24 April 2024
EMA/333545/2024
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal Assessment report

SCENESSE

International non-proprietary name: afamelanotide

Procedure No. EMEA/H/C/002548/II/0044

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

The PRAC/CHMP Rapporteurs should complete the 'actual' date at each stage of the procedure. This is the date of circulation of the report to CHMP/PRAC members.

Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	25 Feb 2023	25 Feb 2023	☐
☐	CHMP Rapporteur Assessment Report	21 Apr 2023	20 Apr 2023	☐
☐	PRAC Rapporteur Assessment Report	28 Apr 2023	20 Apr 2023	☐
☐	PRAC members comments	03 May 2023	n/a	☐
☐	CHMP Co-Rapporteur Assessment	03 May 2023	03 May 2023	☐
☐	Updated PRAC Rapporteur Assessment Report	04 May 2023	04 May 2023	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	12 May 2023	12 May 2023	☐
☐	CHMP members comments	15 May 2023	15 May 2023	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	17 May 2023	17 May 2023	☐
☐	Request for supplementary information	25 May 2023	25 May 2023	☐
☐	Submission of MAH responses	13 Oct 2023	13 Oct 2023	☐
☐	Start of procedure	16 Oct 2023	16 Oct 2023	☐
☐	CHMP Rapporteur Assessment Report	14 Nov 2023	14 Nov 2023	☐
☐	PRAC Rapporteur Assessment Report	17 Nov 2023	14 Nov 2023	☐
☐	PRAC members comments	22 Nov 2023	n/a	☐
☐	Updated PRAC Rapporteur Assessment Report	23 Nov 2023	23 Nov 2023	☐
☐	PRAC Outcome	30 Nov 2023	30 Nov 2023	☐
☐	CHMP members comments	04 Dec 2023	04 Dec 2023	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	07 Dec 2023	07 Dec 2023	☐
☒	Request for supplementary information	14 Dec 2023	14 Dec 2023	☐

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

[2] Criteria for CHMP plenary discussion: substantial disagreement between the Rapporteur and other CHMP members and/or at the request of the Rapporteur or the Chair

Criteria for PRAC plenary discussion: proposal for update of SmPC/PL, introduction of or changes to imposed conditions or additional risk minimisation measures (except for generics aligning with the originator medicinal product), substantial changes to the pharmacovigilance plan (relating to additional pharmacovigilance activities, except for generics adapting aligning with the originator medicinal product), substantial disagreement between the Rapporteur and other PRAC members, at the request of the Rapporteur, any other PRAC member, the Chair or EMA.

[3] Sections related to Risk Management Plan or on non-interventional PASS results. If PRAC advice was ad hoc requested by the CHMP, the relevant Attachment to the assessment report applies and has been endorsed by the PRAC.

Procedure resources	
CHMP Rapporteur:	Janet Koenig (DE)
CHMP Co-Rapporteur:	Alexandre Moreau (FR)

Table of contents

List of abbreviations

ACTH	Adrenocorticotrophin hormone
B/R	Benefit / risk
CNS	Central nervous system
CRH	Corticotropin-Releasing-Hormon
EPP	Erythropoietic protoporphyria
EU	European Union
FECH	Ferrochelatase
FEP	Free erythrocyte protoporphyrin
FSH	Follicle-stimulating hormone
GCP	Good clinical practice
GCs	Glucocorticoids
GH	Growth hormone
HPA	Hypothalamic-pituitary-adrenal
LBW	Low body weight
LH	Luteinizing hormone
MAA	Marketing authorisation application
OT	Oxytocin
PASS	Post-authorisation safety studies
PDCO	Paediatric Committee
PIP	Paediatric investigation plan
PK	Pharmacokinetics
PPIX	Protoporphyrin IX
PVN	Paraventricular nucleus
RCR	Retrospective chart review study
RMP	Risk Management Plan
SmPC	Summary of product characteristics
TEAE	Treatment emergent adverse event
TSH	Thyroid-stimulating hormone
XP	Xeroderma Pigmentosum

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Clinuvel Europe Limited submitted to the European Medicines Agency on 30 August 2022 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication for the prevention of phototoxicity in adolescent patients (12 to under 18 years of age) with erythropoietic protoporphyria (EPP), based on the analysis of the safety and efficacy data available. As a consequence, sections 4.1, 4.2 and 4.4 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 9.4 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce a minor editorial correction to the PI.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information relating to orphan designation

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0060/2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA-000737-PIP02-11-M02 was not yet completed as some measures were deferred.

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 MAH 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.

Protocol assistance

The MAH did not seek Protocol assistance at the CHMP.

2. Scientific discussion

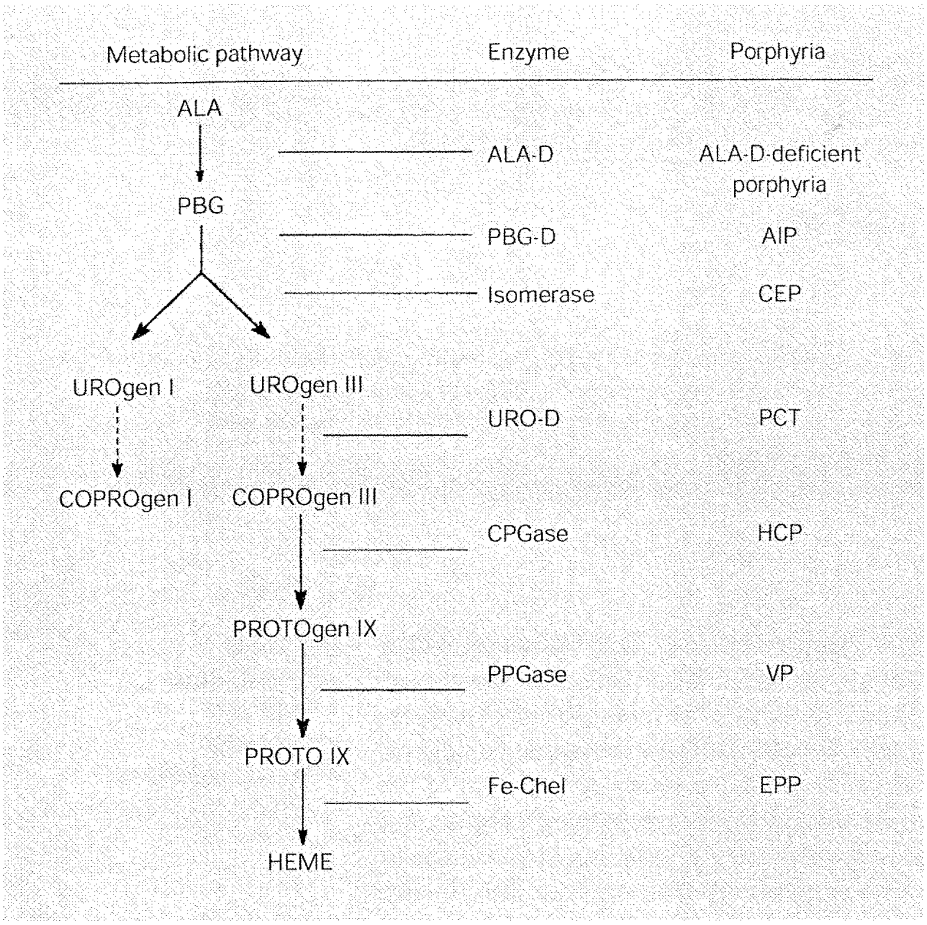
2.1. Introduction

2.1.1. 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. Haeme, an iron-containing pigment, is an essential cofactor of numerous haemoproteins. Virtually all cells of the human body require and synthesize haeme. However, most haeme is synthesized in the bone marrow (by erythroblasts and reticulocytes) and is incorporated into haemoglobin. The liver is the second most active site of haeme synthesis, most of which is incorporated into cytochrome P-450 enzymes. Haeme 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 protoporphyrins in bone marrow cells, resulting in its accumulation in erythrocytes, plasma, and other tissues. In these patients, skin protoporphyrins can produce free radicals under sunlight, causing painful cutaneous damage.

Its predominant characteristics include bullous cutaneous photosensitivity to visible light from early infancy, progressive photomutilation and chronic haemolytic anaemia. 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, ocular, oral and skeletal manifestations also contribute to disease severity and impact on quality of life, in addition to the haematological complications.

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 porphyrins are found in the urine of EPP patients (Murphy, 2003).

EPP presents as acute photosensitivity with erythema, edema, and a painful burning sensation, very similar to sunburn, although it only requires between 1 and 30minutes 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 is 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 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 dermatosis. In the most severe cases an absolute intolerance to sun-exposure is observed, with intolerable burning pain on exposed skin. Phototoxic effects include:

(i) painful burning (immediate or delayed);

(ii) itching, pruritus;

(iii) loco-regional oedema and erythema;

(iv) ulceration, especially of the face (nasal region) and dorsa of the hands (Todd, 1994).

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 sun exposure and wearing sun protective clothing. Current supportive care involves the use of analgesics, anti-histamines, topical corticosteroids 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, and 10% felt depressed (Holme et al., 2006).

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, progressive hepatocellular disease with end-stage liver disease and acute liver failure. Liver damage is the major risk in EPP patients, so surveillance and frequent clinical and biochemical liver follow-up is mandatory (Casanova-Gonzalez et al., 2010).

