spend in direct sunlight (for the study) by the number of days that each subject was on the study and compared between the treatment groups.

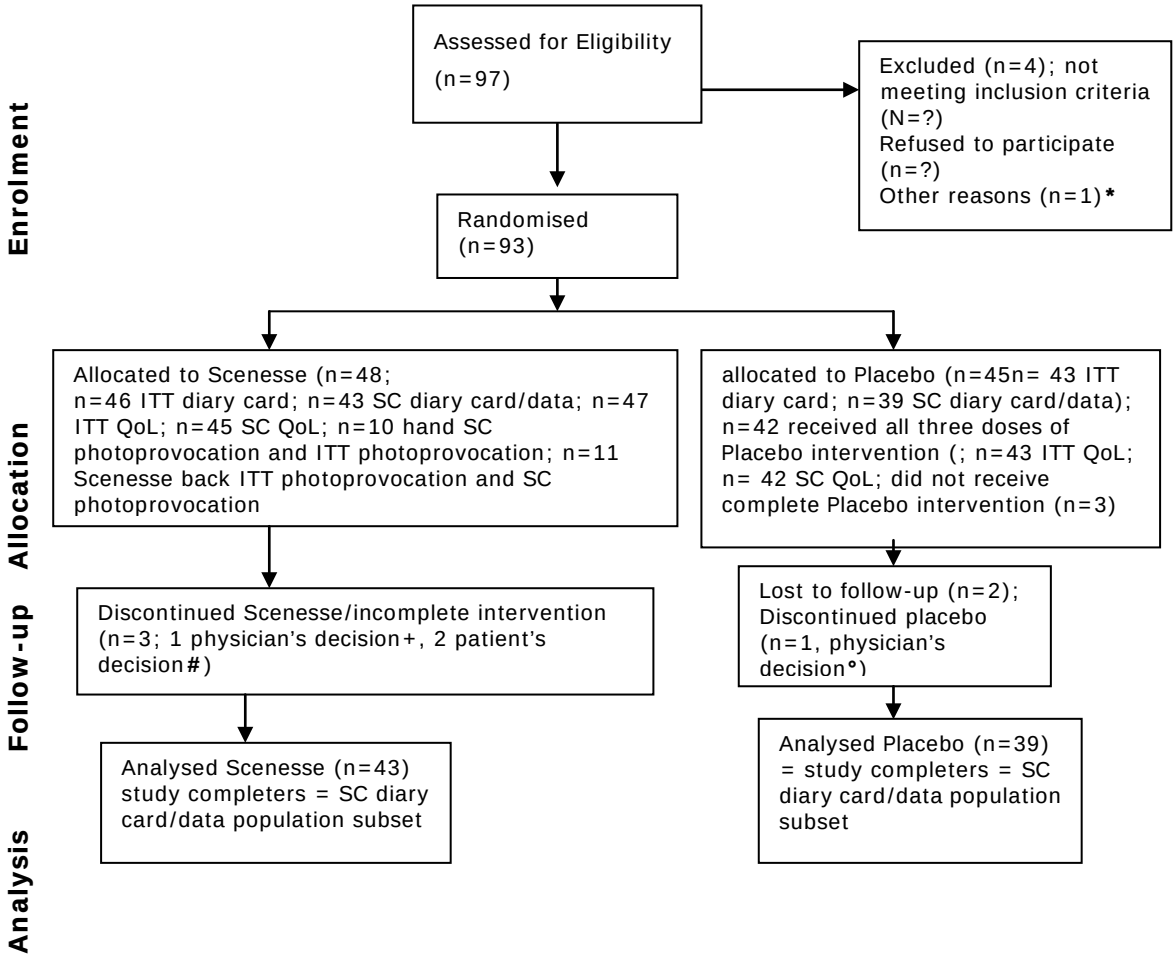
For the secondary endpoints, between-group comparisons were performed as for the primary analysis. For secondary endpoints related to sun exposure time, total daily duration was calculated as well as mean daily duration, where mean daily duration was calculated by dividing the exposure time by number of days that each subject was on study.

Additional endpoints were added post-hoc. Supportive exploratory analyses of the total number of pain-free days (per subject over the 6 month study period) with some direct sunlight exposure between 10:00 and 18:00 hours, and between 10:00 and 15:00 hours were undertaken, comparing treatment groups by Kruskal-Wallis test and Hodges-Lehmann estimates; similarly, days with sun exposure between 10:00-18:00 hours on 'days with mild pain' and 'all days' were analysed. In a further supportive exploratory analysis, the median of the individual 7 day moving average for time in direct sunlight on pain-free days was calculated for each treatment group and plotted against the study day number.

According to the statistical analysis plan (SAP), a partial unblinding was planned following data management entry of efficacy assessments and diary entries at 6 months (including data entry, validation, and query resolution), to allow for an interim efficacy analysis to be performed. Due to a change in the deadline for a response to outstanding issues, an interim analysis was not required and not conducted. The study blind was to be maintained for physicians, site staff, participants, data management group, monitors, and all other Clinuvel personnel, until after database lock following the 12-month follow-up safety visits.

Results

Participant flow



One patient was withdrawn prior to drug administration due to choroidal nevus in his/her left eye. The indicated clinical follow-up by an ophthalmologist was not provided for in the protocol.

+ Patient 6005, Physician's decision, clinical reasons not related to IMP, Subject non-compliant with visit schedule, (site) unable to contact subject.

Two Scenesse patients in the active group did not receive complete treatment: Patient 2009: withdrawal of consent, reason not given, lost to follow-up, no early termination visit; patient 3009: withdrawal of consent, reason not given.

° Three placebo patients did not receive complete allocated treatment: Patient 1017, lost to follow-up; no early termination visit; 3006, Physician's decision Serious adverse event, clinical reasons not related to IMP; 4008, Patient lost to follow-up.

The above data were extracted from the CSR section 10.1.

Ninety seven (97) patients were screened and 93 met the inclusion and exclusion criteria and were enrolled in the study. Of these, 48 were randomized to receive active treatment, and 45 other individuals were randomized to the placebo group. Three (3) patients in each treatment group terminated early from the study leaving 45 active and 42 placebo patients who completed the study.

With the correction of the CUV039 CSR the Applicant redefined the analysis populations:

The intent to treat (ITT) population for the diary card endpoints [ITT (Diary Card)] comprised 89 subjects (46 subjects on afamelanotide and 43 on placebo). This excluded the three subjects who terminated early from the study without returning any diaries (afamelanotide (1) and placebo (2)); one subject on afamelanotide who received all three doses but did not return any diaries and did not attend for Visit 4 and thus was considered not to have completed the study as scheduled; and one subject on placebo who was withdrawn prior to dosing.
The efficacy evaluable population of study completers for the diary card endpoints [SC (Diary Card)] comprised 82 subjects, 43 afamelanotide and 39 placebo, excluding two further randomized subjects who terminated from the study early before receiving all three doses of study drug (one afamelanotide and one placebo and five further randomized subjects who received all three doses but did not return all diaries (two afamelanotide) and three placebo).

The intent to treat population for the quality of life endpoints [ITT (Quality of Life)] comprised 90 subjects (47 afamelanotide group and 43 placebo). This population contains more subjects than the ITT (Diary Card) population since more subjects completed quality of life assessments than returned diary cards.
The efficacy evaluable population of study completers for the quality of life endpoints [SC (Quality of Life)] comprised 87 subjects (45 afamelanotide and 42 placebo).

A photoprovocation sub-study was conducted in 21 subjects (11 afamelanotide, 10 placebo) at study site#1. One subject (afamelanotide) was identified to have peripheral neuropathy which would invalidate testing on the hands. This subject completed the sub-study with photoprovocation undertaken only on the lower back, explaining the ITT (Photoprovocation Subset) and SC (Photoprovocation Subset) populations of 10 (hand) /11 (back) for the afamelanotide group.

Recruitment

The CSR does not name the channels and means the Applicant had used to recruit patients (direct contact, through specialised centres and patients' organisations).

Conduct of the study

With his letter of 11 March 2014 the Applicant notified the EMA and the Rapporteurs about two patients (randomisation numbers 2002 and 2012) having been wrongly recorded but correctly assigned drug and placebo. These errors were explained by wrong transcription from one document to another to the electronic database.

In detail as explained in the "Notification of a proposed revisions of the CUV039 clinical study report", by further review in preparation for the GCP inspection the Applicant and his CRO "found that the information on the Study Treatment and IMP Batch Allocation form did not match the details in the IMP Dispensing Accountability Form for two subjects at study site # 02.

„Both subjects received the correct study treatments (consistent with the randomisation code) but treatment assignments contained in the documentation provided to the CRO by the unblinded study monitors were:

• Placebo rather than Active for Subject and

• Active rather than Placebo for Subject

In due course the Applicant submitted re-calculations for trial CUV039 following correct assignment of these two patients. During the data management process, transcription errors occurred which resulted in two patients being incorrectly assigned to treatment groups for statistical analysis for the original clinical

study report. These errors were corrected and a revised study report prepared.

Baseline data

Subjects enrolled in this study were predominantly Caucasians (90 of 93 subjects, 97%), with a mean age of approximately 40 years. Slightly more than half of the enrolled subjects were males with 60% of males in the afamelanotide group and only 47% in the placebo group.

According to the Applicant there were no clinically relevant or statistically significant differences between groups in any parameter, including age, gender, or BMI (Table 10.2).

Table 10: Demographic Characteristics (ITT Population, Table 10.2 as named by the Applicant):

	Afamelanotide Implant (16 mg) (N=46)	Placebo (N=43)
Age (years)		
Mean (SD)	40.1 (12.4)	39.2 (16.2)
Median (min, max)	37.5 (20, 65)	36.0 (18, 74)
Gender		
Male	28 (61%)	20 (47%)
Female	18 (39%)	23 (53%)
Race		
Caucasian	45 (98%)	41 (95%)
American Indian / Alaskan Native		1 (2%)
Asian		1 (2%)
Hispanic	1 (2%)	
Weight at Screening (kg)		
Mean (SD)	78.39 (17.75)	77.64 (16.72)
Median (min, max)	74.55 (44.9,130.5)	74.70 (53.0,119.0)
Height (cm)		
Mean (SD)	172.2 (10.2)	170.6 (9.9)
Median (min, max)	175.3 (154,188)	172.7 (152,191)
BMI (kg/m^2)		
Mean (SD)	26.27 (4.77)	26.69 (5.36)
Median (min, max)	25.15 (19.0,38.9)	25.80 (18.2,38.8)

BMI = body mass index,

There were no clinically relevant differences between groups in Fitzpatrick skin type and skin cancer risk factors (CSR Section 10.3.2).

Table 11: Fitzpatrick skin type (table 14.1.3 as named by the Applicant)

Table 14.1.3
Fitzpatrick Skin Type and Skin Cancer Risk Factor
(Safety Population)

		Active (N=48)	Placebo (N=45)	Total (N=93)
Fitzpatrick Skin Type				
(I) Never tans, always burns		13 (27%)	10 (22%)	23 (25%)
(II) Tans less than average (with difficulty), mostly burns		19 (40%)	16 (36%)	35 (38%)
(III) Tans about average, sometimes mild burn		12 (25%)	16 (36%)	28 (30%)
(IV) Rarely burns, tans more than average (with ease)		4 (8%)	3 (7%)	7 (8%)
Skin Cancer Risk				
1) Does the subject currently suffer from a form of skin cancer?	No	48 (100%)	46 (102%)	94 (101%)
2) Has the subject suffered from a form of skin cancer in the past?	Yes		1 (2%)	1 (1%)
	No	48 (100%)	45 (100%)	93 (100%)
3) Does anyone in the subject's family have Melanoma at present or have they in the past?	Yes	3 (6%)	7 (16%)	10 (11%)
	No	45 (94%)	39 (87%)	84 (90%)

Study medication compliance was similar in the two treatment groups.

Table 12: Treatment Compliance (Table 10.3 as named by the Applicant)

Number of Doses Administered	Number (%) of Subjects: Afamelanotide Implant (16 mg) (N=48)	Number (%) of Subjects: Placebo (N=45)
3 doses (Visit 1, Visit 2, Visit 3)	46 (96%)	42 (93%)
2 doses (Visit 1, Visit 2)	1 (2%)	1 (2%)
1 dose (Visit 1)	1 (2%)	2 (4%)

Listing 16.2.17 Partial responses to previous treatments including betacarotene, UV-therapy, sun protection creams and red cell exchange/transfusions have been reported in a number of participants. Notable a patient reported complete response with/after “Red cell exchange/transfusions” in May through August every year (randomisation number 7004, placebo).

Numbers analysed

Each of the seven sites recruited between seven and twenty patients, in total ninety-three individuals for CUV039 as the safety population.

Thirty-nine placebo patients and 43 Scenesse recipients completed the trial. Six patients had early termination, three per cohort

Outcomes and estimation

1. Primary endpoint

The primary efficacy endpoint was:

The difference for the duration of time (hours) spent in direct sunlight between 10:00 and 18:00 hours on days when no pain was experienced for the two treatment groups was 28.63 hours (median, 55.01 hours difference as mean) in favour of Scenesse during the observation period of 180 days. This difference is statistically significant at the 0.05 level (one-sided); p=0.044; Kruskal-Wallis one-way analysis of variance by ranks). Presented as the mean daily minutes in direct sunlight, the difference is no longer statistically significant (see table 14).

The statistical results are further characterised by a large variability.

Table 14:

Parameter	Active (n=46)	Placebo (n=43)	
Total number of hours per subject in direct sunlight – pain-free 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	
Kruskal-Wallis *p*-value			0.044
Hodges-Lehmann shift, Estimate			24.0
95% Confidence Interval			0.3 – 50.3
Mean daily minutes in direct sunlight – pain-free 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	
Kruskal-Wallis *p*-value			0.075
Hodges-Lehmann shift, Estimate			8.8
95% Confidence Interval			-0.8 – 18.5

There was a subset of 15 patients who were able to experience more than 60 minutes of direct sunlight each day. Of these, 12 were afamelanotide recipients. Further, 6 of these 12 patients reported more than 90 minutes exposure on each day. All of these were afamelanotide recipients.

2. Secondary endpoints

a) Duration of sun exposure

For the data presentation the Applicant used the population called “ITT population, Diary Card“; for definition please see above AR section on statistical methods.

Duration of sun exposure (hours in direct sunlight) between 10:00 and 18:00 hours on days when no pain or mild pain was experienced (Likert pain scores of 0-3):
The difference between the treatment groups was not statistically significant.

Table 15

Parameter	Active (n=46)	Placebo (n=43)	
Total number of hours per subject in Sunlight – days with no pain or mild pain (Likert pain score of 0-3)			
Mean (SD)	141.1 (165.1)	74.6 (67.5)	
Median	80.0	51.0	
Range	0.5 - 825.0	1.25 – 251.0	
Kruskal-Wallis *p*-value			0.053
Hodges-Lehmann shift, Estimate			26.8
95% Confidence Interval			-0.3 – 57.5
Mean daily minutes per subject in Sunlight – days with no pain or mild pain (Likert pain score of 0-3)			
Mean (SD)	47.5 (53.4)	27.1 (22.9)	
Median	27.3	25.2	
Range	0.2 – 263.8	0.7 – 85.0	
Kruskal-Wallis *p*-value			0.094
Hodges-Lehmann shift, Estimate			8.4
95% Confidence Interval			-1.5 – 18.9

An analysis of the sun exposure (hours) between 10:00 and 18:00 hours regardless of pain score showed no statistically significant difference (Table 16)

Table 16

Parameter	Active (n=46)	Placebo (n=43)	
Total number of hours per subject in Sunlight – regardless of pain score			
Mean (SD)	145.0 (164.1)	81.8 (71.2)	
Median	83.5	65.3	
Range	0.5 – 825.0	3.5 – 278.5	
Kruskal-Wallis *p*-value			0.066
Hodges-Lehmann shift, Estimate			26.1
95% Confidence Interval			-2.3 – 57.3
Mean daily minutes per subject in Sunlight – regardless of pain score			
Mean (SD)	48.1 (52.7)	28.3 (23.6)	
Median	27.6	25.1	
Range	0.2 – 263.3	1.8 – 94.4	
Kruskal-Wallis *p*-value			0.092
Hodges-Lehmann shift, Estimate			8.5
95% Confidence Interval			-1.6 – 18.8

With the protocol version 4 of June 2013—a further combined secondary efficacy endpoint (sun exposure and phototoxic pain) was introduced: Duration of direct sunlight exposure between 10:00 and 15:00 hours on days when no pain was experienced (Likert score of 0; CUV039 CSR, p672). This endpoint is identical to the primary endpoints in trials CUV029 and CUV030. Also, for this endpoint the difference between Scenesse and placebo patients was not statistically significant (as in CUV029 and CUV030).

Table 17

Parameter	Active (n=46)	Placebo (n=43)	
Total number of hours per subject in Sunlight – pain-free days (Likert pain score of 0)			
Mean (SD)	71.2 (89.2)	41.6 (45.3)	
Median	39.6	31.8	
Range	0 – 419.0	0 – 198.8	
Kruskal-Wallis *p*-value			0.092
Hodges-Lehmann shift, Estimate			13.1
95% Confidence Interval			-1.3 – 28.0
Mean daily minutes per subject in Sunlight – pain-free days (Likert pain score of 0)			
Mean (SD)	26.9 (33.3)	16.4 (17.3)	
Median	14.9	11.0	
Range	0 – 167.6	0 – 74.1	
Kruskal-Wallis *p*-value			0.134
Hodges-Lehmann shift, Estimate			4.9
95% Confidence Interval			-1.0 – 10.6

The mean daily duration of sun exposure (hours in direct sunlight) between 10:00 and 18:00 hours during the study was calculated for both treatment groups: The difference between the treatment groups is not statistically significant. The Applicant points out the numerical differences as "Overall sun exposure … (being) … much higher in those treated with afamelanotide".

The Applicant performed various post-hoc ancillary analyses as detailed in the corresponding section in this assessment report.

a) Quality of life assessment

The Applicant employed questionnaires for assessing quality of life in this population to demonstrate treatment-related improvements.
Firstly, the Dermatology Life Quality Index (DLQI) was employed. This is a questionnaire not specific for EPP patients but widely used in dermatology for QoL assessment (e.g. in vitiligo, psoriasis, and atopic dermatitis). A second QoL tool was used, a questionnaire "purpose-designed", developed by "expert physicians responsible for the healthcare of EPP patients". This was named EPP-QoL. In CUV039 it was used in two versions, original and revised – their scores cannot be compared with each other.

Following afamelanotide treatment, the quality of life of Scenesse patients—as measured with the EPP-QoL questionnaires—improved significantly from baseline, and compared to placebo recipients. Following afamelanotide treatment, the quality of life—as measured with the DLQI questionnaire—of both placebo and Scenesse patients improved significantly from baseline, with no difference between placebo and Scenesse recipients.

Dermatology Life Quality Index (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 (Table 18).

Table 18:

Quality of Life - DLQI Questionnaire by Item
ITT Quality of Life Population

DLQI Item	Treatment	Visit	Summary of DLQI Item N	Mean	Std Dev	Median	Minimum	Maximum
DLQI Total Score	Active	Visit 1, Day 0	47	10.7	6.3	10.0	0	26
DLQI Total Score	Active	Visit 2, Day 60	47	4.7	5.7	2.0	0	21
DLQI Total Score	Active	Visit 3, Day 120	46	2.8	4.2	0.5	0	16
DLQI Total Score	Active	Visit 4, Day 180 / Early Termination	46	2.4	4.2	1.0	0	16
DLQI Total Score	Placebo	Visit 1, Day 0	43	10.4	5.7	11.0	0	22
DLQI Total Score	Placebo	Visit 2, Day 60	43	6.4	6.0	4.0	0	21
DLQI Total Score	Placebo	Visit 3, Day 120	42	4.1	4.8	2.5	0	19
DLQI Total Score	Placebo	Visit 4, Day 180 / Early Termination	43	3.1	4.1	1.0	0	14

Table 19:
(table 11.10 as named by the Applicant)

Table 11.10 Quality of life - DLQI questionnaire (ITT population, Quality of Life)

(Scale: 0 = no effect at all on subject's life, >20 = extremely large effect on subject's life		Afamelanotide Implant (16 mg) N=47	Placebo N=43
DLQI Total Score at Visit 1 (Day 0)	N	47	43
	Mean (SD)	10.7 (6.3)	10.4 (5.7)
	Median (min, max)	10.0 (0, 26)	11.0 (0, 22)
DLQI Total Score at Visit 2 (Day 60)	N	47	43
	Mean (SD)	4.7 (5.7)	6.4 (6.0)
	Median (min, max)	2.0 (0, 21)	4.0 (0, 21)
DLQI Total Score at Visit 3 (Day 120)	N	46	42
	Mean (SD)	2.8 (4.2)	4.1 (4.8)
	Median (min, max)	0.5 (0, 16)	2.5 (0, 19)
DLQI Total Score at Visit 4 (Day 180)	N	46	43
	Mean (SD)	2.4 (4.2)	3.1 (4.1)
	Median (min, max)	1.0 (0, 16)	1.0 (0, 14)

DLQI = Dermatology Life Quality Index
Source: Table 14.2.6.1

In both groups the median quality of life score improved, as shown by the decreases from 10 at the start to 1 on day 180 at the end of the treatment period, i.e. there was no difference detectable in the extent of improvement (DLQI) between Scenesse and the placebo.

The Applicant calculated Kruskal-Wallis test statistics and Hodges-Lehmann shift estimates for inter-group comparisons for the changes of DLQI total score over time in relation to baseline (see table 20 below). Scenesse recipients and placebo patients did not statistically significantly differ from each other with regard to the scores in this quality of life assessment.

Table 20: Secondary endpoint quality of life as assessed with the DLQI—changes

Secondary endpoint (source: Table 14.2.6.3, CSR revision1)	Scenesse	Placebo	Comparison Scenesse vs. Placebo
Number of subjects (Intention-to-treat quality of life population)	47	43	
	Changes in DLQI questionnaire total score (day 60 compared to day 0)		
Median	-6	-4	
Minimum	2	11	
Maximum	-24	-15	
Mean	-6	-4	
Standard deviation	5.9	5.5	
Kruskal-Wallis p-value			**0.214 (>0.05)**
Hodges-Lehmann shift, estimate			-1

Secondary endpoint (source: Table 14.2.6.3, CSR revision1)	Scenesse	Placebo	Comparison Scenesse vs. Placebo
Number of subjects (Intention-to-treat quality of life population)	46	42	
	Changes in DLQI questionnaire total score (day 120 compared to day 0)		
Median	-7	-6.5	
Minimum	0	14	
Maximum	-26	-17	
Mean	-7.8	-6.5	
Standard deviation	6	6.2	
Kruskal-Wallis p-value			**0.589 (>0.05)**
Hodges-Lehmann shift, estimate			-1

Secondary endpoint (source: Table 14.2.6.3, CSR revision1)	Scenesse	Placebo	Comparison Scenesse vs. Placebo
Number of subjects (Intention-to-treat quality of life population)	46	43	
	Changes in DLQI questionnaire total score (day 180/early termination compared to day 0)		
Median	-7.5	-8	
Minimum	1	5	
Maximum	-26	-19	
Mean	-8.1	-7.3	
Standard deviation	6.2	5.6	
Kruskal-Wallis p-value			**0.799 (>0.05)**
Hodges-Lehmann shift, estimate			0

Erythropoietic Protoporphyria Quality of Life questionnaire (EPP-QoL, original scoring)

For this questionnaire the Applicant calculated Kruskal-Wallis test statistics and Hodges-Lehmann shift estimates for inter-group comparisons for the changes of the EPP-QoL total scores over time (with a value of 0 indicating no change) in relation to baseline.

From day 0 to day 180 the median quality of life score improved as shown by decreases in both groups. The improvement was more pronounced in Scenesse as compared to placebo patients (from 23 to -2.5 for Scenesse; from 24 to 5 for placebo). The results for the two groups differed statistically significantly with regard to the change in median total scores.

Statistically significant differences between the groups were demonstrated at each time point however for the follow-up visit).

Table 21

Table 14.2.7.1
Quality of Life - Supplementary EPP Specific Questionnaire by Item (Original Scoring)
ITT Quality of Life Population

			Summary of EPPQoL Item					
EPPQoL Item	Treatment	Visit	N	Mean	Std Dev	Median	Minimum	Maximum
EPPQoL Total Score	Active	Visit 1, Day 0	47	21.7	8.3	23.0	-1	35
		Visit 2, Day 60	47	3.0	10.2	1.0	-10	33
		Visit 3, Day 120	46	0.4	9.6	-2.0	-10	27
		Visit 4, Day 180 / Early Termination	46	0.5	10.4	-2.5	-10	28
		Follow-up Visit	44	17.0	11.2	19.5	-7	33
EPPQoL Total Score	Placebo	Visit 1, Day 0	43	22.0	8.2	24.0	-1	34
		Visit 2, Day 60	43	12.0	12.5	9.0	-7	31
		Visit 3, Day 120	42	9.4	12.5	8.0	-8	32
		Visit 4, Day 180 / Early Termination	43	6.9	10.6	5.0	-7	27
		Follow-up Visit	40	14.2	11.9	14.0	-6	34

Table 22

Table 14.2.7.3
Changes in Quality of Life - Supplementary EPP Specific Questionnaire (Original Scoring)
ITT Quality of Life Population

EPPQoL Item	Visit		Active Afamelanotide	Placebo	Comparison
Change in EPPQoL Total Score	Visit 2, Day 60	N	47	43	
		Mean	-18.7	-10.1	
		Standard Deviation	11.0	10.5	
		Median	-19.0	-11.0	
		Minimum	-39	-32	
		Maximum	2	6	
		Kruskal-Wallis p-value			<.001
		Hodges-Lehmann shift, estimate			-9
		Hodges-Lehmann shift, lower CL			-15
		Hodges-Lehmann shift, upper CL			-4
Change in EPPQoL Total Score	Visit 3, Day 120	N	46	42	
		Mean	-21.1	-13.0	
		Standard Deviation	11.3	10.8	
		Median	-21.5	-11.5	
		Minimum	-45	-39	
		Maximum	2	2	
		Kruskal-Wallis p-value			0.001
		Hodges-Lehmann shift, estimate			-8
		Hodges-Lehmann shift, lower CL			-14
		Hodges-Lehmann shift, upper CL			-3

Table 14.2.7.3
Changes in Quality of Life - Supplementary EPP Specific Questionnaire (Original Scoring)
ITT Quality of Life Population

EPPQoL Item	Visit		Active Afamelanotide	Placebo	Comparison
Change in EPPQoL Total Score	Visit 4, Day 180 / Early Termination	N	46	43	
		Mean	-21.1	-15.1	
		Standard Deviation	12.2	10.9	
		Median	-22.0	-14.0	
		Minimum	-45	-39	
		Maximum	-1	3	
		Kruskal-Wallis p-value			0.020
		Hodges-Lehmann shift, estimate			-6
		Hodges-Lehmann shift, lower CL			-11
		Hodges-Lehmann shift, upper CL			-1
Change in EPPQoL Total Score	Follow-up Visit	N	44	40	
		Mean	-4.4	-7.9	
		Standard Deviation	11.7	10.1	
		Median	-0.5	-5.5	
		Minimum	-40	-35	
		Maximum	11	9	
		Kruskal-Wallis p-value			0.053
		Hodges-Lehmann shift, estimate			4
		Hodges-Lehmann shift, lower CL			0
		Hodges-Lehmann shift, upper CL			9

Erythropoietic Protoporphyria Quality of Life questionnaire (EPP-QoL, revised scoring)

The Applicant got the EPP-QoL revised by a CRO. The CRO were not able to fully validate the questionnaire but did review the scoring algorithm. Changes were suggested to the original EPP-QoL (e.g. omission of questions). These suggested changes to the EPP-QoL were transferred into the trial CUV039, e.g. three questions were omitted, resulting in a total of 12 questions. As also other aspects related to the questionnaires evaluation were changed, the results of the two versions cannot be compared.
For this questionnaire the Applicant calculated Kruskal-Wallis test statistics and Hodges-Lehmann shift estimates for inter-group comparisons for the changes of the EPP-QoL total scores over time in relation to baseline.

This questionnaire showed improvements for both groups, as indicated by increasing median scores: For Scenesse from 19 on day 0 to 86 on day 180 (+350%); for placebo from 22 to 69 (+ 200%).
The results for the two groups differed statistically significantly with regard to the change in median total scores.
The Applicant states that the differences between the treatment groups at days 60, 120 and 180 were statistically significant in favour of the afamelanotide group.

Table 23: EPP-QoL questionnaire revised version (table 14.2.8.1 as named by the Applicant)

Table 14.2.8.1
Quality of Life - Supplementary EPP Specific Questionnaire by Item (Oxford Scoring)
ITT Quality of Life Population

			------- Summary of EPPQoL Item (Oxford Outcomes Scoring) -------					
EPPQoL Item	Treatment	Visit	N	Mean	Std Dev	Median	Minimum	Maximum
EPPQoL Total Score	Active	Visit 1, Day 0	47	26.6	19.9	19.4	0	83
		Visit 2, Day 60	47	70.6	24.2	77.8	0	100
		Visit 3, Day 120	46	76.9	22.0	81.9	17	100
		Visit 4, Day 180 / Early Termination	46	78.1	24.9	86.1	6	100
		Follow-up Visit	44	38.4	27.0	33.3	0	100
EPPQoL Total Score	Placebo	Visit 1, Day 0	43	26.2	19.4	22.2	3	81
		Visit 2, Day 60	43	49.6	29.8	55.6	6	97
		Visit 3, Day 120	42	55.8	30.2	61.1	6	97
		Visit 4, Day 180 / Early Termination	43	63.0	26.2	69.4	11	100
		Follow-up Visit	40	45.4	29.6	45.8	0	100

Table 24

Table 14.2.8.3
Changes in Quality of Life - Supplementary EPP Specific Questionnaire (Oxford Outcomes Scoring)
ITT Quality of Life Population

EPPQoL Item	Visit		Active Afamelanotide	Placebo	Comparison
Change in EPPQoL Total Score	Visit 2, Day 60	N	47	43	
		Mean	44.0	23.4	
		Standard Deviation	25.8	24.6	
		Median	41.7	25.0	
		Minimum	-2.8	-11.1	
		Maximum	94.4	77.8	
		Kruskal-Wallis p-value			<.001
		Hodges-Lehmann shift, estimate			22.2
		Hodges-Lehmann shift, lower CL			8.3
		Hodges-Lehmann shift, upper CL			33.3
Change in EPPQoL Total Score	Visit 3, Day 120	N	46	42	
		Mean	49.8	30.4	
		Standard Deviation	26.4	25.4	
		Median	50.0	26.4	
		Minimum	-2.8	-8.3	
		Maximum	100.0	88.9	
		Kruskal-Wallis p-value			<.001
		Hodges-Lehmann shift, estimate			19.4
		Hodges-Lehmann shift, lower CL			8.3
		Hodges-Lehmann shift, upper CL			33.3

Table 14.2.8.3
Changes in Quality of Life - Supplementary EPP Specific Questionnaire (Oxford Outcomes Scoring)
ITT Quality of Life Population

EPPQoL Item	Visit		Active Afamelanotide	Placebo	Comparison
Change in EPPQoL Total Score	Visit 4, Day 180 / Early Termination	N	46	43	
		Mean	51.1	36.8	
		Standard Deviation	29.1	25.7	
		Median	52.8	38.9	
		Minimum	2.8	-5.6	
		Maximum	100.0	88.9	
		Kruskal-Wallis p-value			0.021
		Hodges-Lehmann shift, estimate			13.9
		Hodges-Lehmann shift, lower CL			2.8
		Hodges-Lehmann shift, upper CL			27.8
Change in EPPQoL Total Score	Follow-up Visit	N	44	40	
		Mean	10.9	19.4	
		Standard Deviation	27.3	23.9	
		Median	1.4	15.3	
		Minimum	-22.2	-13.9	
		Maximum	100.0	86.1	
		Kruskal-Wallis p-value			0.050
		Hodges-Lehmann shift, estimate			-11.1
		Hodges-Lehmann shift, lower CL			-19.4
		Hodges-Lehmann shift, upper CL			0.0

The scores for the revised EPP-QoL questionnaires, i.e. the perceived quality of life decreased after day 180 but in the Scenesse group as well as in the placebo group at day 360 they were still higher than at day 0 (see table 24 above). According to the Applicant this may reflect the raised expectation of quality of life during afamelanotide treatment and the subjects' response to having the treatment withdrawn.