During adolescence, EPP patients have learned to modify their existence by avoiding light sources and limiting outdoor activities, very much developing a nocturnal existence by seeking comfort in the dark. Characteristic of EPP is the phenomenon of prodromal symptoms, forewarning patients of the start of phototoxic episodes, which make the patients retract to indoor conditions before a full phototoxic episode develops.

While the adolescent patient has the option to wear protective clothing, this option may not be chosen because of the consciousness of drawing attention to themselves or being the subject of ridicule.

Importantly, during adolescence the patient becomes aware of this life-long handicap and is compelled to take career decisions, which seem to be led by future expectations to be restricted in free movement and uninhibited interaction. Choices at high school, college and further education are hampered by the impairment the patient has encountered during their life, and social development is often further restricted at this age. Not surprisingly, patients experience psychosocial consequences of their limited living patterns and "phototoxicity" throughout their life.

2.1.2. About the product

Afamelanotide is a synthetic analogue of the physiologically occurring α-melanocyte stimulating hormone (α-MSH or melanotropin), which stimulates melanoma 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 it's intended action is to protect against phototoxic reactions caused by sunlight.

Scenesse (afamelanotide) was first authorised in the European Union (EU) via a centralised procedure on 22 December 2014 (IBD) in Europe. The Marketing Authorisation was approved under exceptional circumstances. In the EU the product has been marketed in June 2016 under the provisions of the post-authorisation requirements (disease registry study (CUV-PASS- 001/CUV-PASS-002) and the retrospective chart review study (CUV-RCR-001)). The disease registry is a specific obligation of the marketing authorisation under exceptional circumstances and the retrospective chart review is a condition to the marketing authorisation with regard to the safe and effective use of the product.

The renewal of the Marketing Authorisation granted under Exceptional Circumstances (Article 14(8) of Regulation (EC) No 726/2004) was granted by the European Commission on 19 November 2019.

Scenesse was also approved by the FDA on 08 October 2019 to increase pain free light exposure in adult patients with a history of phototoxic reactions from EPP. Scenesse was also approved by the Therapeutic Goods Administration in Australia on 22 October 2020 for the same indication as in the EU. To date, there are no further marketing authorisations for Scenesse.

This application concerns the extension of indication for the prevention of phototoxicity in adolescent patients (12 to under 18 years of age) with erythropoietic protoporphyria (EPP).

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

Persuant to Article 22 of the Regulation (EC) No 1901/2006 as amended, Clinuvel Europe Limited submitted to the European Medicines Agency on 17 October 2022 an application for modification of the agreed paediatric investigation plan with a deferral and a waiver as set out in the European Medicines Agency´s decision P/0292/2011 issued on 2 December 2011.

In January 2023 the PDCO agreed to modify timelines of the PIP (EMEA-000737-PIP02-11-M02), timelines for the studies in the paediatric population were postponed.

Area	Description
Quality	Study 1. Development of age appropriate prolonged release formulation for subcutaneous use.
Non-clinical	Study 2. Juvenile repeat-dose toxicity study in rats followed by 4-week recovery.
Clinical	Study 3. Comparative study to evaluate the pharmacokinetics of afamelanotide and the pharmacodynamic response to afamelanotide between subcutaneous administration of solid implant and the age appropriate prolonged release formulation in healthy adults. Study 4. Open-label, multicentre, multiple dose, dose-escalation pharmacokinetic and pharmacodynamic study of afamelanotide age appropriate prolonged release formulation in children from 6 to less than 18 years with erythropoietic protoporphyria. Study 5. Open-label, multicentre, multiple dose, dose-escalation pharmacokinetic and pharmacodynamic study of afamelanotide age appropriate prolonged release formulation in children from 2 to less than 6 years with erythropoietic protoporphyria.

Area	Description
	Study 6. Placebo controlled, randomised, double-blind safety, pharmacodynamics and efficacy trial of afamelanotide age appropriate prolonged release formulation in children from 6 to less than 18 years with erythropoietic protoporphyria, and with an open-label active-only arm in children from 2 to less than 6 years, with 12 month open-label extension to evaluate safety.

CHMP comment on the initial submission

The MAH did not provide any information on the paediatric development programme for the applied indication for the prevention of phototoxicity in adolescent patients (12 to under 18 years of age) with erythropoietic protoporphyria (EPP). Importantly, in the submission the applicant did neither provide any information on the studies agreed in the aforementioned PIP nor on the recent modification of the PIP.

The Rapporteur is aware, that the MAH has submitted to the European Medicines Agency on 17 October 2022 an application for modification of the agreed paediatric investigation plan with a deferral, which was agreed in January 2023. The MAH has submitted the application for changes (delay) of studies 1-6 after the full PIP should have been finalized in June 2022. In essence, all studies that were included in the European Medicines Agency´s decision P/0292/2011 issued on 2 December 2011 were postponed to a later date. The PIP should now be completed by March 2028.

*Notably, the development of an age-appropriate prolonged release formulation for subcutaneous use in study 1 is the prerequisite for most other studies. The planned completion of study 1 is not completely clear as different dates are included in the PIP (March 2028 or September 2023). It is currently not clear if the other studies 2-6, thus the full PIP, will be fulfilled in March 2028. The completion dates of the other studies may not be reasonably justified. The MAH is asked to clarify (**OC**).*

It is unclear why the applicant now submits this extension of indication application while the whole PIP is still running.

*This extension of indication application includes neither data of any of the studies agreed within the PIP nor any relevant study data in addition to what was submitted with the initial application for marketing authorization in 2011-2014. In particular, the MAH provided no update on the development of an age-appropriate prolonged release formulation for subcutaneous use. To the knowledge of the Rapporteur, no implant formulation is authorized for patients younger than 18 years of age in the EU. The MAH is asked to report on any clinical study data generated since marketing authorization, which may be relevant for this application (**OC**).*

*The MAH is asked to comment on the status and timelines paediatric formulation development as well as the six studies from PIP EMEA-000737-PIP02-11-M02 and provide any relevant data for the extension of indication application for adolescent patients aged 12-18 years of age (**OC**).*

*As per PIP, study 2 "juvenile repeat-dose toxicity study in rats followed by 4-week recovery" was already planned to evaluate the toxicity of afamelanotide. As the MAH is proposing to use the marketed "adult" formulation for adolescents aged 12-18 years of age, the results of the above mentioned study with the adult formulation should be presented. The applicant should also provide additional details on the planned study such as if dose-range finding is planned. Nevertheless, a discussion by the applicant should first make clear whether a juvenile toxicity study is actually necessary in line to the current ICH S11 guideline (**OC**). Study 2 of the actual PIP was not subject of this assessment, as this study is not finished at this time point.*

Summary of the Assessment of the MAH responses to the RSI

*The Applicant summarised, that formulation development activities have been ongoing since Marketing Authorization. Thus, the concerns on appropriateness of the adult device for adolescents (and children) remain. (OCs on formulation integrated into **MO3**).*

*None of the six studies of the PIP were started, therefore no new data was provided and could be assessed. No data from the six studies from PIP EMEA-000737-PIP02-11-M02 was provided. It remains unclear why the MAH first proposed a delay of the studies proposed in the PIPs and then submitted an extension of indication variation for adolescents. While challenges in conducting the PIP are acknowledged, it is not understood why no alternative clinical development plans have been proposed and discussed before submitting this extension of indication variation (OCs on PIP integrated into **MO1**).*

*The applicant should propose alternative clinical development plans to support an extension of indication in adolescents (**MO**).*

Non-clinic:

As part of the request for supplementary information, the applicant provided the study report of the toxicity study "Repeated dose chronic toxicity study in pvg/c arc black hooded rats treated with afamelanotide 16 mg implant and narrow-band ultraviolet b (nb-uvb) light irradiation: main study" (ICPQN1266.B). The study evaluated the toxicity of SCENESSE® 16 mg implant, in which two groups of 40 rats (20 males, 20 females) were administered the drug product or placebo, over a 24-week period (169 days) in combination with NB-UVB irradiation. The rats (7-10 weeks old) used in the study cover the respective adolescent stage 12-18 in humans.

According to the submitted study report, over the whole experimental period of 169 days no statistical significant difference in feed intake were observed for both males and females. Further, the eye observations made for R5229 were unilateral, therefore could not be related to any systemic effect of the treatment. There were no other abnormal clinical observations over the entire observation period in both males and females placebo and test item implanted animals. It has been concluded that the test item had no effect on any of the parameters measured in the ophthalmological examination prior to dosing and during week 24.

The test item by itself or combined with irradiation did not produce any observable skin irritation during the whole experimental period. No gross necropsy findings were considered related to the treatment. However, smaller left brain hemisphere, enlarged heart and smaller spleen were observed in male and female test item implanted and non-irradiated animals, respectively.

The minor statistically significant differences observed in the thyroid and testes were not considered to be of any clinical significance by the MAH. Moreover, no histopathological findings related to treatment were observed in any of the treatment groups.

Toxicokinetic measurements show considerable variability in plasma levels with high standard deviations. The statement in the study that the plasma levels of afamelanotide on day 1 and day 142 are the same cannot be followed.