According to the Applicant the DLQI is established as a quality of life instrument in other dermatological diseases. In EPP it is said to lack the specificity of the EPP-QoL, e.g. not containing any questions that measure the impact of light on the skin and thus no differences in quality of life assessment between Scenesse group and placebo group were detected.

The Applicant concludes on the EPP-QoL results (both versions that following afamelanotide treatment, the quality of life of patients improved statistically significantly compared to placebo recipients and that six months after treatment was discontinued, the quality of life decreased dramatically.

a) **Photoprovocation**

Photoprovocation was conducted on a subset of patients at site # 01 (New York), performed on days 0, 30, 60, 90, and 120 prior to implant administration.
The Applicant performed the evaluation on the ITT photoprovocation subset population.
As an error in conduct several patients received photoprovocation with a maximum of 200 J/cm2 instead of 300 J/cm2. This protocol violation was obviously detected in an intermittent evaluation of study data between day 30 and day 60. The Sponsor/study site realigned the conduct to the protocol with day 60 photoprovocation. The Applicant used mathematical adaptation ("censoring" to account statistically for the underexposure of patients.
The increase from baseline mean minimum symptom dose (MSD) following photoprovocation on the dorsal surface of the hand was greater following treatment with afamelanotide than for the placebo group. The differences were significant at Days 90 and 120 (but not on day 30 or on day 60), with the difference between treatments also characterized using Hodges-Lehmann estimates with a 95% confidence interval. Similar results were observed following photoprovocation on the lower back (Table 27).

The Applicant states that the median response in the Scenesse group appeared to follow a cyclic pattern: The change from baseline in minimum symptom dose (MSD) increased over baseline by day 30 with a small decrease from Day 30 to Day 60 followed by another increase at day 90 and a small decline from Day 90 to Day 120. These changes appear to follow the expected pattern of change in melanin density. While melanin levels were not measured in this study, the CUV017 clinical study report is cited according to which healthy volunteers and EPP patients showed such a cyclic pattern.
Interestingly, the median values for the absolute MSD in afamelanotide recipients reached the maximum dose of 300 J/cm2 at Days 30, 90 and 120 for testing on the dorsum of the hand (predilection place) and at Days 30 and 90 for the lower back.

The Applicant analysed also the change of the individual patient's MSD. A between-group comparison of the change from baseline to each time point in the MSD following photoprovocation on the lower back (skin usually covered by clothes) and dorsal surface of the hand (predilection place). The Applicant focussed on these results.

The Applicant concludes that a treatment-related significant increase in tolerance to visible light irradiation was observed at days 90 and 120 and that afamelanotide recipients have a greater ability to be exposed to visible light with significantly higher doses of light required to provoke prodromal symptoms.

The change of the minimum symptom dose from the previous measurement for days 60, 90, and 120 was not calculated, only the change from baseline (see tables below).

Photoprovocation on the dorsal surface of the hand

Table 25: table 14.2.9.1 (as named by the Applicant, taken from CSR revision 1; absolute values, comparison Scenesse with placebo

Minimum Symptom Dose Following Photoprovocation on the Dorsal Surface of the Hand
(ITT Hand Photoprovcation Population)

		Minimum Symptom Dose on Hand (J/cm^2)									
Visit	Treatment	N	Mean	Std Dev	Median	Minimum	Maximum	Hodges-Lehmann Estimate, Location Shift	Lower CL (Moses), Location Shift	Upper CL (Moses), Location Shift	P-value, Wilcoxon Test (Two-sided)
Visit 1, Day 0	Active	10	61.8	53.1	48.9	2.3	172				
	Placebo	10	70.5	99.0	21.0	1.1	300				
	Comparison							13.1	-55.4	71.3	0.571
Visit 1b, Day 30	Active	10	236.9	102.6	300.0	59.8	300				
	Placebo	10	195.1	139.5	300.0	2.0	300				
	Comparison							0.0	0.0	176.2	0.506
Visit 2, Day 60	Active	10	189.8	110.7	189.9	69.3	300				
	Placebo	9	130.1	119.3	99.7	5.4	300				
	Comparison							55.2	-23.2	200.3	0.229
Visit 2b, Day 90	Active	10	266.2	77.9	300.0	64.2	300				
	Placebo	8	132.4	120.3	122.9	3.3	300				
	Comparison							162.0	0.0	268.1	0.017
Visit 3, Day 120	Active	10	221.4	106.5	300.0	57.8	300				
	Placebo	9	123.8	117.2	85.9	3.0	300				
	Comparison							105.1	0.0	250.8	0.068

Table 26: table 14.2.9.2 (as named by the Applicant, taken from CSR revision 1; changes compared to baseline values, comparison Scenesse with placebo)

Minimum Symptom Dose Following Photoprovocation on the Dorsal Surface of the Hand
(ITT Hand Photoprovcation Population)

		Minimum Symptom Dose on Hand (J/cm^2)									
Visit	Treatment	N	Mean	Std Dev	Median	Minimum	Maximum	Hodges-Lehmann Estimate, Location Shift	Lower CL (Moses), Location Shift	Upper CL (Moses), Location Shift	P-value, Wilcoxon Test (Two-sided)
Visit 1b, Day 30	Active	10	175.1	99.2	197.5	6.4	291				
	Placebo	10	124.6	143.4	75.6	-42.7	292				
	Comparison							36.8	-80.9	198.9	0.521
Visit 2, Day 60	Active	10	127.9	142.9	128.3	-62.8	298				
	Placebo	9	54.3	55.3	36.3	-1.5	157				
	Comparison							61.1	-62.8	223.1	0.540
Visit 2b, Day 90	Active	10	204.3	82.0	208.3	41.6	298				
	Placebo	8	55.0	105.9	13.9	-51.3	289				
	Comparison							181.0	41.6	262.7	0.009
Visit 3, Day 120	Active	10	159.6	97.0	162.1	22.9	291				
	Placebo	9	47.9	103.5	1.9	-54.3	289				
	Comparison							119.8	21.0	229.1	0.025

Photoprovocation on the lower back

Table 27: table 14.2.10.1 (as named by the Applicant, taken from CSR revision 1; absolute values, comparison Scenesse with placebo)

Minimum Symptom Dose Following Photoprovocation on the Back
(ITT Population for Back Photoprovocation)

Visit	Treatment	N	Minimum Symptom Dose on Back (J/cm^2) Mean	Std Dev	Median	Minimum	Maximum	Hodges-Lehmann Estimate, Location Shift	Lower CL (Moses), Location Shift	Upper CL (Moses), Location Shift	P-value, Wilcoxon Test (Two-sided)
Visit 1, Day 0	Active	11	40.1	43.2	32.0	2.1	157				
	Placebo	10	82.2	102.3	24.1	3.7	300				
	Comparison							-3.7	-142.2	22.7	0.778
Visit 1b, Day 30	Active	11	208.1	127.8	300.0	23.9	300				
	Placebo	10	152.6	130.6	98.2	8.6	300				
	Comparison							0.0	-9.8	205.3	0.382
Visit 2, Day 60	Active	11	119.0	95.2	88.1	27.4	300				
	Placebo	9	75.6	92.2	45.1	5.9	300				
	Comparison							31.1	-29.1	144.2	0.160
Visit 2b, Day 90	Active	11	237.3	80.4	300.0	99.5	300				
	Placebo	8	96.5	102.6	65.4	5.9	300				
	Comparison							147.9	47.6	248.1	0.012
Visit 3, Day 120	Active	11	152.5	111.5	107.4	16.2	300				
	Placebo	9	93.9	97.6	45.6	2.2	300				
	Comparison							48.3	-37.6	187.4	0.237

Table 28: table 14.2.10.2 (as named by the Applicant, taken from CSR revision 1; changes compared to baseline values, comparison Scenesse with placebo

Minimum Symptom Dose Following Photoprovocation on the Back
(ITT Population for Back Photoprovocation)

Visit	Treatment	N	Minimum Symptom Dose on Back (J/cm^2) Mean	Std Dev	Median	Minimum	Maximum	Hodges-Lehmann Estimate, Location Shift	Lower CL (Moses), Location Shift	Upper CL (Moses), Location Shift	P-value, Wilcoxon Test (Two-sided)
Visit 1b, Day 30	Active	11	168.0	117.5	237.1	9.1	285				
	Placebo	10	70.4	117.1	44.8	-103.8	294				
	Comparison							118.9	-22.4	246.7	0.062
Visit 2, Day 60	Active	11	78.9	112.1	50.7	-56.4	285				
	Placebo	9	-14.0	105.7	4.3	-210.3	124				
	Comparison							63.8	-22.7	211.9	0.197
Visit 2b, Day 90	Active	11	197.2	75.3	227.5	96.0	298				
	Placebo	8	-0.2	75.4	-2.4	-132.6	124				
	Comparison							206.4	113.6	275.5	<.001
Visit 3, Day 120	Active	11	112.3	100.6	82.5	10.0	271				
	Placebo	9	4.2	86.3	12.1	-187.4	124				
	Comparison							79.9	7.8	233.9	0.028

Phototoxicity—phototoxic pain outcomes—secondary endpoints

The maximum and total pain severity scores (Likert scale) for phototoxic episodes were measured as secondary endpoints. Furthermore the number of phototoxic episodes per subject reported by the patient during the study (treatment phase, 180 days) were recorded. The source for these endpoints is the patients' diary data. A between groups comparison of the scores for each of the above parameters was performed using the Kruskal-Wallis test.

No differences were seen in the number or severity of phototoxicity between Scenesse patients and placebo patients.

The Applicant reported that sun avoidance behaviour may have been a contributing factor to this finding, in the sense of too few patients exposing themselves enough to cause events of phototoxicity and the

small number of phototoxicity events (median of 1 in 180 days, in both treatment groups, highlighted), did not allow for statistical analysis to discriminate between Scenesse and placebo.
Table 14.2.12.1 from the CUV039 CSR shows the related figures (ITT population, all participants). The three highlighted column headings refer to the secondary endpoints mentioned above.

Table 29:

				------ Total Phototoxicity Per Subject Over the Entire Study ------		
Treatment		Number of Episodes	Number of Days in Longest Episode	Overall Number of Days	Overall Sum of Severity	Overall Maximum of Severity
Active	N	46	46	46	46	46
	Mean	2.0	1.3	3.2	16.3	3.5
	Std Dev	3.3	1.9	6.0	33.2	3.1
	Median	1.0	1.0	1.0	4.0	4.0
	Maximum	15	12	34	196	8
	Minimum	0	0	0	0	0
Placebo	N	43	43	43	43	43
	Mean	3.3	1.7	6.6	34.1	3.9
	Std Dev	6.8	2.1	16.8	86.7	3.3
	Median	1.0	1.0	1.0	6.0	5.0
	Maximum	35	10	98	507	9
	Minimum	0	0	0	0	0
Kruskal-Wallis test	p-value	0.602	0.519	0.503	0.442	0.544

In summary, Scenesse implant recipients and placebo implant recipients had - infrequent phototoxic reactions while on study.

Ancillary analyses

a) pre-specified

With protocol version 2.0 an additional quality of life questionnaire at day 360 was introduced.

EPP Follow Up Questionnaire
The Applicant used an “End-of-study EPP questionnaire/EPP Follow p Questionnaire“ to be completed on Day 360. It was completed by most of the patients in both treatment groups and in conjunction with the EPP-QoL questionnaires, according to the protocol. The Applicant considers it exploratory. The CSR end of study EPP questionnaire‘s results are presented as a part of the secondary efficacy analyses (see table 30 below).
For several questions this questionnaire results in higher rates of positive answers for the Scenesse recipients as compared to the placebo recipients.

As an example a set of two questions and their results is extracted from the complete questionnaire and presented below:

Table 30 (taken from table 11.12 as named by the Applicant, CSR revised version, p73-74)
Summary of results of the EPP follow up questionnaire

Question	Active (n=44)	Placebo (n=40)
1. Which differences have you noticed since you received the drug?		
A) None	7 (16%)	27 (68%)
B) Less sensitivity (phototoxicity) of the skin	26 (59%)	9 (23%)
C) More sensitivity (phototoxicity) of the skin	8 (18%)	1 (3%)
D) Less pain	18 (41%)	5 (13%0
E) More pain	5 (11%)	1 (3%)
F) Am able to tolerate light more	20 (45%)	9 (23%)
2. Which aspect characterizes best your attitude and outlook since receiving the drug?		
A) Less anxious to experience skin symptoms	24 (55%)	10 (25%)
B) More anxious to experience skin symptoms	8 (18%)	5 (13%)
C) Less inclined to go outdoors	9 (20%)	11 (28%)
D) More inclined to go outdoors	24 (55%)	14 (35%)
3. Since receiving the drug, how do you assess your ability and willingness to go outdoors?		
A) No difference	9 (20%)	24 (60%)
B) More confident to expose outdoors	23 (52%)	9 (23%)
C) Skeptical about the ability to go outdoors	8 (18%)	2 (5%)
D) Will gradually test myself to see whether symptoms occur	13 (30%)	8 (20%)
7. How do you best summarize your experience since receiving the drug?		
A) I have less anxiety	23 (52%)	8 (20%)
B) I have more anxiety	6 (14%)	2 (5%)
C) I feel more confident	24 (55%)	10 (25%)
D) I feel less confident	2 (5%)	2 (5%)
E) None of the above	10 (23%)	25 (63%)
8. How has the treatment affected your life?		
A) No improvement	12 (27%)	26 (65%)
B) Much improvement	14 (32%)	3 (8%)
C) Dramatic improvement	19 (43%)	11 (28%)
9. How do you best characterize your experience after receiving the drug?		
A) I would request this drug all year	29 (66%)	15 (38%)
B) I would request this drug during spring and summer	15 (34%)	7 (18%)
C) I am unsure	4 (9%)	15 (38%)
D) I would not request the drug		5 (13%)
10. Since receiving the drug, I expose myself		
A) Less to outdoors conditions	4 (9%)	1 (3%)
B) More to outdoors conditions	27 (61%)	15 (38%)
C) Unchanged to my previous life	13 (30%)	24 (60%)

Source: Listing 16.2.35

a) Post-hoc analyses

The study report for CUV039 presented a number of post-hoc analyses.

Related to the primary endpoint (efficacy)

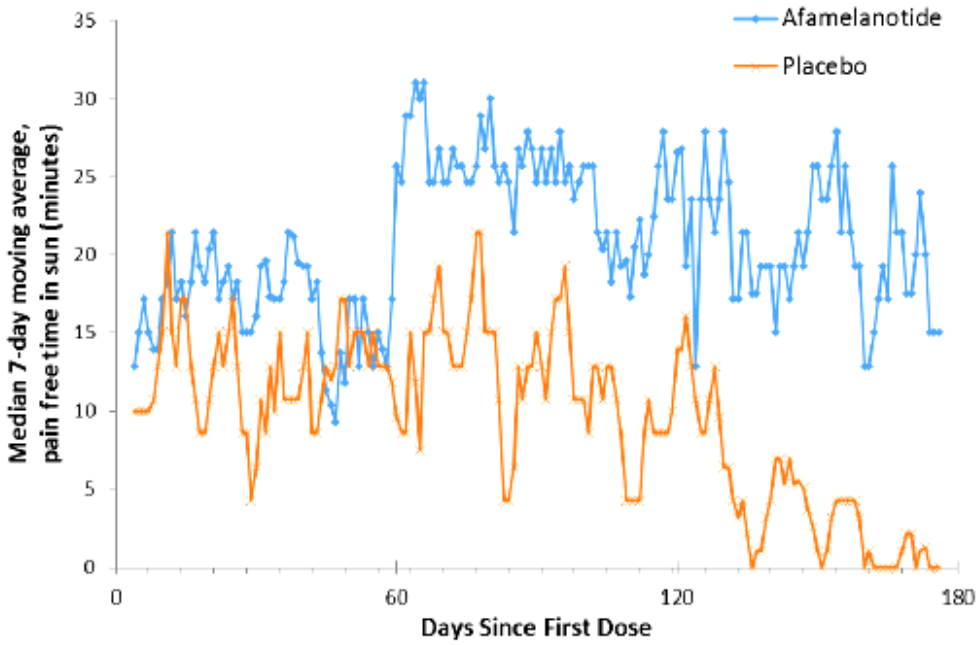
The difference according to the Hodges-Lehmann estimate was 24.0 hours (95% CI: 0.3, 50.3) in favour of Scenesse in the ITT diary card population. This effect was attributed to the treatment and was, compared with the median of the placebo group about, 60 % higher.

The total number of pain-free days (per subject) with some direct sunlight exposure between 10:00 and 18:00 hours was statistically significantly (Kruskal-Wallis test, p=0.005) different in favour of afamelanotide. The Hodges-Lehmann shift estimate for the ITT diary card population is 29 days over the 6-month trial period. The sensitivity analyses using the study completers population (SC, diary card) produced similar results.

The median of the individual patients' 7 day moving average for pain-free daily exposure to direct sunlight was calculated. From day 60 onwards, the Applicant reported a consistent difference in pain-free direct sunlight exposure between the treatment groups with regard to this construct.

Figure 06 (figure 11.1 as named by the Applicant)

Figure 11.1 Longitudinal trends in direct sunlight exposure (ITT population, Diary Card)



The Applicant concludes from these results that there is a consistent difference in pain-free direct sunlight exposure between the treatment groups and that the differences between the treatment groups in the longitudinal patterns support the hypothesis that subjects treated with afamelanotide are better able to tolerate direct sunlight exposure and overcome the anxiety previously associated with such exposure.

<u>Related to secondary endpoints</u>

The Applicant calculated for "Sun exposure (hours) between 10:00 and 18:00 on days when no or mild pain was experienced (ITT population, Diary Card)" the estimate for the Hodges-Lehmann shift. For this statistically non-significant difference between Scenesse and placebo patients, the estimate was 26.8 hours (95% CI: -0.3, 57.5) numerically in favour of Scenesse across the 6 month study period.

When expressed as the corresponding mean daily direct sunlight sun exposure on days when no or mild pain (Likert score 0-3) was experienced the estimated difference was 8.4 minutes (as per Hodges-Lehmann shift estimate, 95% CI: -1.5, 18.9); per day in favour of Scenesse, not being statistically significant with either of the methods applied Kruskal-Wallis test, p=0.094).

The Applicant calculated also the "total number of pain-free or mild pain days (Likert pain scores of 0 to 3) … with some direct sunlight exposure between 10:00 18:00 hours". The Applicant found astatistically significant difference of 32 days in favour of afamelanotide according to the Hodges-Lehmann shift estimate (95% CI: 9.0, 54.0;p=0.004<0.05, Kruskal-Wallis test) over the 6 month study period.

The sensitivity analyses using study completers population (SC, Diary Card) produced similar results to the ITT, Diary Card population.

Post-hoc analyses related to the secondary efficacy endpoint "duration of direct sunlight exposure between 10:00 and 15:00 hours on days when no pain was experienced (Likert score of 0) yielded no statistically significant difference Scenesse vs. placebo (Kruskal-Wallis test; p=0.092>0.05). The Hodges-Lehmann shift estimate of 13.1 hours in favour of Scenesse was not statistically significant (95% CI: -1.3, 28.0). When expressed as the corresponding mean daily pain-free direct sunlight exposure (10:00 to 15:00 hours), the difference was 4.9 minutes per day (95% CI: -1.0, 10.6); being not statistically significant.

Only one out three analyses, concerning the total number of pain-free days (per subject) with some sunlight (10:00-15:00 hours) showed a statistically significant difference in favour of Scenesse (Kruskal-Wallis test, p=0.013). The treatment difference (estimate Hodges-Lehmann shift) was 20.0 days (95% CI: 4.0, 39.0).

Figure 07:

Table 11.5 Pain-free sun exposure (hours) between 10:00 and 15:00 hours (ITT population, Diary Card)

Parameter	Active (n=46)	Placebo (n=43)	
Total number of hours per subject in Sunlight – pain-free days (Likert pain score of 0)			
Mean (SD)	71.2 (89.2)	41.6 (45.3)	
Median	39.6	31.8	
Range	0 – 419.0	0 – 198.8	
Kruskal-Wallis *p*-value			0.092
Hodges-Lehmann shift, Estimate			13.1
95% Confidence Interval			-1.3 – 28.0
Mean daily minutes per subject in Sunlight – pain-free days (Likert pain score of 0)			
Mean (SD)	26.9 (33.3)	16.4 (17.3)	
Median	14.9	11.0	
Range	0 – 167.6	0 – 74.1	
Kruskal-Wallis *p*-value			0.134
Hodges-Lehmann shift, Estimate			4.9
95% Confidence Interval			-1.0 – 10.6
Total number of days per subject with some time in Sunlight – pain-free days (Likert pain score of 0)			
Mean (SD)	64.0 (43.2)	41.1 (31.6)	
Median	60.5	40.0	
Range	0 – 166	0 – 120	
Kruskal-Wallis *p*-value			0.013
Hodges-Lehmann shift, Estimate			20.0
95% Confidence Interval			4.0 – 39.0

There were 15 subjects who experienced more than 60 minutes of direct sun light exposure per day, and of those there were 12 on active and 3 on placebo. The 6 subjects who reported more than 100 minutes of daily exposure to direct sunlight between 10:00 and 18:00 were all Scenesse recipients.
The average number of days per subject of exposure to direct sunlight was higher for the afamelanotide group than for the placebo group in each of the 15 minute time intervals between 10:00 and 18:00. This indicates that subjects in the afamelanotide group had a substantial increase in total time outdoors.

Further post-hoc analyses deal with the phototoxicity-related pain severity. The number of days on which patients reported pain for each of the possible pain severity scores (using the 11 point Likert scale) was evaluated (see table 31 below).
The Applicant pre-defined phototoxic pain as the one with a Likert scale score of 4 to 10 (moderate to worst imaginable). These levels of pain were reported twice as often in the placebo as compared to the Scenesse group (3.8 versus 1.8% days).

Table 31:

Table 11.6 Distribution of daily pain scores (ITT population, Diary Card)

Pain Score (11 point Likert Scale)	Afamelanotide Implant (16 mg) (N=46)			Placebo (N=43)		
	Number of Days	Proportion of Total (%)	Cumulative proportion of reported scores (%)	Number of Days	Proportion of Total (%)	Cumulative proportion of reported scores (%)
0	7156	88.8%	88.8%	6245	84.8%	84.8%
1	343	4.3%	93.1%	358	4.9%	89.6%
2	280	3.5%	96.6%	300	4.1%	93.7%
3	130	1.6%	98.2%	182	2.5%	96.2%
4	55	0.7%	98.9%	112	1.5%	97.7%
5	42	0.5%	99.4%	75	1.0%	98.7%
6	30	0.4%	99.8%	52	0.7%	99.4%
7	13	0.2%	99.9%	24	0.3%	99.7%
8	6	0.1%	100.0%	18	0.2%	100.0%
9	0	0.0%	100.0%	2	0.0%	100.0%
10	0	0.0%	100.0%	0	0.0%	100.0%
(Missing)	79			106		

A further post-hoc analysis was directed at the distribution of the maximum pain score per subject. Related data are presented in the table below

Table 32:

Table 11.7 Distribution of maximum pain scores per subject (ITT population, Diary Card)

Maximum Pain Score (11 point Likert Scale)	Afamelanotide Implant (16 mg) (N=46)		Placebo (N=43)	
0	1	(2%)	3	(7%)
1	5	(11%)	4	(9%)
2	4	(9%)	4	(9%)
3	8	(17%)	5	(12%)
4	7	(15%)	3	(7%)
5	3	(7%)	8	(19%)
6	10	(22%)	4	(9%)
7	4	(9%)	6	(14%)
8	4	(9%)	4	(9%)
9	0	(0%)	2	(5%)

Eighteen of 46 subjects in the Scenesse group (39%) and 16 of 43 subjects in the placebo group (37%) did not experience pain of sufficient intensity to be classified in the Applicant's definition as a phototoxic episode (i.e. Likert pain scale score >3).The proportion of subjects who experienced phototoxic reactions with Likert pain intensity scores ≥4 was comparable between treatment groups.

Summary of the main clinical studies

Study no	Period of Conduct	Design	Study treatment	Main Objectives	Sample size	Duration	Primary endpoint	Main results
CUV010	09/2006 to 02/2007	Phase II, one-site, open-label, uncontrolled Study to evaluate the safety and efficacy of subcutaneous implants of CUV1647 in patients with EPP	Scenesse 20 mg implant s.c., every 2nd month, 6 doses in total	To reduce the susceptibility to photoprovocation with standardized light source Effect on use of rescue medication	5	120 days	Appearance of provoked symptoms following phototesting	Average minimum time to response after photoprovocation from 1.9 min (SD 1.3) at BL to 13.3 min (SD 2.6) at D120 Melanin density increased, with an increase of approximately 1 MD unit *Safety*: implant site reactions, headache, somnolence, nausea
CUV017	05/2007 to 12/2009	Phase III, Multicentre, Randomised, Placebo-Controlled crossover study to evaluate the safety and efficacy of CUV1647 implants in Patients with EPP	Group A: Scenesse 16 mg implant s.c. on days 0, 120, 240 and placebo implant on days 60, 180 and 300 Group B: Treatment sequence vice versa	To reduce the number of phototoxic reactions with sunlight in patients with EPP; Safety and Tolerability	100	360 days	Number and severity of phototoxic reactions	Distribution of frequency of days with pain of different severity differed between active and placebo p=0.0042) Significantly more sun exposure in patients receiving afamelanotide (p = 0.0136; Cochran-Mantel-Haenszel test) No marked effects on QoL *Safety*: nausea, flushing

CUV030	04/2010 to 01/2011	Phase II, Multicentre, Double-Blind, Randomised, Placebo-Controlled Study to Confirm the Safety and Efficacy of Subcutaneous Bioresorbable Afamelanotide Implants in Patients with EPP	Scenesse 16 mg implant s.c., every 2nd month, 3 doses in total	Severity of phototoxic reactions in patients with EPP; Safety and Tolerability- artificial light source	77	180 days	Severity of phototoxic reactions. **Post hoc changed** to time (h) of sun exposure	**Study not GCP compliant** No difference between groups in number of severe phototoxicity reactions Verum patients more direct sunlight exposure between 10:00 and 15:00 hours on days when no pain was experienced (pain score of 0; p=0.012), no difference between groups for overall time spent outdoors. *Safety*: nausea, fatigue, pyrexia, nasopharyngitis
CUV029	01/2010 to 05/2011	Phase III, Multicentre, Double-Blind, Randomised, Placebo-Controlled Study to Confirm the Safety and Efficacy of Subcutaneous Bioresorbable Afamelanotide Implants in Patients with EPP	Scenesse 16 mg implant s.c., Every 2nd month, 5 doses in total	Severity of phototoxic reactions in patients with EPP; Safety and Tolerability- artificial light source	74	270 days	Number and severity of phototoxic reactions **Post hoc changed** to time (h) of sun exposure	**Study not GCP compliant** Significantly fewer phototoxic episodes (p=0.044), with significantly lower maximum pain severity per phototoxic episode (p=0.018) o Verum patients more time in direct sunlight than placebo recipients between 10:00 and 20:00 hours (not significantly different for 10 to 15 hrs) *Safety*: pigmentation disorders and implantation site discolouration
CUV039*	05/2012 to 07/2013	, Multicentre, Double-Blind, Randomised, Placebo-Controlled Study to Confirm **the Safety and Efficacy** of Subcutaneous Bioresorbable Afamelanotide Implants in Patients with Erythropoietic Protoporphyria	Scenesse 16 mg implant s.c., Every 2nd month, 3 doses in total	Exposure to sunlight without incurring pain and phototoxic reactions	93	180 days	Duration of direct sunlight exposure between 10:00 and 18:00 hours on pain-free days	Verum patients more pain-free direct sun exposure, p=0.044 (Kruskal-Wallis) *Safety*: Fatigue, implant site reactions/pain, arthralgia, myalgia, headache

***** As study CUV039 is the only pivotal study for this application a more detailed listing of the efficacy are provided in the table below.

Summary of efficacy for trial CUV039

The following tables summarise the efficacy results from the main study CUV039 supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Title: A Phase III, Multicentre, Double-Blind, Randomized, Placebo-Controlled Study to Confirm the Safety and Efficacy of Subcutaneous Bioresorbable Afamelanotide Implants in Patients with Erythropoietic Protoporphyria (EPP). [Short Title: Multicentre Phase III EPP Study 3]			
Study identifier	Protocol No: CUV039 IND Number: 103,131 EUDRACT Number: Not applicable		
Design	randomized placebo-controlled, in two parallel study arms for a six month period (three doses)		
	Duration of screening phase: Duration of main phase (treatment and efficacy assessment): Duration of Run-in phase: Duration of Extension phase: Duration of observation period following efficacy assessment: Maximum duration per participant:	Up to 14 days 180 days not applicable not applicable 180 days 284 days	
Hypothesis	There is no difference between the treatment arms in the time spent in direct sunlight on days when no phototoxic pain was reported.		
Treatments groups	Group A		afamelanotide implants on Days 0, 60 and 120 48 patients randomized
	Group B		placebo implants on Days 0, 60 and 120 45 patients randomized
Endpoints and definitions	Primary endpoint	Efficacy	Duration of time (hours) spent in direct sunlight between 10:00 and 18:00 hours on days when no pain was experienced (pain score of 0)
	Secondary endpoints Efficacy	Combined sun exposure and phototoxic pain	Duration of sun exposure (hours in direct sunlight) between 10:00 and 18:00 hours on days when no pain or mild pain was experienced (Likert pain scores of 0-3)
			Duration of direct sunlight exposure between 10:00 and 15:00 hours on days when no pain was experienced (Likert score of 0)
			The difference in the patient's average daily duration of direct sunlight exposure between 10:00 and 15:00 hours on days when no pain was experienced (Likert score of 0)

			Duration of sun exposure (hours in direct sunlight) between 10:00 and 15:00 hours on days when no pain was experienced (Likert score of 0).
			Mean daily duration of sun exposure (hours in direct sunlight) between 10:00 and 15:00 hours on days when no pain was experienced (Likert score of 0)
		Sun exposure	Duration of sun exposure (hours in direct sunlight) between 10:00 and 18:00 during the study
		Quality of life	Quality of life assessment score according to the DLQI and EPP-QoL questionnaires
		Photoprovocation (subset of 21 patients)	Minimum symptom dose following photoprovocation on the lower back and dorsal surface of the hand
		Phototoxicity – phototoxic pain	Maximum and total pain severity scores (Likert scale) for phototoxic episodes
		Phototoxicity – phototoxic pain	Number of phototoxic episodes during the study
	Secondary endpoints	Safety	Physical examination changes from Screening
			Changes in blood pressure and heart rate from screening to all subsequent visits; and significant abnormalities identified in ECG
			Changes in clinical chemistry, haematology and urinalysis parameters from Screening to all subsequent visits
Database lock	11 Oct 2013		

Results and Analysis			
Primary endpoint			
	Afamelanotide	**Placebo**	**Statistics**
Total daily duration of time (hrs) spent in direct sunlight 10:00-18:00 hrs on days when no pain was experienced	N=46 Median 69.4h Range 0-650.5h Mean (SD) 115.6h (140.6h)	N=43 Median 40.8h Range 0-224.0h Mean (SD) 60.6h (60.6h)	p=0.044 (Kruskal-Wallis) 24.0h (95%CI 0.3-50.3h; Hodges-Lehmann shift, estimate)
Secondary endpoints			
Mean daily duration of sun exposure (hrs in direct sunlight) 10:00-18:00 hrs on days when no pain or mild pain was experienced*	N=46 Median 0.46h (27.3min); range 0.003h-4.4h (0.2-263.8min); mean (SD) 0.79h (0.89h) (47.5min [53.4min])	N=43 Median 0.45h (25.2min); range 0.01h-1.42h (0.7min-85min); mean (SD) 0.45h (0.38h) (27.1min [22.9min])	p=0.094 (Kruskal-Wallis); **n.s.** 8.4 min (95%CI -1.5-18.9 min Hodges-Lehmann shift estimate)
Mean daily duration of sun exposure (hours in direct sunlight) 10:00-18:00 hrs regardless of pain score*	N=46 Median 0.46h (27.6min); range 0.003h-4.38h (0.2-263.3min); mean (SD) 0.80h (0.88h) (48.1min [52.7min])	N=43 Median 0.42h (25.1min); range 0.03h-1.57h (1.8-94.4min); mean (SD) 0.47h (0.39h) (28.3min [23.6min])	p=0.092 (Kruskal-Wallis); **n.s.** 8.5 min (95%CI -1.6-18.8; Hodges-Lehmann shift estimate)
Mean daily duration of sun exposure (hrs in direct sunlight) 10:00-15:00 hrs on days when no pain was experienced (Likert score of 0)*	N=46 Median 0.25h (14.9min); range 0h-2.79h (0-167.6min); mean (SD) 0.45h (0.56h) (26.9min [33.3min])	N=43 Median 0.18h (11.0min); range 0h-1.24h (0-74.1min); mean (SD) 0.27h (0.29h) (16.4min [17.3min])	p=0.134 (Kruskal-Wallis); **n.s.** 4.88 min (95% CI -0.97-10.58min; Hodges-Lehmann shift estimate)