Results of the toxicity study were briefly presented by the MAH. The study was conducted with the adult formulation to support the use in adolescents (age 12-17) with the same formulation as used in adults.

Development of CNS was not in particular evaluated as behavioural testing is missing. Further, possible effects on the immune system could have been more deeply discussed considering ICH S8. Altogether, the submitted study can be accepted and a new juvenile toxicity study covering

behavioural assessment will not be requested. This non-clinical study is finally regarded as supportive to/for clinical investigations to use SCENESSE® 16 mg implant in adolescents aged from 12–17 years (OC on juvenile toxicity study solved).

2.1.4. General comments on compliance with GCP

N/A

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application. However, as per PIP a juvenile repeat-dose toxicity study in rats followed by 4-week recovery is planned to assess the effects of repeat exposure to afamelanotide in young developing rats with particular attention to neurobehavioral and immunotoxic potential.

In response to the first request for supplementary information, the applicant provided the study report of the toxicity study *"Repeated dose chronic toxicity study in pvg/c arc black hooded rats treated with afamelanotide 16 mg implant and narrow-band ultraviolet b (nb-uvb) light irradiation: main study"* (ICPQN1266.B). The assessment of the study report is detailed in section 4.1.3.

2.3. Clinical aspects

2.3.1. Introduction

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).

The marketing formulation is comprised of afamelanotide in a bioresorbable 50:50 polylactide-co-glycolide implant core. This polymer is fully resorbed within 50 to 60 days after implantation. According to the Applicant this is consistent with a dosing interval of 60 days. The implant core also has a thin coating of 50:50 polylactide-co-glycolide to further control the rate of release of afamelanotide.

The MAH presented no new clinical pharmacology, PK or PK/PD data in this application.

2.3.2. Pharmacokinetics

The MAH presented no new clinical PK data in this application.

CHMP comment on the initial submission

The absorption and bioavailability of the final formulation have been characterized in a number of studies in healthy volunteers at MAA.

*At the times of marketing authorization information regarding clearance (elimination) and half-life of afamelanotide in humans was not considered complete. PK data from EPP patients and in special populations were missing. The Applicant committed to perform an additional PK study CUV052 (part of the RMP). No information on the results of study CUV052 were presented here, the MAH is asked to present to available data (**OC**).*

*No data has been submitted that would have allowed the extrapolation of clinical efficacy or safety from adults to adolescents, e.g. based on comparable plasma exposures in adolescents and adults. A discussion on possible extrapolation of adult PK data to children is lacking, too. No information was provided how the dose in adolescents was selected and administration of the correct dose is ensured given that the applicant intends to use the same device as in adult patients (**MO**).*

As outlined above study 3 of the PIP "comparative study to evaluate the pharmacokinetics of afamelanotide and the pharmacodymanic response to afamelanotide between subcutaneous administration of solid implant and the age appropriate prolonged release formulation in healthy adults" has been deferred to September 2024.

Summary of the Assessment of the MAH responses to the RSI

The MAH considered that the fixed dose of 16 mg afamelanotide every 2 months is appropriate for the treatment of adolescent EPP patients due to the significant overlap between the weights of lower bodyweight patients being treated with SCENESSE® in the PASS and those of the general adolescent population.

However, the similitude of the dose-response relationship between adolescents and adults is not substantiated by any data. The applicant should well justify the choice of the same dosing and posology of adults in adolescents and the assumption that the same exposure as in adults translates in a similar efficacy and safety profile in adolescents (MO).

No new PK data could be assessed, as CUV052 was not conducted due to various challenges. The MAH however outlines that carrying out the study is now considered possible and has submitted a modified study synopsis. The OC on CUV052 is therefore integrated into MO1.

The assessment of a study synopsis outside of the scope of this procedure. In fact, the results of this study may have been of interest for this procedure, but are not available. In conclusion, the PK-profile in adult patients is still considered incompletely characterised, as PK study CUV052, which was already requested in the scope of the MA of Scenesse® in 2014 has not been conducted yet. The incomplete PK data in adults further aggravates the discussion on possible extrapolation of adult PK data to children. The MAH is requested to submit the CUV052 data as soon as possible without further delay.

2.3.3. Pharmacodynamics

The MAH presented no new clinical PD data in this application.

CHMP comment on the initial submission

In the initial MAA, the pharmacodynamic studies at MAA relied on the melanin density as a sole marker; a surrogate value for clinical improvement in EPP patients is plausible, but has not been shown. Since marketing authorization including this application no further PD data was submitted.

2.3.4. PK/PD modelling

N/A

2.3.5. Discussion on clinical pharmacology

No data has been submitted with this extension of indication application that would have allowed the extrapolation of clinical efficacy and safety from adults to adolescents, e.g. based on comparable

plasma exposures in adolescents and adults. In addition, no discussion on the acceptability of an extrapolation based on assumptions that the disease, mechanism of action and thus PK/PD are the same in paediatric patients as in adults was provided.

The agreed comparative study in PIP EMEA-000737-PIP02-11-M02 to evaluate the pharmacokinetics of afamelanotide and the pharmacodymanic response to afamelanotide between subcutaneous administration of solid implant and the age appropriate prolonged release formulation in healthy adults.

2.3.6. Conclusions on clinical pharmacology

Adequate data on clinical pharmacology to support the extension of indication in adolescent patients aged 12-17 years of age is lacking.

2.4. Clinical efficacy

No new efficacy data have been submitted.

The Table 1 below summarises the clinical studies performed to support the afamelanotide programme in EPP.

Table 1. Clinical Efficacy Trials to Support Development of Afamelanotide

Study No.	Study Design	Patients Enrolled	Endpoint
CUV010	A Multicentre, Phase II, Open Label Study to Evaluate the Safety and Efficacy of Subcutaneous Implants of Afamelanotide in Patients with Erythropoietic Protoporphyria (EPP)	5	Photoprovocation times
CUV017	A Phase III, Multicentre, Randomised, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Subcutaneous Bioresorbable CUV1647 Implants in Patients with Erythropoietic Protoporphyria (EPP).	100	Number and severity of phototoxic reactions
CUV030	A Phase II, Multicentre, Double-Blind, Randomised, Placebo-Controlled Study to Confirm the Safety and Efficacy of Subcutaneous Bioresorbable Afamelanotide Implants in Patients with Erythropoietic Protoporphyria (EPP)	77	Severity of phototoxic reactions / amount of sun exposure
CUV029	A Phase III, Multicentre, Double-Blind, Randomised, Placebo-Controlled Study to Confirm the Safety and Efficacy of Subcutaneous Bioresorbable Afamelanotide Implants in Patients with Erythropoietic Protoporphyria	74	Number and severity of phototoxic reactions / amount of sun exposure
CUV039	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)	93	Amount of sun exposure

Presently, there are limited clinical data available on the use of afamelanotide in paediatric patients, as only a few adolescent patients have been treated with SCENESSE®.

The MAH believes there to be sufficient safety information to support the treatment of adolescent EPP patients (ages 12 to 17 years) with a bodyweight of 60 kg or more.

The MAH proposes to treat adolescents with bodyweight of at least 60 kg, based on:

- safety and effectiveness data collected since 2006
- pharmacovigilance database maintained since 2016 (first EU distribution of SCENESSE®)
- analyses of safety data from current patients with bodyweight of 60kg and higher

In the view of the MAH, there is an urgent need to treat adolescent EPP patients. Since the start of the development of SCENESSE® (afamelanotide 16 mg) in EPP nearly 17 years ago, and the years since marketing authorization in 2014 (EU/1/14/969), the MAH claims that there has been unwavering demand from parents, children and patient organizations to make the treatment available to adolescents, who do not have access therapy at present. Based on experience and data accumulated, there are special considerations to make SCENESSE® available for adolescent patients.

The MAH further claims that the treatment has been demanded by the parents and patients themselves for the past three years, and it is owing to the selection process of the Head of Metabolic Diseases at the Erasmus Medical Center that adolescent patients are now being selected on a weight basis for treatment with SCENESSE®. No rationale for this bodyweight cut-off is presented.

The Table 2 below provides an overview about the clinical efficacy study, which have been submitted with this application. All studies outlined below have been included and discussed in the initial MAA in 2012-2014.