DLQI Quality of life Questionnaire (total score) a) Change at day 60 (visit 2) compared to baseline	a) n=47; median -6.0; range 2 to -24; mean (SD) -6.0 (5.9)	a) n=43; median -5.0; range 11 to -15; mean (SD) -4.0 (5.5)	a) p=0.214 (Kruskal-Wallis); Hodges-Lehmann shift estimate (95%CI) -1 [1,-4]
b) Change at Day 120 (visit 3) compared to baseline	b) n=46; median -7; range 0 to -26; mean (SD) -7.8 (6.0)	b) n=42; median -6.5; range 14 to -17; mean (SD) -6.5 (6.2)	b) p=0.589 (Kruskal-Wallis); Hodges-Lehmann shift estimate (95%CI) -1 [2,-3]
c) Change at Day180 (visit 4) compared to baseline	c) n=46; median -7.5; range 1 to -26; mean (SD) –8.1 (6.2)	c) n=43; median –8.0; range 5 to -19; mean (SD) –7.3 (5.6)	c) p=0.799 (Kruskal-Wallis); Hodges-Lehmann shift estimate (95%CI) 0 [2,-3] **<u>not</u> statistically significant for any time point**

EPP - quality of life Questionnaire			
Original scoring: 1) change at day 60 (visit 2) compared to baseline	Original scoring: 1) n=47; median -19.0; range 2, -39; mean (SD) -18.7 (11.0)	Original scoring: 1) n=43; median -11.0; range 6, -32; mean (SD) -10.0 (10.5)	Original scoring: 1) p<0.001 (Kruskal-Wallis); Hodges-Lehmann shift estimate (95%CI) -9 [-15, -4]
2) change at Day 120 (visit 3) compared to baseline	2) n=46; median -21.5; range -45, 2; mean (SD) -21.1 (11.3)	2) n=42; median -11.5; range -39, 2; mean (SD) -13.0 (10.8)	2) p<0.001 (Kruskal-Wallis); Hodges-Lehmann shift estimate (95%CI) -8 [-14, -3]
3) change at Day180 (visit 4) compared to baseline	3) n=46; median -22.0; range -45, -1; mean (SD) -21.1 (12.2)	3) n=43; median -14.0; range -39, 3; mean (SD) -15.1 (10.9) (	3) p<0.02 (Kruskal-Wallis); Hodges-Lehmann shift estimate (95%CI) -6 [-11, -1]
Revised scoring: A) change at day 60 (visit 2) compared to baseline	Revised scoring: A) n=47; median 41.7; range -2.8, 94.4; mean (SD) 44.0 (25.8)	Revised scoring: A) n=43; median 25.0; range -11.1, 77.8; mean (SD) 23.4 (24.6)	Revised scoring: A) p<0.001 (Kruskal-Wallis); Hodges-Lehmann shift estimate (95%CI) 22.2 [8.3, 33.3]
B) change at day 120 (visit 3) compared to baseline	B) n=46; median -50.0; range -2.8, 100; mean (SD) 49.8 (26.4)	B) n=42; median 26.4; range -8.3, 88.9; mean (SD) 30.4 (25.4)	B) p<0.001 (Kruskal-Wallis); Hodges-Lehmann shift estimate (95%CI) 19.4 [8.3, 33.3]
C) change at day180 (visit 4) compared to baseline	C) n=46; median 52.8; range 2.8, 100; mean (SD) 51.1 (29.1)	C) n=43; median 38.9; range -5.6, 88.9; mean (SD) 36.8 (25.7)	C) p<0.02 (Kruskal-Wallis); Hodges-Lehmann shift estimate (95%CI) 13.9 [2.8, 27.8]
Absolute values for quality of life supplementary EPP-specific questionnaire, d 360 follow-up visit	n=44; median 33.3; range 0, 100; mean (SD) 38.4 (27.0)	n=40; median 45.8; range 0, 100; mean (SD) 45.4 (29.6)	p=0.05

Photoprovocation (21 patients): Minimum symptom dose, dorsal surface of hand			
a) day 0	a) N=10 Median (range) 48.9 J/cm^2 (2.3-172); mean (SD) 61.8 (53.1) J/cm^2	a) N=10 Median (range) 21.0 J/cm^2 (1.1-300); mean (SD) 70.5 (99.0) J/cm^2	a) p=0.571 (Wilcoxon); Hodges-Lehmann shift estimate (95% CI) 13.1 [-55.4,71.3]
b) day 30	b) N=10 Median (range) 300.0 J/cm^2 (59.8-300); mean (SD) 236.9 (102.6) J/cm^2	b) N=10 Median (range) 300.0 J/cm^2 (2-300); mean (SD) 195.1 (139.5) J/cm^2	b) p=0.506 (Wilcoxon); Hodges-Lehmann shift estimate (95% CI) 0 [0,176.2}
c) day 60	c) N=10 Median (range) 189.9 J/cm^2 (69.3-300); mean (SD) 189.8 (110.7) J/cm^2	c) N=9 Median (range) 99.7 J/cm^2 (5.4-300); mean (SD) 130.1 (119.3) J/cm^2	c) p=0.229 (Wilcoxon); Hodges-Lehmann shift estimate (95% CI) 55.2 [-23.2,200.3]
d) day 90	d) N=10 Median (range) 300.0 J/cm^2 (64.2-300); mean (SD) 266.2 (77.9) J/cm^2	d) N=8 Median (range) 122.9 J/cm^2 (3.3-300); mean (SD) 132.4 (120.3) J/cm^2	d) p=0.017 (Wilcoxon); Hodges-Lehmann shift estimate (95% CI) 162.0 [0,268.1]
e) day 120	e) N=10 Median (range) 300.0 J/cm^2 (57.8-300); mean (SD) 221.4 (106.5) J/cm^2	e) N=9 Median (range) 85.9 J/cm^2 (3.0-300); mean (SD) 123.8 (117.2) J/cm^2	e) p=0.068 (Wilcoxon); Hodges-Lehmann shift estimate (95% CI) 105.1 [0,250.8] **<u>not</u> statistically significant at four out of five time points**

Photoprovocation (21 patients): Minimum symptom dose, lower back			
a) day 0	a) N= 11 Median (range) 32.0 J/cm^2 (2.1-157); mean (SD) 40.1 (43.2) J/cm^2	a) N= 10 Median (range) 24.1 J/cm^2 (3.7-300); mean (SD) 82.2 (102.3) J/cm^2	a) p=0.778 (Wilcoxon); Hodges-Lehmann shift estimate (95% CI) -3.7 (-142.2, 22.7)
b) day 30	b) N=11 Median (range) 300.0 J/cm^2 (23.9-300); mean (SD) 208.1 (127.8) J/cm^2	b) N= 10 Median (range) 98.2 J/cm^2 (8.6-300); mean (SD) 152.6 (130.6) J/cm^2	b) p=0.382 (Wilcoxon); Hodges-Lehmann shift estimate (95% CI) 0 (-9.8, 205.3)
c) day 60	c) N=11 Median (range) 88.1 J/cm^2 (27.4-300); mean (SD) 119.0 (95.2) J/cm^2	c) N=9 Median (range) 45.1 J/cm^2 (5.9-300); mean (SD) 75.6 (92.2) J/cm^2	c) p=0.160 (Wilcoxon); Hodges-Lehmann shift estimate (95% CI) 31.1 (-29.1, 144.2)
d) day 90	d) N=11 Median (range) 300.0 J/cm^2 (99.5-300); mean (SD) 237.3 (80.4) J/cm^2	d) N=8 Median (range) 65.4 J/cm^2 (5.9-300); mean (SD) 96.5 (102.6) J/cm^2	d) p=0.012 (Wilcoxon); Hodges-Lehmann shift estimate (95% CI) 147.9 (47.6, 248.1)
e) day 120	e) N=11 Median (range) 107.4 J/cm^2 (16.2-300); mean (SD) 152.5 (111.5) J/cm^2	e) N=9 Median (range) 45.6 J/cm^2 (2.2-300); mean (SD) 93.9 (97.6) J/cm^2	**<u>not</u> statistically significant at four of five time points**
Phototoxicity episodes	n=46	N=43	
a) maximum pain severity score (Likert scale)	a) Median 4.0;range 0-8; mean (SD) 3.5 (3.1)	a) Median 5.0; range 0-9; mean (SD) 3.9 (3.3)	a) 0.544 (Kruskal-Wallis), **n.s.**
b) total pain severity score (Likert scale)	b) Median 4.0; range 0-196; mean (SD) 16.3 (33.2)	b) Median 6.0; range 0-507; mean (SD) 34.1 (86.7)	b) 0.442 (Kruskal-Wallis), **n.s.**
c) number of episodes	c) Median 1.0; range 0-15; mean (SD) 2.0 (3.3)	c) Median 1.0; range 0-35; mean (SD) 3.3 (6.8)	c) 0.602 (Kruskal-Wallis), **n.s.**

* divided by the total number of diary cards completed.

n. s.: not statistically significant

Analyses for the total number of hours per subject in direct sunlight showed also numerical trends in favour of Scenesse, however consistently no statistically significant differences between groups and are thus not displayed separately in this summary table.

Analysis performed across trials (pooled analyses and meta-analysis)

Not available.

Clinical studies in special populations

Not available.

Supportive study

Supportive studies were not submitted. Efficacy data from an expanded access/compassionate use programme are discussed in section 3.3.6.

2.5.3. Discussion on clinical efficacy

The discussion focusses on the studies CUV017, CUV029, CUV030 and study CUV039.

For this marketing authorisation application the Applicant submitted the clinical trials CUV029 and CUV030 as pivotal studies. In the course of the studies' assessment, a number of clinically relevant protocol deviations were observed and the CHMP triggered a GCP inspection that was done in 2013. As a reply to address CHMP questions, the applicant submitted the clinical trial CUV039. This study then served as sole pivotal study.

Design and conduct of clinical studies

Study CUV017 had been intended to be submitted as pivotal study for the MAA of Scenesse in 2009. However, in the CHMP protocol assistance it stated that the crossover design was unsuitable and that pivotal, confirmatory parallel group studies should be run.

Studies CUV029 (Europe) and CUV030 (US) were submitted as pivotal studies in support of the marketing authorisation application.

These studies were both placebo-controlled and investigated the efficacy of repeat administration of a 16 mg afamelanotide implant at 60-day intervals over 270 days (CUV029) or 180 days (CUV030), respectively.

Due to the results seen in study CUV017 the Applicant changed the objectives of the studies while the studies were ongoing. The new final primary end point of both studies was sunlight exposure between 10:00-15.00 hours (updated from initial 10:00-20:00 hours interval). The secondary end points included overall sun exposure, sun exposure and pain, phototoxicity, QoL measures (EPP-QoL and DLQI) and photoprovocation.

The CHMP discussed this issue and while the design of these studies followed in many respects the CHMP protocol assistance given in 2009, they did not follow the advice in terms of choice of the comparator group, considered essential to be able for maintenance of blinding. At the Ad hoc Expert Group meeting in April 2014 the clinical experts and the patients regarded the background treatment with betacarotene as not feasible and explained that recruitment for a treatment with this substance would have been very difficult in a patient population who in majority had not had success with betacarotene treatment.

This led to difficulties in the interpretation of the efficacy results, as all the primary endpoints and most of the secondary endpoints were based on subjective assessments. The studies had to be regarded as insufficiently blinded due to the pharmacodynamic effect (increase in pigmentation) of afamelanotide. Thus, the results from these studies are prone to bias. This adds to the difficulty to provide comprehensive information on efficacy in treatment with afamelanotide. However, it is also recognised that blinding of the studies would have been very difficult without measures that would have made the study impossible to conduct.

In a GCP-inspection of studies CUV029 and CUV030 several critical and major findings led to the conclusion that these studies could not be considered pivotal for the efficacy assessment of Scenesse.

Study CUV039 (USA) was a placebo-controlled phase III clinical study set up by the Applicant.

A GCP inspection was performed on this trial in 2014 and did not reveal any critical issues, which would preclude the assessment of its results (only one major finding, e.g. affecting safety/AE reporting).

This study was also planned to be conducted in a double-blind manner. Again, the blinding issue discussed above make it difficult to interpret the data from the subjective end points.

The Applicant argued that the definition of the primary endpoint was not fully clear, permitting different interpretations. In total, the Applicant mentioned three different possibilities of primary endpoints that could be derived from the wording.

1. Total duration of time (hours) spent in direct sunlight between 10:00 and 18:00 hours on days when no pain was experienced (Likert score of 0) (primary endpoint in original and revised CSR)
2. Mean daily duration in direct sunlight exposure between 10:00 and 18:00 hours on days when no pain was experienced was calculated for each subject by dividing the total duration of time spend in direct sunlight (for the study) by the number of days that each subject was on the study (revised CSR).
3. Mean daily duration in direct sunlight exposure calculated as time spent in direct sunlight between 10:00 and 18:00 hours on days when no pain was experienced divided by the number of pain-free days (primary endpoint according to protocol, objected to in the original CSR; no results presented).

The CHMP was of the view the primary endpoint in a confirmatory (pivotal) clinical trial should be defined unambiguously in the study protocol to avoid the post-hoc choice of the 'most favourable' primary endpoint. Retaining one of the possible endpoints as the only primary endpoint post-hoc is not considered best practice. However, if the primary endpoints interpreted in different fashions show consistent results in direction of positive efficacy, the concern over post-hoc selection is reduced. The assumptions made for missing values (here: diary entries) have their own effect on the primary endpoints, on all diary based endpoints, and lead themselves to an uncertainty of the effect size.

The magnitude of the effect size is considered small and is in line with the trend for positive efficacy of primary endpoint results in CUV029 and CUV030.

Efficacy data and additional analyses

In study CUV017, a placebo-controlled study on efficacy and safety with a treatment duration of one year, 100 patients were recruited, of whom 93 completed the study. The primary endpoints were the number and severity of phototoxic reactions. The secondary endpoints included sunlight exposure, melanin density, quality of life, and safety and tolerability.

On initial analysis of the results it was found that a large proportion of the patients did not expose themselves to the sun and that the total pain scores were very low. In an attempt to better understand the impact of treatment, the Applicant *post hoc* defined a new 'efficacy' population excluding those patients who had not exposed themselves sufficiently to sunlight to experience phototoxicity. This new population consisted of a subset of 60 patients. The differences seen in the number and severity of phototoxicity reactions, as measured by days with pain showed statistically significant differences in favour of the active but the differences were small and compromised by the sun avoidance behaviour of the patients. Similar observations were made for sunlight exposure: There were no statistically significant differences in exposure times between Active and Placebo in the groups "Any outdoors" and "Combination or Sun". Significant differences were seen in the group "Direct Sunlight". Melanin density was increased by afamelanotide. The effect observed in clinically relevant skin areas was small though, with a

15-20%increase in melanin density measured on the forehead and a cheeks a 6-12% increase on the cheeks' skin). The difference in the extent of pigment increase between these neighbouring body regions cheeks and forehead indicated a non-homogeneous pigment distribution. The quality of life (QoL) measure Short Form 36 (SF-36) questionnaire evaluated the quality of life at baseline as high and showed no improvement in QoL during and after treatment with Scenesse. Study CUV030 recruited 77 patients, of whom 67 completed the study; study CUV029 recruited 76 patients, 74 of whom received treatment with 68 completing the study. Due to GCP non-compliance the efficacy data from these trials were not considered pivotal for the assessment. However, as pointed to by the Applicant there is an unambiguous trend for a positive effect (primary endpoint) in all these two clinical trials CUV029 and CUV030 (and in CUV039, see below). The effect size in the trials appears to be small, but a beneficial effect seems apparent.

Study CUV039 recruited 93 patients, of whom 87 completed the trial (Scenesse: 45 subjects; placebo: 42 subjects). Scenesse as 16 mg implant was administered three times, on days 0, 60, and 120. When preparing for the sites' inspection the Applicant's staff noted for two patients at one site that due to three errors in documentation they were erroneously assigned to the wrong treatment group. With the subsequent correcting switch of these two patients back to the group they were originally assigned to the analysis of the primary efficacy endpoint, i.e. "the difference in the total number of hours in direct sunlight between 10:00-18:00 hours on days when no pain was experienced", turned from statistically not significant to statistically significant in favourof Scenesse.