Table 2. Description of Clinical Efficacy and Safety Studies

Study ID	Number of Study Centers Location(s)	Study Start Enrollment Status, Date Total Enrollment / Enrollment Goal	Design Control Type	Study & Ctrl Drugs Dose & Regiment	Study Objective	# subs by arm entered / compl.	Duration	Gender M/F Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoint(s)
Erythropoietic Protoporphyria										
CUV039	7 USA	1st subject dosed 23.05.12, last subject completed 31.07.13, a total of 93 subjects were recruited.	Multicentre, phase III, randomized, double-blind, placebo-controlled	Study drug: 16mg implant, 3 active implants given on Days 0, 60 and 120. Control drug: placebo implant, 3 placebo implants given on Days 0, 60 and 120.	Determine whether afamelanotide can enable EPP patients to expose themselves to sunlight without incurring pain and phototoxic reactions	Active arm: 48 patients enrolled, 45 completed Placebo arm: 45 patients enrolled, 42 completed	May 2012 – July 2013	Active arm: 28 M, 18 F Mean age 40.1 years (SD 12.4) Placebo arm: 20 M, 23 F Mean age 39.2 years (SD 16.2)	Male or female EPP patients; aged 18 years and above; written informed consent; precautions to prevent pregnancy.	The number of hours on pain-free days that patients exposed themselves to direct sunlight between 10:00-18:00 hours
CUV030	6 USA	1st subject dosed 28.04.10, last subject completed 31.01.11, a total of 77 subjects were recruited.	Multicentre, phase II, randomized, double-blind, placebo-controlled	Study drug: 16mg implant, 3 active implants given on Days 0, 60 and 120. Control drug: placebo implant, 3 placebo	To determine whether afamelanotide can enable patients to expose themselves to direct sunlight during the most intense periods of sunlight during the day in spring and summer.	Active arm: 39 patients enrolled, 34 completed. Placebo arm: 38 patients enrolled, 33 completed	April 2010 – January 2011	Active arm: 23 M, 16 F Mean age 38.1 years (SD 14.5) Placebo arm: 20 M, 18 F	Male or female EPP patients; aged 18 years and above; written informed consent; precautions to prevent pregnancy.	The number of hours that patients exposed themselves to direct sunlight between 10:00-15:00 hours and between 10:00 – 20:00 hours.

Study ID	Number of Study Centers Location(s)	Study Start Enrollment Status, Date Total Enrollment / Enrollment Goal	Design Control Type	Study & Ctrl Drugs Dose & Regiment	Study Objective	# subs by arm entered / compl.	Duration	Gender M/F Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoint(s)
				implants given on Days 0, 60 and 120.				Mean age 42.6 years (SD 15.7)		
CUV017	8 Australia, EU and Switzerland	1st subject dosed 14.05.07, last subject completed 09.12.09	Multicentre, phase III, randomized, double-blind, placebo-controlled, multiple crossover	Study drug: 16mg implant, 3 active implants given, alternating with placebo implants in a crossover fashion	To determine whether afamelanotide implants can: - reduce the number of phototoxic reactions - reduce the severity of phototoxic reactions	100 patients enrolled/ 92 completed	May 2007 – December 2009	47 M/53 F Mean age 38.9 years (SD 12.8)	Male or female EPP patients; aged 18-70 years; written informed consent	Mean number and mean severity of phototoxic reactions for patients receiving afamelanotide and placebo
CUV029	8 Europe	1st subject screened 14.01.10, last subject completed 09.05.11	Multicentre, phase III, randomized, double-blind, placebo-controlled	Study drug: 16mg implants, 5 active implants given on Days 0, 60, 120, 180 and 240. Control drug: 5 placebo implants given on Days 0, 60, 120, 180 and 240.	To determine whether afamelanotide can enable patients to expose themselves to direct sunlight during the most intense periods of sunlight during the day in spring and summer.	Active arm: 38 patients enrolled, 34 completed Placebo arm: 36 patients enrolled, 34 completed	January 2010 – May 2011	Active arm: 21 M, 17 F Mean age 38.3 years (SD 13.0) Placebo arm: 16 M, 20 F Mean age 38.6 years (SD 11.6)	Male or female EPP patients; aged 18-70 years; written informed consent	The number of hours that patients exposed themselves to direct sunlight between 10:00-15:00 hours on days when patients did not experience pain.

Study ID	Number of Study Centers Location(s)	Study Start Enrollment Status, Date Total Enrollment / Enrollment Goal	Design Control Type	Study & Ctrl Drugs Dose & Regiment	Study Objective	# subs by arm entered / compl.	Duration	Gender M/F Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoint(s)
CUV010	1 Switzerland	1st patient screened 01.09.06, 1st patient dosed 07.09.06 5 patients enrolled at one centre Planned enrollment 10 patients at two centres	Multicentre, phase II, open label	Study drug: 20mg implant, 2 doses given at an interval of 60 days Control drug: not applicable	- To determine whether afamelanotide implants can reduce the susceptibility of patients with EPP to provocation with a standardized light source. - To determine the effect of afamelanotide on the amount of rescue medication required.	5 patients entered/ 5 patients completed	Sept 2006 – Feb 2007	3 M/2 F Average age 39 years (range 23-67 years)	EPP (confirmed by elevated free photporphyrin IX in peripheral erythrocytes and/or ferrochelatase mutation; aged 18-70 years; Fitzpatrick skin type I-IV; written informed consent	- Time to appearance of provoked symptoms - Amount and type of rescue medication used

In the MAH´s view this application is made at this stage of commercial distribution and product development cycle, since a number of clinical criteria have been achieved. In the view of the MAH these criteria were discussed during the initial PRAC assessments of the post-authorization safety study (PASS) in November 2014. The MAH states that as the EMA (PIP reference EMEA-000737-PIP02-11) considered, testing in juvenile patients should not commence before 5 years of real-world experience with SCENESSE® had occurred. Safety data have now been collected since SCENESSE® was first made commercially available in the European Union in June 2016.

Three further arguments supporting the need for SCENESSE® to be available to adolescents with a total bodyweight of 60 kilogram and above are as follows:

- Marketing authorization (MAA) has been unconditionally continued by the EMA in 2019. The decision was based on the ongoing safety reporting on the commercially distributed product, as well as the pharmacovigilance systems established and maintained by the MAH. To this effect, the MAH has maintained a restricted and direct distribution to a limited number of trained and accredited centres within the European Union to enable the MAH to follow up patients longitudinally. The same direct distribution approach as well as pharmacovigilance system will be applicable when adolescent patients are being treated with SCENESSE®.
- Secondly, the safety profile has recently been re-analysed. Safety data included all reports from patients (n=1218) followed up during 17 years of drug administration. The MAH has administered over 10,000 implants to EPP patients, with total human exposure for the drug implant of 50,000 to 70,000 days. This is considered to be adequate safety data to support the use of SCENESSE® in adolescents.
- Thirdly, a more specific estimate of adolescent patient numbers has been made among the seven European countries where SCENESSE® has been made available to adult patients. Of the total eligible adult patient population within the countries, a maximum of 66 adolescent patients aged 15, 16 or 17 years could be imagined as eligible for treatment.
- Fourthly, no serious safety concerns have been reported in adult patients, since the initial collection of safety data in 2006. Based on the comparison of TEAEs reported in the total population of patients in the PASS and the subset of low bodyweight patients in the PASS, the MAH now considers there to be adequate safety data to demonstrate that the use of SCENESSE® in adolescent patients of body weight 60 kg and above.
- No off-label use is permitted with SCENESSE® which further mitigates the prevalence of unexpected adverse events reported in patients.

Experience of SCENESSE® treatment in adolescents

Five adolescent patients – aged 17 at the time of the initial administration – have been treated with SCENESSE®. One patient was treated for Xeroderma Pigmentosum (XP), four other patients with EPP were treated under the PASS. The demographics for the EPP patients treated are tabulated below (see Table 3 below). These patients had been selected on a weight basis owing to the selection process.

Table 3. Demographics for the EPP adolescent patients treated under PASS

Gender	Age	Bodyweight	Height
		79.5 kg	185.2 cm
		88.6 kg	178 cm
		76.0 kg	170 cm
		73.3 kg	171 cm

Similar requests for treatment of other adolescent patients have been received from other EU countries. Thus far, the MAH has consented to treatment pending this application for treatment of adolescents with a bodyweight of 60 kg and above.

CHMP comment on the initial submission

No new clinical study data in addition to what was submitted with the initial application for marketing authorization in 2011-2014 is provided in this application. Importantly, the applicant did not perform any clinical studies in patients under 18 years of age. Recently (in January 2023) the PDCO agreed to modify timelines of the PIP (EMEA-000737-PIP02-11-M02), timelines for clinical studies in the paediatric population were postponed. The completion of the open-label study in children from 12 to 18 years of age resp. 6 to12 years of age was deferred to 2025. It is not comprehensible for the Rapporteur why the MAH is shifting the timelines of the clinical study and quasi simultaneously applies for an extension of indication for the same age group. It is not clear why the clinical study in patients under 18 years of age was not carried out first and thereafter the extension of indication was applied for. If there is a compelling clinical need to treat patients under 18 years of age, as argued by the MAH, adolescent patients could also have been treated in a timely manner and under close surveillance in a clinical trial.

The application to extend the indication of Scenesse to treat adolescents aged 12-17 years is purely based on some safety data gathered since start of commercialisation. No efficacy data was presented to support the treatment of adolescents aged 12-17 years or of adolescents. A discussion on possible extrapolation of adult efficacy data to adolescents is lacking, too. The MAH also did not report on any efficacy parameter/ outcome for the four patients before and after the therapy.

From the scarce information provided and the almost unchanged SmPC, the Rapporteur assumes that it is the MAH´s proposal to treat adolescents aged 12-17 years of age exactly as adults. In terms of efficacy, no rationale or relevant information was provided on why this dose should be appropriate and how the dose in adolescents was selected.

The lack of an age-appropriate prolonged-release formulation is discussed further below.

In addition, the four individuals treated were > 73 kg of weight. The proposed bodyweight cut-off is not included in the SmPC and no rationale is presented for using a cut-off of 60 kg bodyweight.