In addition, when the total duration of time spent in direct sunlight between 10:00-18:00 on days when no pain was experienced was divided for each subject by the number of subject's days on the study as in the analysis of mean exposure time, the difference was as well not statistically significant in favour of Scenesse. This finding implies that the statistical significance observed in the primary analysis depends on the handling of missing values: in the analysis of total exposure time, by imputing no data the implicit assumption of no sun exposure on days without diary entries was made, while for the analysis of mean e*xposure time, the implicit assumption was made that on days with missing data, the exposure was the same (on average) as on the days with available data.*

The difference between the treatment groups according to the Hodges-Lehmann shift estimate was now 24 hours with a very wide inter-individual variability (95% CI 0.3 to 50 h). With respect to the mean daily sun exposure (presented as secondary endpoint in the efficacy summary table, see above), the difference is numerically still favouring the Scenesse group (8.4 minutes more per day, with a wide 95% CI of -1.5 to 18.9 min, Hodges-Lehmann shift estimate), but no statistically significant difference was demonstrated. The Applicant conducted numerous pre-planned secondary, but also several unplanned (i.e. post-hoc and exploratory) analyses. All secondary endpoints tend to favour afamelanotide numerically, however show statistically inconsistent results, lacking a robust proof of efficacy:

- Both secondary endpoints related to direct sunlight exposure (diary-based) do not show a statistically significant difference between the Scenesse and the placebo patients.
- The number of phototoxic reactions, another secondary efficacy endpoint, was not statistically significantly different between groups. The EPP patients understandably rarely allow painful phototoxicity to occur. A very small number of phototoxicity reactions during the trial period (for both groups) might carry limitations to show a potential difference between Scenesse patients and placebo patients regards this endpoint.
- Two of the QoL measures used (SF-36 and DLQI) both confirmed by high scores for patients at baseline due to disease-adapted behaviour that the patients did not have a great impairment of quality of life—and neither showed a significant improvement, as measured by these validated tools. Thus these two questionnaires apparently do not measure an expected impairment in QoL in this adapted population. The Applicant's purpose-designed and population-oriented EPP-QoL

questionnaire did show significant differences between Scenesse recipients and placebo recipients. This applies to both, the original and the revised version of the questionnaire. However, as both EPP-QoL versions are not validated, the clinical meaning of the results is unknown. It would remain unclear anyhow, how scoring results could be transferred in MAA-relevant proof of clinical efficacy. According to the CHMP scientific advice of 2009, with reference to the "Guideline on Clinical Trials in Small Populations" (CHMP/EWP/8356 112005) the QoL assessment results have to be seen in conjunction with robust efficacy data and a positive benefit/risk assessment.

- The photoprovocation testing shows a statistically significantly different result in favour of Scenesse recipients only in one of four time points of measurements (day 90; without baseline). For changes to baseline in photoprovocation times (leading to a minimum symptom dose) the Applicant showed a statistically significant advantage on behalf of Scenesse in half of the measurements (four of eight). But these results also have to be interpreted with caution, as several limitations apply: surrogate parameter, upper limit of exposure frequently reached (skewed distribution), founded on non-objectifiable symptom(s), uneven patient distribution between groups regards gender. Note that numerical changes in favour of Scenesse are seen at all time points.

In conclusion, study CUV039 did not unequivocally show efficacy. However, as mentioned above, CUV039 as well as CUV029 and CUV030 show a positive trend favouring the efficacy of Scenesse. The effect size in CUV039, measured as a mean difference, appears to be small, but beneficial effect appears to be present in spite of the identified limitations. The numerous post-hoc analyses presented by the Applicant in their majority support a clinical benefit from Scenesse, acknowledging the statistical limitations in terms of inference due to non-specified post-hoc analyses.

The Applicant also provided efficacy data on up to 73 patients of the Swiss and Italian Expanded Access / Compassionate Use programs. Overall the data are described as indicating a low quality of life before treatment that rises soon after treatment and remains constantly high after that. However, the validity of these results is hampered by the fact that the questionnaire has not been validated, that the revised EPP-QoL version was not available from the start of these programs and that therefore most subjects did not have baseline data.

Additional expert consultation

On 29 April 2014 an Ad Hoc Expert Group Meeting was convened at the EMA in the context of the ongoing assessment of the MAA for Scenesse (afamelanotide). Patients affected by EPP, patient representatives, and expert physicians participated in this meeting (Minutes and Answers to Questions: EMA/CHMP/601433/2014).

The positions of the group are summarized below.

Responses from the ad-hoc expert group

1. **The expert group is invited to give a general discussion (i.e. without regard to this particular dossier) on the challenges in conducting clinical trials in this patient population, with particular regard to recruitment, definition of the patient population to be included, choice of control arm, and appropriate clinical outcome measures considering well-established patient behaviour.**

The panel shared the view that EPP is a condition that is very difficult to investigate in clinical studies. The key challenge is to overcome the learnt behaviour of EPP patient aiming at a life-long avoidance of sunlight because of the intense pain it induces, which is established in childhood. Due to their experience with phototoxicity EPP patients are generally reluctant to modify their behaviour. The time it takes to change the behaviour creates an inherent difficulty of designing clinical trial studies. In terms of duration, an observation period of six months of less in this population makes it challenging to show significant

efficacy as EPP patients tend to require a long time until they trust an intervention and dare to expose themselves to sunlight. This was highlighted by both clinicians and patients. It was noted by the experts that in the studies with afamelanotide the pain scores were low across treatment arms suggesting that patients didn't expose themselves to sunlight.

An additional difficulty is to measure improvement of quality of life, which was considered by the experts a very important measure in this condition. However, too limited data was collected in the programme to make a meaningful evaluation and no validated quality of life questionnaire tailored for EPP patients is available. Methodologically it was noted by one expert that there is a lack of a device to measure the natural solar light exposure (in "lux"[2]) making it difficult to quantify the amount of total light exposure EPP patients exposed themselves to. In this regard, one expert mentioned that an increase of 2 minutes in sunshine corresponds to an increase of exposure of more than 4 hours in the shade. The expert panel concurred that it is not necessary the direct sunlight exposure itself, but also the light exposure even in the shade that is relevant to patients, and that few minutes exposure increase may translate into more when light exposure in considered in a wider sense.

2. **The applicant has conducted a number of randomised controlled trials with pre-specified primary endpoints. Which of the endpoints included in the pivotal trials should be prioritised when assessing the therapeutic efficacy of Scenesse?**

The expert panel considered sun/light exposure and symptoms (like pain) as primary endpoint for clinical trials. A combination of the two was broadly supported. It was noted that each patient has his/her own threshold, and that behavioural changes do not come rapidly (see response to question 1).

One expert expressed the view that one important endpoint would be the asymptomatic period of sun exposure (the symptoms patients would experience such as tingling, pain…) as any of these symptoms would be enough for patients to stop their exposure to the sun. Regarding pain, both acute pain felt and duration of pain should be considered. Pooling asymptomatic periods without symptoms such as pain (total number of pain free days) from the placebo-controlled trials is however challenging as EPP patients would have been trying to avoid pain as part of their behaviour.

The expert panel discussed that total light exposure time would be a good endpoint in a standardised environmental setting. However in the clinical trials performed the EPP patients would have exposed themselves to different environmental settings influenced by weather conditions making total light exposure difficult to measure. In addition it was recognised that the disease presentation could also vary depending on the season which also affected the amount of light they were exposed to.

When asked for the usefulness of the prodromal phase for clinical study design, the panel considered this too difficult to reliably measure and therefore not appropriate as outcome measure in the context of a clinical trial.

3. **Scenesse is associated with a tanning effect, which is not present in the control arm, effectively unblinding the trial. Patient behaviour is cited as a challenge for establishing efficacy for Scenesse (patients unwilling to expose themselves to sunlight). Is it plausible that patient behaviour will be influenced by knowledge of treatment assignment? Can this influence be quantified?**

The expert panel, and particularly the patients, acknowledged that study subjects will likely have had the knowledge of the treatment assignment due to the tanning effect of afamelanotide on their skin but did not consider it measurable on the perceived effect. This is because beta carotene that was evaluated in EPP patients and causes tanning has no treatment effect and therefore do not translate in a change in the EPP patient's behaviour.

[2] SI unit of illuminance and luminous emittance, measuring luminous flux per unit area

The expert panel did reflect on a double-dummy trial design with supportive care to blind the tanning character of afamelanotide (e.g. UV therapy), however did not consider this feasible.

Asked about their experience with exposure to sunlight, patients expressed that based on experience they are able to individually judge how much they can tolerate and that this exposure is fairly constant over time.

4. **Based on the clinical trial data alone, are the estimated effects statistically and clinically persuasive in light of the unblinding, analytical and GCP issues identified?**

The experts stated that the magnitude of effects observed in the clinical trials were minimal and in a way disappointing but the expert panel argued that the totality of evidence was perceived convincing. Relative small changes were observed in a minority of individuals with small increase in sun light exposure observed and might be an underestimation of the true beneficial effect due to the patient behaviour. At the same time the experts noted that a translation of the small effect in terms of exposure to direct sunlight can translate into a significant time in the shade (see response to question 1). The so-called 'super-responders' were noted with interest even if no explanation to this response could be given.

Important for the expert panel was that the data were pointing to the same positive direction. Overall the experts, clinicians and patients, were reasonably convinced of the trial data showing an effect of afamelanotide.

The expert panel considered to explore a behavioural psychology test sub-analysis on the super-responders. This test would help to better understand how the results were strikingly different from other patients in the clinical trials.

5. **The applicant emphasizes that there is a substantial and consistent clinical benefit reported informally by expert physicians/patients (e.g. letter dated 3 July 2013). How would the group value this evidence?**

Some clinical experts reported preliminary reluctance to afamelanotide but were later more in favour due to patient reports coming in from the compassionate use. Two countries (Italy and Switzerland) are providing afamelanotide to EPP patients through national compassionate use programmes. One clinician reported from her experience where 39 out of 40 patients were responding to afamelanotide through increased daily sun light exposure and number of pain free days. What the expert panel has drawn from the experience on the individual reports/compassionate use is the EPP patients is an increased record of daily sun light exposure and pain free days through a change of behaviour over a prolonged period which translated into taking up outdoor activities such as sports or commute to work.

Overall the experts and patients considered that additional evidence through individual case description has its value and should be taken into account in particular for this condition.

6. **Is it possible to identify, based on pre-treatment characteristics, any subpopulation of EEP patients who will experience benefit of treatment with Scenesse?**

The expert panel agreed that there were no scientific grounds to support the creation of EPP subpopulations. The expert panel added that behavioural analysis would maybe conclude in a possible characterisation of patients that would be more likely to benefit the treatment with afamelanotide through their earlier and more progressive behavioural adjustment which includes increased exposure to daily light. The expert panel also acknowledged that there is a need to encourage patients under treatment and change lifestyle to understand the value of the treatment.

7. **To the perspectives of patients and treating physicians, is the level of benefit that is established for Scenesse of relevance and how will this benefit manifest in everyday life?**

The expert panel agreed that the beneficial evidence (increased exposure to light with absence of pain) of afamelanotide by the nature of the chronically debilitating EPP condition translated into significant improvement of their quality of life enabling them to taking up jobs and sports and being more integrated into society. Also of value that even if pain episodes occur, these were reported by EPP patients as being of considerable shorter duration.

The expert panel unanimously supported a strict follow up of the EPP patients taking afamelanotide through EPP reference centres and creation of a disease register, should afamelanotide be granted a marketing authorisation in the EU. The challenges caused by the impact of behavioural changes could be addressed through further data collection to assess the efficacy of afamelanotide in EPP patients in everyday use.

MA under exceptional circumstances

In accordance with Article 14(8) of Regulation (EC) No 726/2004 and Annex I, of the Directive 2001/83/EC the applicant applied for a marketing authorisation under exceptional circumstances. The applicant argued that he was unable to provide comprehensive data on the efficacy and safety under normal conditions of use because the indications for which afamelanotide is intended is encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, 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 CHMP agreed on these three justifications and considered that the criteria defined in the above-mentioned provision are met for the claimed therapeutic indication:

1. *The indication for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence.*

The indication for which afamelanotide is intended is rarely encountered. Indeed, afamelanotide has been designated as Orphan Medicinal Product, EU/3/08/541 on 8 May 2008 by the European Commission for the treatment of erythropoietic protoporphyria. At the time of designation, erythropoietic protoporphyria affected approximately 0.02 in 10,000 people in the EU. 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.

2. *Inability to collect comprehensive information because it would be contrary to medical ethics*

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 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.

3. *In the present state of scientific knowledge, comprehensive information cannot be provided*.

Comprehensive clinical data for MA is usually based on randomised controlled trials. In this setting the randomised controlled trial appears to be a less effective tool for determining treatment effects. The ad-hoc expert group confirmed two important points; firstly that these 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. Taking into account the nature of the disease, Scenesse would be used for long-term treatment, yet because the disease course is variable between patients, long-term data will remain difficult to interpret in the absence of a control group against which to make comparisons. There is, arguably, no control arm that could be used in a long-term randomised controlled trial; no medicinal products have consistently shown efficacy for these patients and the possibility to be randomised to a placebo control group would likely discourage a change from the learnt behaviour. It is argued that this is borne out by the clinical trial data presented, in which a majority of patients did not modify their behaviour to an important degree and hence the relatively short-term trials were not able to provide a sensitive comparison to placebo.

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.

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 light of the discussion above the CHMP is of the view that comprehensive data on the efficacy and safety under normal conditions of use could not be generated and that therefore the criteria for a Marketing Authorisation under exceptional circumstances are fulfilled.

2.5.4. Conclusions on the clinical efficacy

CUV039 pivotal trial's results though not meeting the recommended quality referring to current guidelines and lack of robustness show a beneficial effect. Treatment with afamelanotide led to a small increase in sun exposure, as measured by a patient diary. The results of the secondary endpoints related to sun exposure, to phototoxic events, quality of life and photoprovocation testing, numerically favour the Scenesse group.The clinical efficacy was established through:

- photoprovocation tests that differentiated between afamelanotide and placebo in terms of phototoxicity

Photoprovocation has been evaluated in 70 patients, while variability intra- and inter-individually makes interpretation of results difficult. It has been deemed unethical by expert physicians and Ethics Committees to 'force' patients to expose to light and sunlight for more than 15 minute intervals, whereby no minimum duration was allowed to be imposed in the trials.

- 5 clinical trials with trends in favour of afamelanotide in comparison to placebo, including post-hoc analyses that nominally reach statistical significance. CUV039 pivotal trial's results though not meeting

the recommended quality referring to current guidelines and lack of robustness show a beneficial effect. Treatment with afamelanotide led to a small increase in sun exposure, as measured by a patient diary. The results of the secondary endpoints related to sun exposure, to phototoxic events, quality of life and photoprovocation testing, numerically favour the Scenesse group.

CUV029 and CUV030 trials had critical GCP findings and were recommended to be excluded from the efficacy evaluation, however the trends in CUV029 and CUV030 studies were consistent with the CUV039 trial.

In addition, data from 73 patients of the Swiss and Italian Expanded Access / Compassionate Use programs have been presented, purporting to show long-term adherence to treatment with few withdrawals based on lack of efficacy or tolerability. Although efficacy data were not collected in these programmes it was observed the relatively high long-term adherence rates of patients might suggest some effectiveness of the treatment.

2.6. Clinical safety

Patient exposure

The Applicant has conducted clinical trials with afamelanotide in a number of different indications and with different preparations.

Until 06 October 2014, 137 subjects received single or multiple doses of afamelanotide as an aqueous subcutaneous injection. 73 subjects have received multiple injections of afamelanotide as an aqueous subcutaneous injection (approximately 1,700 injections). Following formulation development, which resulted in the controlled-release bioresorbable implant, approximately 611 subjects (186 females) have been administered around 2,747 implants containing afamelanotide, 429 in clinical trials (Module 2 Common Technical Document Summaries; 2.7.4 Summary of Clinical Safety, 06 October 2014)

A total of 231 patients with EPP have been exposed to 16mg afamelanotide implants in trials.