*Similarities and differences between adults and adolescents with relevance for efficacy are not discussed. For example, differences regarding the maturation of melanocytes and keratinocytes between adults and adolescents should be discussed (**OC**).*

Of note as referenced in the initial MAA procedure trials CUV029 and CUV030, presented as supportive evidence here, were inspected due to GCP issues and it was concluded from the GCP inspection that GCP compliance could not be confirmed for those parts of the two trials, which were inspected, and that the main efficacy data of these trials were not valid and reliable.

<u>Summary of the Assessment of the MAH responses to the RSI</u>

No new efficacy data was provided with the MAH´s responses. Hence, the major objection on efficacy in adolescent population remains.

The MAH provided an updated discussion on extrapolation of adult efficacy data to adolescents with the responses to the RSI. The MAH outlined that there is only limited information available and that based on the available data no negative effects are anticipated. In addition, the MAH again noted the urgent need due to psychological burden, increased number of participants in the PASS study from 4 to 6, and reported that the same photoprotective efficacy and similar safety profile in adolescents is expected compared to low bodyweight adults. Other aspects, which may directly affect distribution of the drug

and relevance and frequencies TEAEs, were discussed to limited extent. The MAH had been asked to discuss similarities and differences between adults and adolescents with relevance for efficacy, e.g. differences regarding the maturation of melanocytes and keratinocytes.

*The MAH´s discussion is hampered by a critical lack of data to underpin the expectations on efficacy (and safety) being comparable between adolescents and low bodyweight adults. The limited information on afamelanotide´s effect on factors such as puberty, gender differences and hormonal influences on melanin levels adds uncertainty in extrapolating data from adults to adolescents. In summary, insufficient justification was provided on why efficacy in low body weight adults should be considered comparable to adolescents and why weight should be regarded as the decisive factor. It is concluded that based on the lack of data, efficacy of afamelanotide in adolescents currently cannot be extrapolated from adults (OC integrated into **MO1**).*

2.5. Clinical safety

Safety Considerations

Size/weight considerations

The following data were collected for the assessment:

- Weight by age for Australia, England and United States.
- Adverse event/reaction data in CLINUVEL's database for all patients in the PASS database, and for patients weighing less than 55/60 kg

Weight by age considerations

The following weights by age group that are mostly closely matched to the 60 kg category are:

Table 4. Mean Body weight by Age Bracket

Territory	Male		Female	
	Average Weight	Age Bracket	Average Weight	Age Bracket
Australia: 2017-18 National Health Survey	56.3	12-15*	61.8	16-17
England: 2019 Health Survey	60.4	13	62.2	14
United States: 2015-8 Anthropometric Reference Data	61.0	13-15	59.7	13-15

*There is less granularity in Australian data

The weight bracket chosen for the assessment of adverse event/reaction data in lower weight patient was less than 60 kg. Using the weight distribution data across Australia, England and the United States, bodyweight of at least 60 kg best aligns with adolescents.

The threshold of 60 kg was chosen on the basis of the safety analysis performed on data from low bodyweight patients compared with all safety data reported through the PASS. The bodyweight limit of 60 kg also equates to the average bodyweight of adolescents. To date, adolescents treated have bodyweights that exceed 60 kg.

Treatment emergent adverse event (TEAE) data on low body weight (LBW) patients treated under the PASS were extracted and compared with the PASS data for the full patient population, to give an

understanding of the characterisation of risk for the potential treatment of adolescent patients (see Table 5 below).

Sixty-one (61) patients with body weight <60 kg (range 42-59.8 kg) have been enrolled and treated under the PASS at twelve EPP expert centres in Europe. Age range 18-66 years. Of these, 29 patients are under 55 kg (age range 18-58 years). Patients had received between one and 26 implants each (median nine implants). Forty-seven (47) of these 61 patients (77.0%) reported one or more AE, which is comparable to the whole patient population (356 out of 430 [82.8%]).

Six of the 61 patients have received seven years of treatment, eight have received six years, nine have received five years, seven have received four years, 12 have received three years of treatment, 11 two years and eight patients have had one year of treatment.

Table 5. Comparison of safety information for all PASS patients (from PSUR #12 and PASS Intermediate Report #4) and for LBW patients.

	All PASS patients (430 patients)	**LBW patient subgroup (61 patients)**
At least one TEAE:	82.8% (356 out of 430)	77.05% (47 out of 61)
At least one TEAE assessed as related to treatment:	55.1% (237 patients)	47.5% (29 patients)
At least one serious TEAE:	18.1% (78 patients)	16.4% (10 patients)
At least one serious TEAE assessed as related:	1.2% (5 patients)	3.3% (2 patients)
The TEAEs listed by MedDRA SOC – listed in order of frequency (per All PASS population)	General disorders and administration site conditions 616 TEAEs in 185 patients (43.0% of the patients)	General disorders and administration site conditions 65 TEAEs in 26 patients (42.6% of the patients)
	Infections and infestations 330 TEAEs in 161 patients (37.4%)	Infections and infestations 28 TEAEs in 16 patients (26.2%)
	Gastrointestinal disorders 458 TEAEs in 153 patients (35.6%)	Gastrointestinal disorders 35 TEAEs in 15 patients (24.6%)
	Nervous system disorders 323 TEAEs in 123 patients (28.6%)	Nervous system disorders 24 TEAEs in 11 patients (18.0%)
	Skin and subcutaneous tissue disorders 248 TEAEs in 113 patients (26.3%)	Skin and subcutaneous tissue disorders 28 TEAEs in 12 patients (19.7%)
	Metabolism and nutrition disorders **110 TEAEs in 94 patients (21.8%)**	Metabolism and nutrition disorders 10 TEAEs in 9 patients (14.7%)
	Musculoskeletal and connective tissue disorders 151 TEAEs in 79 patients (18.4%)	Musculoskeletal and connective tissue disorders 5 TEAEs in 5 patients (8.2%)
	Vascular disorders 127 TEAEs in 70 patients (16.3%)	Vascular disorders 7 TEAEs in 4 patients (6.5%)
	Injury, poisoning and procedural complications 104 TEAEs in 68	Injury, poisoning and procedural complications 18 TEAEs in 10 patients (16.4%)

	patients (15.8%)	
	Surgical and medical procedures 84 TEAEs in 66 patients (15.3%)	Surgical and medical procedures 12 TEAEs in 8 patients (13.1%)
	Neoplasms benign, malignant and unspecified (including cysts and polyps) 66 TEAEs in 44 patients (10.2%)	Neoplasms benign, malignant and unspecified (including cysts and polyps) 11 TEAEs in 7 patients (11.5%)
	Hepatobiliary disorders 49 TEAEs in 38 patients (8.8%)	Hepatobiliary disorders 7 TEAEs in 4 patients (6.5%)
	Investigations 60 TEAEs in 36 patients (8.4%)	Investigations 17 TEAEs in 4 patients (6.5%)
	Respiratory, thoracic and mediastinal disorders 73 TEAEs in 35 patients (8.1%)	Respiratory, thoracic and mediastinal disorders 5 TEAEs in 4 patients (6.5%)
	Psychiatric disorders 40 TEAEs in 28 patients (6.5%)	Psychiatric disorders 7 TEAEs in 4 patients (6.5%)
	Reproductive systems and breast disorders 27 TEAEs in 22 patients (5.1%)	Reproductive systems and breast disorders 4 TEAEs in 4 patients (6.5%)
TEAEs (by MedDRA PT) – listed in order of frequency (per All PASS population)	Nausea 237 TEAEs in 95 patients (22.1%)	Nausea 18 TEAEs in 10 patients (16.4%)
	Headache 205 TEAEs in 85 patients (19.7%)	Headache 17 TEAEs in 8 patients (13.1%)
	Vitamin D deficiency 78 TEAEs in 77 patients (17.9%)	Vitamin D deficiency 8 TEAEs in 8 patients (13.1%)
	Fatigue 136 TEAEs in 68 patients (15.8%)	Fatigue 12 TEAEs in 9 patients (14.7%)
	COVID-19 56 TEAEs in 55 patients (12.8%)	COVID-19 8 TEAEs in 8 patients (13.1%)
	Nasopharyngitis 66 TEAEs in 45 patients (10.5%)	Nasopharyngitis 6 TEAEs in 4 patients (6.5%)
	Erythema 47 TEAEs in 26 patients (6.0%)	Erythema 5 TEAEs in 4 patients (6.5%)
	Skin hyperpigmentation 20 TEAEs in 15 patients (3.5%)	Skin hyperpigmentation 8 TEAEs in 4 patients (6.5%)
	Feeling hot 29 TEAEs in 20 patients (4.6%)	Feeling hot 4 TEAEs in 4 patients (6.5%)
	Melanocytic naevus 34 TEAEs in 25 patients (5.8%)	Melanocytic naevus 4 TEAEs in 4 patients (6.5%)
	Pyrexia 27 TEAEs in 25 patients (5.8%)	Pyrexia 4 TEAEs in 4 patients (6.5%)

		Note: no other TEAE was experienced by more than three patients
Severity of Aes	In 76.7% of patients (330 out of 430) the highest severity of TEAE(s) reported was mild. This represents 92.7% of the patients who experienced at least one TEAE (330 out of 356 patients)	In 72.1% of patients (44 out of 61) the highest severity of TEAE(s) reported was mild. This represents 93.6% of the patients who experienced at least one TEAE (44 out of 47 patients)
	Forty-one patients experienced one or more severe TEAEs (9.5% of all patients; 11.5% of patients who reported at least one TEAE)	Three patients experienced one or more severe TEAEs (4.9% of all patients; 6.4% of patients who reported at least one TEAE)
Relationship of AEs to SCENESSE®	55.1% of patients (237 out of 430) experienced one or more TEAEs assessed as related to treatment. This represents 66.6% of the patients (237 out of 356 patients) who experienced at least one TEAE.	47.5% of patients (29 out of 61) experienced one or more TEAEs assessed as related to treatment. This represents 61.7% of the patients (29 out of 47 patients) who experienced at least one TEAE
Serious Aes	A total of 222 TEAEs were reported by 78 patients (18.1%)	A total of 29 TEAEs were reported by 10 patients (16.4%)
	Twenty-nine patients experienced at least one serious TEAE that was reported as severe.	Two patients experienced at least one serious TEAE that was reported as severe.

*TEAEs = Treatment emergent adverse events

The profile of adverse events reported by low body weight patients was similar to that reported by the general PASS population, as shown above. Of the patients who experienced at least one adverse event, the highest severity reported was mild in 82.8% (356 out of 430 patients) in the PASS general population and 77.05% (47 out of 61 patients) in the low body weight group.

A total of 222 serious adverse events were reported by 78 patients (18.1% of all patients and five patients (1.2%) had at least one serious adverse event was assessed as being related to treatment) in the PASS general population. In comparison, the low body weight group had 29 serious adverse events were reported by ten patients (16.4% of all low body weight patients and two patients (3.3%) had at least one serious adverse event was assessed as being related to treatment).

Of the patients who experienced at least one adverse event, the highest severity reported was mild in 92.7% (330 out of 356 patients) in the PASS general population and 93.6% (44 out of 47 patients) in the low body weight group.

Of the patients who experienced at least one adverse event, 71.4% (225 out of 315 patients) in the PASS general population and 65.2% (30 out of 46 patients) of the low body weight group experienced one or more related to treatment.

Metabolic considerations

In order to discuss metabolic considerations for adolescents receiving SCENESSE, we approximate the effects expected in adolescents by comparing all data generated in young adults of 18-25 years of age and adults of low body weight, compared to the overall group of adults who have received afamelanotide in the past two decades, since 1995. A summary of the relevant endocrine pathways is provided further below.

Hypothalamic-pituitary-adrenal axis (HPA) in development

The HPA begins to develop as early as fetal life and becomes sexually dimorphic during puberty due to differing levels of gonadal hormones. This pathway is the central regulator of various physiological responses to external and internal stressors.

In the hypothalamus, the key nucleus which is relevant to this discussion is the paraventricular nucleus (PVN). The PVN comprises three functional neuronal types that act as central regulators of the stress response: parvocellular, neurosecretory magnocellular, and long-projecting neurons.

The pituitary gland functions largely in response to releasing factors and hormones from the hypothalamus. The pituitary gland is divided into two structures: the adenohypophysis or anterior pituitary (80%) and the neurohypophysis (20%).

Of relevance to this summary on the use of SCENESSE - an alpha-MSH analog – is the adenohypophysis. In this gland one distinguishes the pars distalis, pars intermedia, and the pars tuberalis. The pars distalis is composed of chromaffin and chromophobe cells and is where most hormone synthesis occurs. The pars tuberalis is an extension of the pars distalis and houses epithelial cells and the hypophyseal portal vessels that connect the anterior pituitary to the hypothalamus. However, it is in the pars intermedia, located between the pars distalis and neurohypophysis, that products are produced and secreted by activation of the proopiomelanocortin (POMC) gene, particularly melanocyte-stimulating hormone.

The adrenal gland composed of the medulla and cortex is developed during later stages of embryonic development. Of importance is that the human foetal adrenal responds to centrally released ACTH (larger POMC molecule), but because of the absence of the 3-hydroxysteroid dehydrogenase enzyme, the foetal adrenal mainly produces DHEA and DHEA sulphate. The infant and growing child respond gradually less to ACTH, while no effect is seen from the physiological form of alpha-melanocyte stimulating hormone (α-MSH), des-acetyl- α-MSH since it has weak to no binding affinity to all 5 melanocortin receptors.

Generally, the HPA is central to the secretion of glucocorticoids (GCs) from the adrenal cortex. The circulating GCs act on a variety of tissues to mobilize energy stores, induce lipolysis and proteolysis, potentiate vasoconstriction driven by the ANS, suppress reproduction, and alter stress-related behaviours, to allow homeostasis. The physiological responses to acute elevations in GCs occur following stressors, such as enhanced cognition and metabolism and inhibition of immune function, as this hormone permits the "fight, flight, fright" reaction.

In adolescents, as seen in adults of lighter body weight of 60 kilogram and more, afamelanotide 16 mg is expected to have limited biologically availability, based on the:

a. dosage form,

b. half-life, and

c. metabolism.

Parameters of HPA feedback circuitry

Over the course of two decades, during which afamelanotide has been administered in the 'implant' dosage form, consistent observations were made and confirmation obtained on the possibility of HPA feedback effects caused by afamelanotide administered via the controlled-release drug product (resorbable implant, SCENESSE®). The pharmacokinetic profile shows that afamelanotide is controlled to a release of up to seven days post-administration (Module 2.7.4.1.2 and Module 5.3.4 Clinical Study Report CUV038).

In addition, the half-life of afamelanotide 16 mg has a maximum of 48 minutes (EP001 CSR in Module 5.3.5.4) once it enters in the systemic circulation, and to date no central effects have been observed in adults or adults of lesser bodyweight. A central hormonal feedback via the HPA axis is lacking and has not been observed at these active drug concentrations.

An essential parameter providing evidence of the existence of possible negative HPA feedback mechanism is found by assessing plasma cortisol levels at regular intervals post-SCENESSE® administration. During the clinical development of SCENESSE®, no cortisol elevation has been observed in any of the adults who have been administered afamelanotide. In parallel, the impact of afamelanotide on glycaemic control was also monitored. Table 6 summarises the cortisol and glucose level data obtained during placebo-controlled clinical trials. No clinically significant changes were observed during the clinical development program.

Table 6. Effect of afamelanotide on cortisol and glucose

Study	Number of patients (active/ placebo)	Data collection points	Cortisol	Glucose
Pivotal pharmacokinetic/ pharmacodynamic studies				
CUV006	12 (active)	Cortisol and glucose: Baseline and Days 1, 3, 10, 15, 30 and 60.	No clinically significant treatment-related change.	A single clinically significant result was obtained for fasting glucose at screening. However, on repeat testing undertaken the following day the glucose value had returned to within normal range. There were no other clinically significant findings.
CUV009	10 (active)	Cortisol and glucose: Baseline and Days 1, 2, 28, 30, 35 and 84.	One subject had low cortisol level (187nmol/L) on Day 84; however this value returned to normal one week later (561 nmol/L). There were no other clinically significant results.	No clinically significant changes in glucose levels.
CUV028	24 (active)	Cortisol and glucose: Baseline and Days 1, 3, 7, 15, 30 and 60.	There were no clinically significant findings.	There were no clinically significant findings.

CUV038	12 (active)	Glucose: Baseline and Days 2, 7, 14, 60 and 90.	n/a	No clinically significant changes nor trend over time.
EPP clinical trials				
CUV010	5 (active). Two doses: Days 0 and 60.	Cortisol and glucose: Baseline and Days 1, 30, 61, 90 and 121.	No clinically significant changes nor trend over time.	No clinically significant changes nor trend over time.
CUV017	100 (alternating active and placebo every 60 days). Three doses of each treatment.	Cortisol and glucose: Baseline and Days 1, 14, 30, 61, 74, 90, 121, 181, 241, 301 and 360.	No clinically significant changes nor trend over time.	One patient had an elevated blood glucose at Day 1 only. For all other patients and timepoints, there was no clinically significant changes nor trend over time.
CUV029	39 (active)/ 37 (placebo). Five doses.	Glucose: Baseline and Days 60, 120, 180, 240 and 270.	n/a	There were no clinically relevant differences between groups.
CUV030	39 (active)/ 38 (placebo) Three doses.	Glucose: Baseline and Days 60, 120 and 180.	n/a	There were no clinically relevant differences between groups and no clinically relevant changes or trends in in either group.
CUV039	48 (active)/ 45 (placebo). Three doses.	Glucose: Baseline and Days 60, 120 and 180.	n/a	There were no clinically relevant differences between groups and no clinically relevant changes or trends in in either group.

It is well documented that GC-dependent negative feedback relies on the rhythmic release of GC in diurnal and ultradian patterns, which prove fundamental to the termination of the stress response (Gjerstad et al., 2018).

In considering the maturation of the HPA-axis, both the hypothalamic nuclei and pituitary gland require discussion. It is shown that the hypothalamic nuclei are the first to develop as part of the functional HPA axis, as early as 11 to 14 years of age. The paraventricular nuclei contain three projecting neurons, parvocellular, neurosecretory magnocellular, and long-projecting neurons which are fully functional at the start of puberty.