Table 5: Human exposure to afamelanotide implants

Indication/Population	Persons	Total number of implants used	Average number of implants per person
Healthy volunteers	124	134	1.1
EPP	231	793	3.4
Adjunctive therapy in patients undergoing PDT	9	9	1
Polymorphic light eruption (PLE)	60	133	2.2
Solar urticaria (SU)	5	5	1

Table 6: Fitzpatrick skin types of participants in afamelanotide implant studies submitted with the MAA

Skin Type	Description	Overall number of study participants	Numbers in studies CUV029, 030, 039
Type I	Never tans, always burns	56	29
Type II	Tans less than average (with difficulty), mostly burns	172	50
Type III	Tans about average, sometimes mild burn	105	35
Type IV	Rarely burn, tans more than average (with ease)	15	12
Type V	Very rarely burns, tans very easily	0	0
Type VI	Never burns, tans very easily, deeply pigmented.	0	0

Adverse events

Table 7: The ten most common adverse events by incidence for all clinical afamelanotide implant studies (EP005, EP006, EP008, EP012; CUV006, 007, 009, 010, 015, 016, 017, 025, 028, 029, 030, 038, and CUV039; total number of subjects differs from statement in other table, n=429

MedDRA (v14.0) Preferred Term	MedDRA (v14.0) System Organ Class	Active (n=425)	Placebo (n=285)
Headache	Nervous system disorders	133 (334)	81 (265)
Nausea	Gastrointestinal disorders	95 (148)	40 (58)
Nasopharyngitis	Infections and infestations	48 (55)	39 (46)
Fatigue	General disorders and administration site conditions	37 (53)	16 (32)
Ephelides	Skin and subcutaneous tissue disorders	31 (53)	0 (0)
Migraine	Nervous system disorders	17 (44)	18 (35)
Back pain	Musculoskeletal and connective tissue disorders	30 (41)	24 (46)
Upper respiratory tract infection	Infections and infestations	32 (34)	20 (24)
Influenza	Infections and infestations	25 (28)	16 (18)
Dizziness	Nervous system disorders	22 (28)	10 (34)

Table 8: The five most common adverse events by number of reports for erythropoietic protoporphyria (EPP) implant studies CUV010, CUV017, CUV029, CUV030, and CUV039

MedDRA (v14.0) Preferred Term	MedDRA (v14.0) System Organ Class	Number of Patients / (Number of Events Bracketed)					
		Active (n=231)			Placebo (n=220)		
		Total	*Related to study drug	*Not related to study drug	Total	*Related to study drug	*Not related to study drug
Headache	Nervous system disorders	87 (259)	54 (161)	46 (98)	75 (251)	39 (116)	50 (135)
Nausea	Gastrointestinal disorders	60 (106)	53 (93)	11 (13)	36 (54)	25 (31)	17 (23)
Nasopharyngitis	Infections and infestations	41 (46)	0 (0)	41 (46)	36 (43)	0 (0)	36 (43)
Migraine	Nervous system disorders	13 (38)	6 (22)	8 (16)	15 (32)	4 (8)	11 (24)
Back pain	Musculoskeletal and connective tissue disorders	23 (34)	4 (4)	19 (30)	21 (43)	4 (7)	18 (36)

Most adverse reactions (AR) were mild in severity. However, adverse reactions of moderate severity were reported at relevant numbers (≥ 2 patients; for upper abdominal pain, diarrhoea, gastrointestinal reflux disease, nausea (39 events), vomiting (10 episodes), fatigue (17 episodes), implant site discolouration, implant site pain, pain, influenza, blood creatine phosphokinase increased, muscle spasms, musculoskeletal pain, dizziness, headache (77 events), migraine, somnolence, erythema, melanocytic nevus, flushing and for several terms related to focal or generalised changes in skin pigmentation changes (in sum 20 events).

Adverse reactions (AR) rated as severe (any frequency) pertained to dyspepsia (3 events), dry mouth, nausea , fatigue, implant site pain, increased blood creatine phosphokinase, headache (10 events), migraine (13 events), somnolence, lethargy, and flushing.

Serious adverse event / deaths / other significant events

Four deaths were reported during clinical studies with the afamelanotide implant, all of which were regarded as definitely not related to study treatment by the investigators.

Altogether 31 serious adverse events were reported with afamelanotide in the clinical trial programme (unblended), all of which were considered unlikely or definitely not related to study drug.

Laboratory findings

In most studies changes in laboratory findings (haematology, biochemistry, urinalysis) were not considered clinically significant, were transient or part of a pre-existing condition. For the study with the first afamelanotide implant (single-dose, EPP006) very few singular changes judged as clinically relevant were reported. These related to elevations of creatine kinase, increased triglycerides and increased liver enzymes. These are not considered meaningful for the final formulation. Elevations in creatine phosphokinase (CPK, blood) in three patients were ascribed to physical activity. For a single subject an alteration in the HPT hormonal axis was diagnosed: cortisol and ACTH low in blood. Deviations from normal in urinalysis were ascribed to urinary tract infections.

Safety in special populations

No studies have been conducted investigating the safety in special populations. Therefore, the safety of afamelanotide in special populations, e.g. patients with renal, hepatic, or blood-brain barrier impairment, older or paediatric patients is currently unknown.

There have been five women reported becoming pregnant following afamelanotide implantation and two partners of afamelanotide recipients who have become pregnant. According to the Applicant all resulted in the birth of a live infant with no birth defects noted. Period of time between last implant and pregnancy detection: five weeks, six weeks and twice 10 weeks. Follow up on one child (Scenesse, period of time between last implant and date of pregnancy detection is six months) is not available.

Immunological events

No specific anti-afamelanotide antibodies of the IgG subtype have been detected in the sera of EPP patients that had been exposed repeatedly to afamelanotide (implants) for up to 6 years The pathogenesis of implant site reactions in patient receiving Scenesse is not completely understood, whereas implant site hyperpigmentation may result from physiological reaction (post-traumatic) and the pharmacodynamic effects of afamelanotide, other immunological reaction cannot be excluded.

The fourth most common adverse event reported was hypersensitivity. In total, 5 events were reported by 5 patients. All events were deemed to be unrelated to afamelanotide.

In summary, so far there have been no reports on immunological adverse events in patients with long-term exposure to Scenesse that were attributed to the drug.

A copy of the developed ELISA and the corresponding validation report was presented as requested. Also the study report "Evaluation of the immunogenicity of the synthetic α-MSH analogue afamelanotide ([Nle4,D-Phe7]- α-MSH, SCENESSE) in Erythropoietic Protoporphyria Patients" was provided. Based on the plasma screening from 17 EEP patients following repeated (maximum is n=22 16 mg implants, i.e. total of 400 mg afamelanotide per patient) and prolonged (up to 6 years) exposure, no immunoreactivity was found in 15 of the 17 patients. Pre-existing immunoreactivity against afamelanotide as well as α-MSH was found in two patients. However, this immunoreactivity did not change during long term application of afamelanotide.

Thus based on the current small clinical data pool there is no sign that afamelanotide is immunogenic during long term exposure and induces the formation of afamelanotide-specific antibodies following repeated afamelanotide implant administration.

Safety related to drug-drug interactions and other interactions

No drug-drug or food interaction (drug is given parenterally) studies have been conducted, this was regarded as acceptable by the CHMP.

Discontinuation due to adverse events

Overall, discontinuations were rare. One patient withdrew from study CUV015 because of flare-up of Crohn's disease. Four patients requested implant removal and withdrawal from study EP004 because of a greater than expected rate of skin darkening. One participant experiencing repeated episodes of migraine withdrew from study CUV029. One patient each withdrew from study 039 due to malignant melanoma in situ (placebo-group) or compound nevus with mild dysplasia after two implants (unlikely related to study drug).

The Applicant reported on 27 subjects with discontinuations during Compassionate Use and Expanded Access programs in Italy and Switzerland up to September 2014. Discontinuations were due to heart disease (n=1; patient deceased), pregnancy (n=5), and weight gain (n=1) as adverse events (AE).

Post marketing experience

Not applicable.

2.6.1. Discussion on clinical safety

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

The most common adverse events seen (all Scenesse implants, clinical trials n=425; as of 03 December 2013) were headache, nausea, nasopharyngitis, fatigue, ephelides, migraine, back pain, upper respiratory tract infection, influenza, and dizziness. For all AEs but back pain and dizziness Scenesse recipients experienced more events than placebo recipients.

In EPP patients the five most common AEs in clinical studies were headache, nausea, nasopharyngitis, migraine, back pain, with only nausea being more frequent (double as) in Scenesse than in placebo

recipients. Headache and nausea in Scenesse patients (CUV039) appear to last longer than in placebo patients.

In order to avoid off-label use of Scenesse, a controlled access programme will be implemented to ensure that Scenesse will be distributed only to recognised porphyria centres. Furthermore, specific risk minimisation measures in the form of educational material will be used to ensure that Scenesse can only be administrated by a physician trained and accredited by the marketing authorisation holder to administer Scenesse in accordance with the recommendations reflected in section 4.2 of the SmPC.

In the animal model afamelanotide did not cross the intact blood brain barrier. For the metabolites (active or inactive) respective data is not available. Thus, it can only be assumed that nausea and other complaints with the gastrointestinal tract as well as other potentially CNS-originated AEs (headache, fatigue, and somnolence) may be related to peripheral effects.
Patients on Scenesse apparently developed infections more frequently (207 vs. 145 patients); whether this is a chance finding or due to a direct or indirect effect of afamelanotide remains unexplained. In the majority these AE were considered by the investigator as unrelated to Scenesse (related: 11 vs. 2;unrelated: 196 vs. 143). Appropriate collection of post-authorisation data will also include a follow-up on administration site reactions in EPP patients (RMP).

Induction of dysplastic proliferation of melanocytes may be considered possible (AE listings CUV029, CUV030, and CUV039). There is currently no evidence to suggest a clinically relevant cancer risk of patients. For a long term follow up, changes in EPP patient's pigmentary lesions like melanocytic nevi will be included as a possible risk in the RMP and addressed by the collection of post-authorisation data through the disease registry data and retrospective chart review study.

The assessment of safety based on the data from the clinical trials is based on limited treatment periods (maximum of one year). The safety data set has been expanded with information from longer-term use in the special access/compassionate use programs in Italy and Switzerland.

In addition, there is the clinical efficacy & safety study CUV011 ("A Multicentre, Randomised, Double-Blind, Placebo Controlled, Phase II Study to Evaluate the Safety and Efficacy of Subcutaneous Bioresorbable Implants of Afamelanotide (CUV1647) for the Prophylactic Treatment of Pre-Cancerous Skin Lesions of the Head, Forearms and Hands in Immune Compromised, Organ Transplant Patients". A total of 85 subjects were enrolled. The study is still ongoing, and "the study is still blinded").

The five most reported adverse events (blinded) were: headache (n=69), nausea (41), diarrhoea (32), back pain (27), and fatigue (25). This is broadly in line with the findings in other clinical trials; at this stage there is no evidence perceivable that would suggest unexpected adverse effects in these patients with significant co-morbidities and with significant levels of multiple immune suppressive and other medications".

Additional expert consultations

A summary of the minutes of the **Ad hoc Expert Group meeting** on 29 April 2014 is given in the section 3.3.6 of this report. Safety issues were not discussed in this meeting.

At the CHMP Oral Explanation (London, 23 September 2014) the Applicant panel constituted of clinical experts presented safety data from the Swiss and the Italian Compassionate Use and Expanded Access programs. Of 27 discontinuation, most of them (14/27) during the first year of treatment, the reasons provided were weight gain in one patient, death due to heart disease in a second; causality assessment not mentioned, lack of efficacy in 3 patients and pregnancy in five cases.

Additional safety data needed in the context of a MA under exceptional circumstances
As comprehensive data on the safety under normal conditions of use could not be generated, the CHMP considers the following specific obligation necessary to address the missing safety data in the context of a MA under exceptional circumstances:

- Disease registry (Specific Obligation)

Prior to launch in Member States, the MAH shall establish a disease registry to gather long term safety data and outcome endpoints in patients with EPP. The registry should collect data from both patients and physicians.

The CHMP also concluded that further characterisation of the long-term safety profile of this medicinal product is needed and could significantly impact on its benefit/risk balance. As a consequence, the following study is requested and will be mentioned in annex II of the marketing authorisation

- Retrospective chart review study (Condition in Annex II)

The MAH shall conduct a retrospective study comparing long term safety data and outcome endpoints in patients receiving and not receiving Scenesse, or having discontinued Scenesse use.

The second primary objective of the study should be the assessment of the compliance with risk minimization recommendations and the controlled access program for patients receiving Scenesse.

2.6.2. Conclusions on the clinical safety

Based on the available data there are no indications for safety signals that would preclude the grant of a marketing authorisation.

Currently, the most relevant safety concern is the lack of long-term data. The long term data is considered essential, as Scenesse is intended as a life-long therapy. Appropriate collection of post-authorisation data through the disease registry data and the retrospective chart review study will include a follow-up on changes in EPP patients' pigmentary lesions like melanocytic nevi (RMP).

In order to avoid off-label use of Scenesse, afamelanotide presented in an implant of 1.7cm in size, 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 as reflected in section 4.2 of the SmPC.

There is an apparently higher rate of infections in the Scenesse treated patients. Appropriate collection of post-authorisation data will also include a follow-up on administration site reactions in EPP patients' (RMP).

Information is also missing regards the safety of afamelanotide in special populations, e.g. in hepatic or renal or blood/brain barrier impairment, the paediatric population, in older patients or with regard to drug-drug interactions. The hepatic and renal impaired are contraindicated in section 4.3 of the SmPC. Since available data in treatment of the elderly are limited afamelanotide should not be used in patients over 70 years of age is reflected in section 4.4 in the SmPC. The use of afamelanotide is not recommended in the paediatric population due to the lack of data and the size of the implant which is not suitable for children as reflected in section 4.4 of the SmPC. There are no or limited amounts of data from the use of afamelanotide in pregnant women, and afamelanotide should not be used in pregnancy as reflected in section 4.6 of the SmPC. No clinical data are available on the use of afamelanotide in breastfeeding women, a risk to the newborns/infants cannot be excluded this is reflected in section 4.6 of the SmPC.

As comprehensive data on the safety under normal conditions of use could not be generated, the CHMP considers the following specific obligation necessary to address the missing safety data in the context of

a MA under exceptional circumstances:

- Disease registry (Specific Obligation)

Prior to launch in Member States, the MAH shall establish a disease registry to gather long term safety data and outcome endpoints in patients with EPP. The registry should collect data from both patients and physicians.

The CHMP also concluded that further characterisation of the long-term safety profile of this medicinal product is needed and could significantly impact on its benefit/risk balance. As a consequence, the following study is requested and will be mentioned in annex II of the marketing authorisation

- Retrospective chart review study (Condition in Annex II)

The MAH shall conduct a retrospective study comparing long term safety data and outcome endpoints in patients receiving and not receiving Scenesse, or having discontinued Scenesse use.

The second primary objective of the study should be the assessment of the compliance with risk minimization recommendations and the controlled access program for patients receiving Scenesse.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The Applicant has submitted a Summary of the Applicant's Pharmacovigilance System. Additionally, the Applicant has provided individual responses to each question posed and states that the details provided in the responses will be included in the PSMF.

Pharmacovigilance System Master File fully complies with the legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module; the CHMP accepts the substitution of QPPV.

The submitted summary states – as required - the location of the PSMF. The Pharmacovigilance system master file, MFL5706 for the medicinal product is kept at the following location:

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan submitted could be acceptable if the applicant implements the changes to the RMP as described in the PRAC Assessment Report.