The development of the pituitary gland, however, comes to full expression before the start of puberty. Some specific nuclei and anatomical parts of the adenohypophysis and neurohypophysis are still in development during puberty with its marked effects on the release of growth hormone (GH), thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteinizing hormone (LH) and prolactin. The neurohypophysis with its main hormone expression found in oxytocin (OT) and arginine vasopression (AVP).

However, when studying the ACTH expression, the axis CRH-ACTH-cortisol is fully developed at the start of puberty, ensuring that adequate levels of diurnal cortisol are maintained for the child in development (Scanes, C. G., 2015, Boccia et al., 2001).

Human endocrine and cerebral imaging studies show that the HPA axis matures at various stages in different parts of the cerebrum first (Romeo, R. D., 2010).

Of relevance to this discussion on exposing adolescents to afamelanotide, it is important to note that HPA axis reactivity is significantly greater before puberty than after puberty. Human studies and rodent experiments have shown an increased and prolonged stress-responsive release of ACTH and GC prepubertally in comparison to post-pubertal. A first study by Goldman et al. in 1973 showed this phenomenon, which was confirmed by Romeo et al. in 2004 (Goldman et al.,1973). Whereas pre-pubertal changes in gonadal hormones are observed in all studies, the HPA -axis concerning CRH-ACTH-cortisol shows no evidence of significant further development during puberty (Romeo et al., 2004). The changes in the HPA axis seem not to be the result of pubertal rises in gonadal hormones. Since the initial increase of gonadotropin-releasing hormone (GnRH) secretion near the onset of puberty, one possibility remains that changes in the HPA axis observed across puberty are pre-programmed developmental events which remain independent of changes in gonadal hormones (Romeo, R. D., 2003).

It is further shown that the stress-induced activity of CRH neurons in the prepubertal PVN is greater than that of adults, demonstrating that the prolonged prepubertal pattern of corticosterone and ACTH may be driven by increased hypothalamic CRH synthesis (Romeo, R. D., Lee, S. J., and McEwen, B. S., 2004). These findings indicate a flat GC-dependent negative feedback in prepubertal males but no longer during puberty. Studies in pre-pubertal male rodents show elevated HPA activation, with increases in CRH activation following restraint in comparison to adults, indicating that PVN CRH neuron activity changes across puberty (Romeo, R. D., and McEwen, B. S., 2006). In summary, while many endocrine changes are seen during the stages of growth continuing through puberty, the intact functionality of the HPA-axis at the start of puberty and adequate cortisol response to stressors, indicate that an equivalent response - or lack thereof, observed in adults receiving afamelanotide - can be expected in adolescents from the age of 15 years onwards.

Implant administration device

The method of SCENESSE administration in adolescent EPP patients will be identical to that proposed for adult patients. The following is taken from the approved SmPC:

"- Anaesthetise the insertion area if deemed necessary and in consultation with the patient.

- Select a 14 gauge (1.6 mm inner diameter) catheter with needle …

- Hold the catheter at its base using a sterile technique, pinch and hold the skinfold cranial to, or overlying the patient's supra-iliac crest with two fingers …

- With the bevel of the needle facing upwards, insert the catheter laterally 1.5 to 2 cm into the subcutaneous layer at a 30 to 45 degree angle to the skin surface in one continuous flowing movement."

This method of administration is considered appropriate for adolescent patients for the following reasons:

• All SCENESSE administrations are performed by trained and accredited staff at specialist porphyria centres.

• Adolescent patients suitable for treatment must have a bodyweight of not less than 60 kg. This means that the adolescent population will be equivalent in size to lower bodyweight adult patients so the "trauma" of administration should not be different to that in an adult patient.

• All patients will be offered a local anaesthetic prior to implant administration.

• From the SCENESSE safety database, there is no evidence that any lasting administration site adverse effects occur following implant administration.

It is well established practice for 14G needles to be successfully used in children. Examples of such use includes biopsies, body piercings, infusion of large volumes of fluids or colloids, facial surgery to harvest fat periorally, needlescopic appendectomy and other invasive procedures.

Risks

Implant administration

The method of implant administration proposed for adolescent patients will follow what is outlined in the SmPC for the following reasons:

• All SCENESSE administrations are performed by trained and accredited staff at specialist porphyria centres.

• Adolescent patients suitable for treatment must have a bodyweight of not less than 60 kg. This means that the adolescent population will be equivalent in size to lower bodyweight adult patients so the "trauma" of administration should not be different to that in an adult patient.

• All patients will be offered a local anaesthetic prior to implant administration.

• From the SCENESSE safety database, there is no evidence that any lasting administration site adverse effects occur following implant administration.

Risk mitigation

In order to minimise potential risks, the following risk mitigation measures apply:

• All SCENESSE administrations will only be performed by trained and accredited staff at specialist porphyria centres.

• Adolescent patients weighing 60 kg and over will be eligible for treatment

• All adolescent patients will be followed longitudinally through the PASS and disease registry

• Pharmacovigilance systems for afamelanotide to be maintained worldwide indefinitely for the entire lifecycle management of SCENESSE until the product's cessation.

• Based on available data, limited patient numbers are anticipated.

CHMP comment on the initial submission

*In the submitted documentation, the MAH repeatedly emphasises that the use of the medicinal product is only suitable for patients with a body weight of more than 60 kg. The MAH outlines that the threshold of 60 kg was chosen on the basis of the safety analysis performed on data from low bodyweight patients compared with all safety data reported through the PASS. However, there is insufficient justification for choosing this weight cut-off (**MO**). The Rapporteur assumes that this proposal is based on considerations regarding the feasibility of the current method of administration. The implants are solid sterile rods of approximately 1.7 cm in length and 1.5 mm in diameter, which need to be inserted into a skinfold cranial or overlying the patient's supra-iliac crest via a catheter laterally inserted 1.5 to 2 cm into the subcutaneous layer of the skin surface.*

Figure 1: Scenesse implant

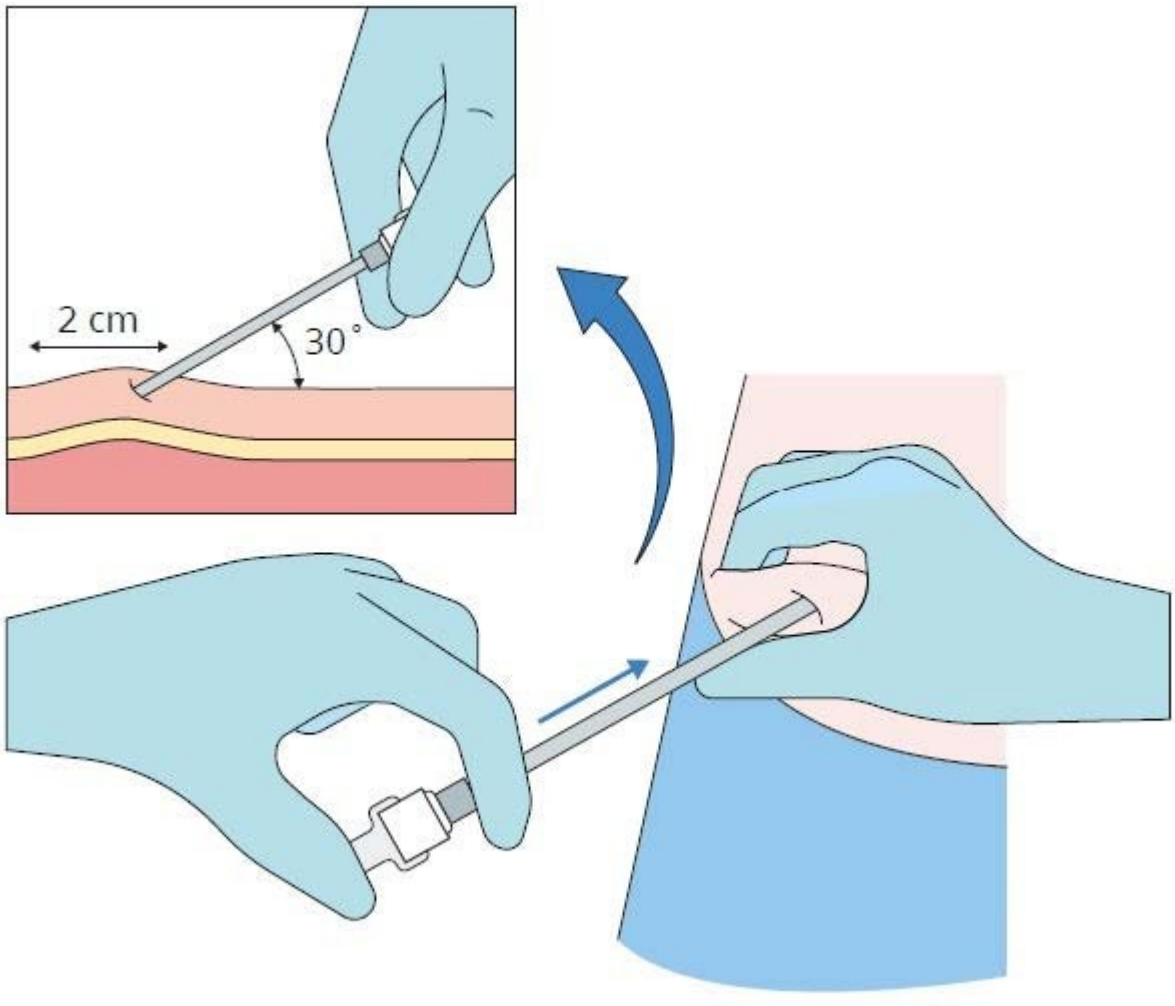


Figure 2: FDA label - Instructions for Implantation of Scenesse

However, the proposed patient population to be treated in section 4.1 of the SmPC is outlined as "adolescents and adult patients" without any restrictions regarding weight.