Post PRAC meeting RMP update:

The applicant implemented the changes in the RMP as requested by PRAC. The CHMP endorsed the Risk Management Plan version 5.0 with the following content:

Safety concerns

The applicant identified the following safety concerns in the RMP:

Summary of the Safety Concerns

Important identified risks	• Change of pigmentary lesions

	• Administration site reactions
Important potential risks	• Allergy and hypersensitivity • Off-label use in paediatric patients • Off-label use in adults • Use in pregnancy and lactation • Administration error
Missing information	• Use in the elderly (greater than 70 years of age) • Use in patients with co-morbidities such as clinically significant renal, hepatic or cardiac impairment • Long-term safety data • Pharmacokinetic data

Pharmacovigilance plan

On-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

Study/activity type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
Retrospective chart review (study to measure the effectiveness of risk minimisation measures) (Category 1)	Study comparing long term safety data and outcome endpoints in patients receiving and not receiving Scenesse, or having discontinued Scenesse use. The second primary objective of the study will be the assessment of the compliance with risk minimization recommendations and the controlled access program for patients receiving Scenesse.	Safety parameters: • Changes of pigmentary lesions • Administration site reactions • Allergy and hypersensitivity • Off-label use in paediatric patients • Off-label use in adults • Use in pregnancy and lactation • Administration error	Protocol submission	To be submitted within 2 months of the notification of the European Commission decision
			Study start	6 months after study protocol approval
			Intermediate reports	Reports will be submitted annually
			Final report	6 years after protocol approval

Study / activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
SCENESSE disease registry years (Category 2)	Registry will gather long term safety data and outcome endpoints in patients with EPP. The registry will collect data from both patients and physicians in a web-based data collection form	Safety parameters: • Changes of pigmentary lesions • Administration site reactions • Allergy and hypersensitivity • Administration error	Protocol submission	To be submitted within 2 months of the notification of the European Commission decision
			Study start	Immediately after study protocol approval
			Intermediate reports	Reports will be submitted annually
Pharmacokinetic study in EPP patients (Category 3)	CUV052: SCENESSE PK profile in EPP patients Determine the PK profile in at least 12 EPP patients after administration of implant 1 on Day 1 and implant 2 on Day 60.	Safety parameters: • Pharmacokinetics data	Study start	Immediately after authorisation
			Study finish	3Q 2015
			Final study reports	December 2015

The CHMP, having considered the data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The CHMP also considered that the studies in the post-authorisation development plan are sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risk – Change in pigmentary lesions	Section 4.4 Special warnings and precautions of the SmPC includes a section on skin monitoring and sun protection Section 4.8 lists the undesirable effects relating to this risk	None
Important identified risk – administration site reactions	Section 4.2 Posology and method of administration of the SmPC states that the use of SCENESSE is restricted and also provides detailed instructions on the administration technique Section 4.8 Undesirable effects relating to this risk	Educational materials for healthcare professionals that detail the correct administration procedure for the SCENESSE implant. This will include the SmPC and the

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
		educational video.
Important potential risk – Allergy and hypersensitivity	Section 4.2 Posology and method of administration states that the patient needs to be observed for 30 minutes to ensure that he/she does not experience allergic or hypersensitivity reactions (immediate type). Section 4.3 states the contraindications Section 4.8 Undesirable effects relating to this risk	None
Important potential risk - Off-label use in paediatric patients	Section 4.1 Therapeutic indications of the SmPC states SCENESSE is indicated for the prevention of phototoxicity in adult patients with erythropoietic protoporphyria (EPP) Section 4.2 Posology and method of administration *Paediatric population* The safety and efficacy of afamelanotide in children and adolescents aged 0 to 17 years have not yet been established. No data are available (see section 4.4). Section 4.4 Special warnings and precautions for use <u>Paediatric population</u> Use of SCENESSE is not recommended in the paediatric population due to the lack of data and the size of the implant which is not suitable for children.	None
Important potential risk - Off-label use in adults	Section 4.1 Therapeutic indications of the SmPC states SCENESSE is indicated for prevention of phototoxicity in adult patients with erythropoietic protoporphyria	Controlled access programme to porphyria centres.
Important potential risk – Use in pregnancy and lactation	Section 4.6 Fertility, pregnancy and lactation of the SmPC states: <u>Women of childbearing potential/contraception in females</u> Women of childbearing potential should, use effective contraception during treatment with SCENESSE and for a period of three months thereafter. <u>Pregnancy</u> There are no or limited amounts of data from the use of afamelanotide in pregnant women. SCENESSE should not be used during pregnancy. <u>Breastfeeding</u> It is unknown whether afamelanotide or any of its metabolites are excreted in breast milk. No clinical data are available on the use of afamelanotide in breastfeeding women. Animal studies are insufficient with respect to developmental toxicity (see section 5.3). A risk to newborns/infants cannot be excluded. SCENESSE should be avoided during breastfeeding.	None
Important potential risk – Administration error	4.2 Posology and method of administration 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.	Educational materials for healthcare professionals (SmPC and educational video)

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Method of administration Subcutaneous use. SCENESSE is subcutaneously under aseptic conditions as described below. Administration should be performed by a physician trained and accredited by the marketing authorisation holder to administer the implant. Instruction for use A detailed description of the method of administration is provided in the SmPC.	that details the correct administration procedure for the SCENESSE implant. The educational material will be provided prior to prescription.
Missing information – use in the elderly (greater than 70 years of age)	Section 4.2 Posology and method of administration and section Section 4.4 Special warnings and precautions for use of the SmPC states that SCENESSE should not be administered to elderly patients (over 70 years of age)'	None
Missing information – Patients with co-morbidities such as clinically significant renal, hepatic or cardiac impairment	Section 4.3 of the SmPC states: Contraindications • Presence of severe hepatic disease • Hepatic impairment • Renal impairment	None
Missing information – Long term safety data	Section 4.4 Special warnings and precautions for use of the SmPC states that the safety of SCENESSE has not been evaluated in clinical trials of duration longer than 2 years.	None

The CHMP, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

2.9. Product information

2.9.1. User consultation

User testing has not been submitted yet. This has to be submitted prior to launch.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Afamelanotide increases the melanin density by 6 to 30 percent, depending on anatomical site. The increase in melanin is supposed to improve light protection by contributing to blocking the harmful wavelengths of light that cause phototoxicity episodes in EPP patients. The melanin increase would allow EPP patients to spend more time exposed to sunlight i.e. to lead a more "normal" life. Scenesse recipients with EPP can spend more time in direct sunlight compared to placebo patients (on days without pain). The

estimated difference between placebo and Scenesse (Hodges-Lehmann shift, in favour of Scenesse) is 24 hours in total for 180 study days, translating into a difference of 8 minutes of additional direct sunlight exposure per day (Hodges-Lehmann shift)). This could be translated into a lot more time outdoors in the shade or under cloudy skies. Phototoxicity as measured by photoprovocation testing in 21 patients was delayed (CUV039), numerically consistent for all the measurements. In addition, the specific but non-validated EPP-questionnaire showed an improvement of the quality of life in the study participants over the course of the treatment phase, being more pronounced for the Scenesse-treated patients.

Uncertainty in the knowledge about the beneficial effects.

Due to the GCP issues discovered in the conduct of CUV029 and CUV030 these studies cannot be considered as pivotal data for the assessment of efficacy in this application. The results from the sole pivotal trial CUV039 can be considered robust enough to support a Marketing Authorisation.

The tanning effect of afamelanotide probably led to in factual unblinding in many patients (although no practical way of blinding has yet been described). The expert panel, and particularly the patients, acknowledged that study subjects will likely have had the knowledge of the treatment assignment due to the tanning effect of afamelanotide on their skin but did not consider it measurable on the perceived effect. This is because beta carotene that was evaluated in EPP patients and causes tanning has no treatment effect and therefore do not translate in a change in the EPP patient's behaviour.

This is particularly important when the assessment depends on subjective efficacy criteria as this may result in an overestimation of beneficial effects. Only the non-validated EPP-QoL but not the standard DLQI questionnaire showed a statistical significant effect. Moreover, statistical significance for with primary endpoint is borderline, e.g. depends on the way missing data are handled in the primary analysis.

The results of the secondary endpoints related to sun exposure, phototoxic events, quality of life and photoprovocation testing do all numerically favour the Scenesse group, though differences between groups only inconsistently achieve statistical significance. With respect to quality of life measurements the only validated instrument, the DLQI, has not shown statistically significant differences between the groups, only the non-validated EPP-QoL indicated a benefit for the Scenesse-treated participants.

In conclusion, the strength of evidence of efficacy from CUV039 pivotal trial can be considered robust enough to recommend the grant a Marketing Authorisation. In particular there are limitations in the statistical methodology employed and the clinical relevance of the effects estimated in the clinical trials is not unequivocal. Methodologically it was noted that there is a lack of a device to measure the natural solar light exposure (in "lux"[3]) making it difficult to quantify the amount of total light exposure EPP patients exposed themselves to in the clinical trials. On the other hand, almost all results from CUV039—were in line with results from not GCP-compliant CUV029 and CUV030—that show a trend in direction of a beneficial Scenesse efficacy. Overall the experts and patients consulted during the ad hoc meeting considered that additional evidence through individual case description has its value and should be taken into account in particular for EPP. The CHMP agreed with the experts, clinicians and patients and were reasonably convinced of the trial data showing an effect of Scenesse.

Risks

Unfavourable effects

Adverse effects known so far are not considered severe and are reversible. The most common adverse events were headache, nausea, nasopharyngitis, migraine, abdominal pain, fatigue, lethargy and

[3] SI unit of illuminance and luminous emittance, measuring luminous flux per unit area

somnolence. In addition, viral and bacterial infections, flushing, implant site discolouration, and changes in the pigmentation of the skin, including lentigines and ephelides were reported more frequently with afamelanotide. No adverse events have been identified for the afamelanotide implant that would preclude a Marketing Authorisation.

Uncertainty in the knowledge about the unfavourable effects

There is currently very limited knowledge of the distribution, metabolism, and excretion of afamelanotide and its active metabolites. Information on the safety in special populations is missing, such as those with renal/hepatic impairment (the use of afamelanotide is therefore contraindicated in these populations in the SmPC section 4.3) and in older patients (this is reflected in the SmPC section 4.4). Long-term safety needs to be characterised which will be done in the post-authorisation phase. The MAH shall conduct a retrospective study comparing long term safety data and outcome endpoints in patients receiving and not receiving Scenesse, or having discontinued Scenesse use.

The second primary objective of the study should be the assessment of the compliance with risk minimization recommendations and the controlled access program for patients receiving Scenesse. Important are uncertainties with regard to the long term effects of Afamelanotide on differentiation and proliferation of cells of melanocytic lineage.

Furthermore, a disease registry will be established by the MAH prior to launch in Member States, to gather long term safety data and outcome endpoints in patients with EPP. The registry should collect data from both patients and physicians.

Benefit-risk balance

Importance of favourable and unfavourable effects

Afamelanotide is intended to prevent phototoxicity in EPP patients, resulting in better tolerance for sunlight or visible light and enabling the patients to lead life with increased time spent outside (commuting, work, leisure /sport, social). However, the difference in time with direct sunlight exposure between Scenesse and placebo appears small, and although it is plausible that a few minutes in sunlight could be translated into longer periods in the shade or outside on cloudy days, this has, so far not been shown. The statistical significance in CUV039 pivotal study is nominally reached

On the other hand, there is an unmet medical need for a therapy of EPP — and individual patients' testimonies and expert panel agreed that the beneficial evidence (increased exposure to light with absence of pain) of Scenesse by the nature of the chronically debilitating EPP condition translated into significant improvement of their quality of life enabling them to taking up jobs and sports and being more integrated into society.

Based on the currently available data the unfavourable effects are considered as not severe and reversible. In view of the chronic life-long treatment, the lack of long-term safety data is considered an important missing information that is addressed in the post-authorisation phase through the setting up of a disease register and long-term safety study.

Benefit-risk balance

Discussion on the benefit-risk balance

There are no medicinal products in the Community available for the therapeutic indication apart from supportive care such as avoidance of sun exposure, use of analgesics, anti-histamines, topical corticosteroids cold compress, beta carotene. As EPP is connected with uniquely painful, disfigurating, debilitating, socially disabling and in the long run potentially life-threatening phenotypic manifestations

and no authorised medicinal products exists for EPP there is currently a clear unmet medical need for treatment of patients with EPP.

Afamelanotide increases the melanin density by 6 to 30 percent, depending on anatomical site, the evidence of efficacy based on study CUV039 pivotal trial must be regarded as limited due to the various deficiencies identified in its design and the data analyses. Even when regarding the statistical significant difference in the primary endpoint as valid, it is not clearly evident from the clinical trials whether the apparently small increase in sunlight would translate into a meaningful change in the patients' life.

However, patient and EPP experts have confirmed that the increase in outdoor light exposure possible with Scenesse was enabling to alter patients' quality of life and translated in the uptake of outdoor lifestyle.

As the adverse effects identified so far are not severe and are reversible, even any modest benefit may be sufficient outweigh the risks.

Changes to the behavioural lifestyle pattern of EPP patients do not necessarily occur within days, weeks, or months regarding such learned behaviour as the pattern would have been adopted from early childhood extensively to cope with the condition.

Therefore it appears impossible to expect meaningful results on the number of phototoxicity episodes within the observation periods used in the clinical trials submitted, in particular in a randomised trial against placebo.

The arguments put forward by the applicant to justify the criteria of a marketing authorisation under exceptional circumstances are recognized. In view of the above the CHMP concluded that a positive benefit/risk balance for Scenesse has been established and recommends the grant of a marketing authorisation under exceptional circumstances subject to the obligations laid down in the annex II of the opinion.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the risk-benefit balance of Scenesse in the prevention of phototoxicity in adult patients with erythropoietic protoporphyria (EPP) is favourable and therefore recommends the granting of the marketing authorisation under exceptional circumstances subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and

published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

  Education and training programme for physicians

  Prior to launch of Scenesse in each Member State, the Marketing Authorisation Holder (MAH) must agree the content and format of the educational package, including communication media, distribution modalities, and any other aspects, with the National Competent Authority. The MAH shall also agree the details of the controlled access programme to ensure distribution of Scenesse only to centres where the physicians have received the educational materials and have been trained.

  The MAH shall ensure that in each Member State where Scenesse is marketed, all healthcare professionals who are expected to use the product are provided with the following educational package and trained:
  - Summary of product characteristics,
  - Face to face training material,
  - Educational video,
  - Registry information sheet.

  The face to face training material, including the educational video, shall contain the following key messages:
  - Demonstration of the correct application technique, highlighting the measures needed to ensure the implant is not damaged during use.
  - The importance of maintaining aseptic conditions.
  - Methods to prevent or minimise application errors and application site reactions

  Registry information sheet shall contain the following key messages:
  - The importance of recruiting and entering patients in the EU Registry,
  - How to access and use the EU Registry.

- **Obligation to complete post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Retrospective chart review study The MAH shall conduct a retrospective study comparing long term safety data and outcome endpoints in patients receiving and not receiving Scenesse, or having discontinued Scenesse use. The second primary objective of the study should be the assessment of the compliance with risk minimization recommendations and the controlled access program for patients receiving Scenesse.	Draft protocol to be submitted 2 months after notification of the European Commission decision. Intermediate reports: annual submission. Final report: 6 years after approval.

Specific Obligation to complete post-authorisation measures for the marketing authorisation under exceptional circumstances

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Description	Due date
Disease registry Prior to launch in Member States, the MAH shall establish a disease registry to gather long term safety data and outcome endpoints in patients with EPP. The registry should collect data from both patients and physicians.	Draft protocol to be submitted 2 months after notification of the European Commission decision Intermediate reports: annual submission.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

The divergent position to the majority recommendation is appended.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that afamelanotide is qualified as a new active substance.

APPENDIX

DIVERGENT POSITION EXPRESSED BY CHMP MEMBERS

It is agreed that the strength of evidence of efficacy from the single pivotal trial is not strong enough to grant a Marketing Authorisation not subject to Specific Obligations. It is agreed that there are limitations in the statistical methodology employed and that the clinical relevance of the effects estimated in the clinical trials is not unequivocal. In addition, whilst the trials submitted in the dossier report effects in favour of afamelanotide, it remains unclear to what extent the functional unblinding of patients treated with Scenesse has impacted on the estimated effects. The ad-hoc expert group reported clinically impressive results that are inconsistent with the findings from the clinical trials. By way of explanation, and in support of an approval under Exceptional Circumstances, the applicant presents a rationale for why a randomised placebo-controlled trial is likely to be a less effective tool for determining treatment effects in this setting, primarily concerning the patient's 'learnt' behaviour. Whilst this rationale was shared by the ad-hoc expert group, it has not been established in an objective and verifiable manner and the extent to which this phenomenon impacts the clinical trial data cannot be estimated. Importantly, other tools to capture data on efficacy have not been explored exhaustively, for example, historical / external controlled clinical trials of longer duration such that the learnt behaviour has time to change, or series of case-reports that also systematically captured patient benefit in terms of exposure to light without phototoxicity, or quality of life. Furthermore, whilst there are no objections based on the observed safety data, in light of the lower than usual standards of evidence for efficacy, it is concerning that long-term safety data have not been systematically collected in the clinical trial programme.

London, 23 October 2014

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