It is not evident that patients aged 12-17 years are per se suitable for this intervention.

*Although the development of an age-appropriate prolonged-release formulation was an integral part of PIP EMEA-000737-PIP02-11-M02, no age-appropriate prolonged release formulation resp. age appropriate device for a paediatric population has been developed so far. An argumentation that the implant, the implantation procedure and also the dosage scheme are suitable in patients younger than 18 years of age is completely missing. in addition, procedures used as practical examples for use of 14G needles in children (such as biopsies, needlescopic appendectomy) are not suitable as no implant is administered to resp. left in the young patients (**MO**).*

*The MAH estimates the total number of adolescent EPP patients to be 66 patients per calendar year for the 7 countries currently served by the MAH. According to the MAH, adolescent patients suitable for treatment must have a bodyweight of not less than 60 kg. The MAH is asked to estimate the total number of adolescent EPP patients with bodyweight > 60 kg. (**OC**)*

*The medicinal product has so far been used in four EPP-patients under age of 18. All patients were adolescents at the time of first implant administration and with a body weight between 73.3 and 88.6 kg. Five adverse events have been reported (all mild of severity), two of them (implant site pain, sleep disorder) were assessed as related to treatment. The 3 others AEs had not been presented in the Clinical Overview. The MAH is asked to detail the cases reporting these 3 AEs. **(OC)***

*In addition, the MAH presented data on 61 adult patients with body weight < 60 kg, enrolled in the PASS. The profile of adverse events reported for low body weight patients was according to the MAH similar to that reported for the general PASS population. These data are provided to extrapolate from the adult population to adolescent. In addition, the MAH outlines to approximate the effects expected in adolescents by comparing all data generated in young adults of 18-25 years of age and adults of low body weight, compared to the overall group of adults who have received afamelanotide in the past two decades. However, no such comparison of young adults of 18-25 years to adolescents was found. The MAH is asked to clarify (**OC**).*

*Out of the 61 adult patients with low bodyweight < 60 kg (LBW), 47 (77.0%) reported one or more AE, which is comparable to the whole PASS population (82.8%). Among them, 10 patients reported 29 serious TEAEs in total. The MAH is asked to present and discuss these serious cases **(OC).***

*In the Table 5, TEAEs Skin hyperpigmentation were higher in the LBW patient subgroup (6.5%) compared to all PASS patients (3.5%). The MAH is asked to discuss this difference, in particular if this could be the sign of an overdose in LBW patients, and if the posology should be adapted on patient weight **(OC)**.*

*Moreover, apart from HPA axis the MAH did not discuss differences in safety of adolescents and adults to full extent. No discussion on potentially important topics such as bone growth, hormone balance, psyche etc. and the effect of Scenesse thereof is missing. The MAH is asked to discuss and present data (**OC**).*

It has previously been discussed that afamelanotide is considered as MC1R agonist, which may potentially interfere with other hormonal systems (e.g. HPA axis). Additional follow-up to detect potential long-term deleterious effects on maturation of the HPA axis and measures to detect proliferative effects for at least 5 years, possibly even for longer in pre-pubertal children, are foreseen for the PIP indicating its relevance for the use of Scenesse in adolescents.

The MAH presents a discussion on hypothalamic-pituitary-adrenal axis (HPA) in adolescents younger than 18 years of age. Nevertheless, this discussion is not convincingly supportive of treating adolescents at the age of 12 years and older. The discussion centers in large parts on developmental changes in puberty and conclude that "…adequate cortisol response to stressors, indicate that an equivalent response - or lack thereof, observed in adults receiving afamelanotide - can be expected in

adolescents from the age of 15 years onwards". It is unclear how this is supportive of treating patients younger than 15 years of age (down to 12 years of age), in particular when any further data in this age group seems absent.

*For about 95 percent of all boys, puberty begins between the ages of ten and 14, and for girls puberty starts between ages of nine to 13. This also does not support the lower age boundary of 12 years. However, the MAH has applied for an extension of indication in adolescents aged 12-18 years. Notably, in a subset of children, puberty may also start later and may be delayed in particular in male patients up to the age of 18 years. Adequate discussion on potential consequences of the use of afamelanotide in patients not having started and finished puberty are missing (**OC**).*

Summary of the Assessment of the MAH responses to the RSI

The MAH outlined that a staggered approach in regard to weight and age was taken for exposure to afamelanotide over time in order to limit any potential risks and sufficiently review and assess the safety profile of afamelanotide treatment in the subgroups of EPP patients. The MAH reports on safety data obtained from low body weight patients and data of 6 adolescents included in the PASS as well as on the comparison of the safety profile of adults <60 kg to adults >60 kg. The MAH concluded that no significant differences in safety could be observed.

The requested information and discussion of cases and other safety topics was provided by the MAH and the corresponding OCs are considered solved or integrated into MOs. However, the reasons why an approach staggered by weight, and not any other parameter (e.g. only age), was chosen is not provided.

*The MAH´s discussion on differences of adults and adolescents is acknowledged, but the MAH´s conclusions, which largely yield into expectations, are not considered sufficient (OC integrated into MO1). While the data on safety in adults < 60 kg and all patients (including those < 60 kg and > 60 kg) may be considered reassuring for the safety in adults <60 kg, it is not directly transferrable to adolescents. Moreover, the two population (<60 kg vs. > 60 kg) were not described and not directly compared. No demographics of the two groups were provided. It was not outlined whether there was difference in drug exposure (e.g. duration of treatment, treatment interruption etc.) (**MO2**). Additionally, the safety data obtained from six adolescent patients is too small to allow any conclusion. In addition, the lack of information on demographics of these six adolescent patients prevents thorough assessment of the data (**MO1**).*

The MAH further outlined that a body weight of 60 kg was chosen as the MAH´s review of adult safety data of 60 kg weight compared with the safety data of the group of adults of 75 kg revealed no differences, while drug exposure is comparable. However, the respective data was not presented and is thus not assessable.

*In summary, the underlying rationale why weight in general as well as the specific weight cut-off of 60 kg was chosen remains unclear. Due to the lack of data safety in adolescent patients regardless of weight cut-offs is not considered established (**MO2**).*

*The MAH did not comment on the assumptions that the 60 kg cut-off proposal is based on considerations regarding the feasibility of the current method of administration. Less cutaneous tissue could make injection of the implant difficult or even impossible. In thin patients, the proposed method of administration may not be feasible and cause traumatic experience to adolescent patients. The MAH has not addressed these factors at all and these potential "technical limitations" of the administration have not been addressed (**MO1**).*

In agreement with the PIP (EMEA-000737-PIP02-11-M02) the development of an age-appropriate formulation is still considered needed for the paediatric patients (age 12-17 year old). It is requested

*that possible safety and efficacy issues for adolescents and factors like height, weight, BMI, pain, feasibility of the administration of the adult device and traumatic experiences are discussed. The MAH is asked to justify why the "adult" implant and the proposed method of administration are suitable for adolescents and why no age-appropriate formulation is needed (**MO3**).*

Age limit of 12 years of age

*The MAH argues that the lower age limit of 12 years is part of a staggered risk-based approach to make afamelanotide available to younger patients. This is acknowledged, but does not compensate for the complete lack of clinical trial data in adolescents aged 12 -17 years. No adequate reasons for the lower age limit of 12 years of age was provided (**MO1**). In summary, it remains questionable why afamelanotide should be authorised for adolescents aged 12 -17 years without have been tested in a clinical trial. It remains unclear why the MAH has not initiated a clinical trial in adolescent patients thereby making Scenesse available to these patients and obtained the safety and efficacy data needed in this population.*

2.5.1. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

3. Risk management plan

The MAH submitted an updated RMP (version 9.5) with their responses to the request for supplementary information.

Rationale for submitting an updated RMP (according to the MAH):

There has been enough collected data, through review and treatment of adolescent patients under special circumstances and patients with low body weight, in order to evaluate the safety profile of SCENESSE® in this population, thereby justifying the treatment of SCENESSE® in adolescent patients aged 12 years to under 18 years.

Summary of significant changes in this RMP:

Change to the SCENESSE® product indication from the current: "SCENESSE® is indicated for the prevention of phototoxicity in adult patients with erythropoietic protoporphyria (EPP)" to: "SCENESSE® is indicated for the prevention of phototoxicity in adults and adolescents (aged 12 to less than 18 years and weighing 60 kg or more) patients with erythropoietic protoporphyria (EPP)."

The main proposed RMP changes were the following:

Change to proposed SCENESSE® indication to: "SCENESSE® is indicated for the prevention of phototoxicity in adolescent and adult patients with erythropoietic protoporphyria (EPP)."

- Part I: Product(s) Overview: change to proposed SCENESSE® indication to include prevention of phototoxicity in adolescent patients with EPP.
- Part II: Module SI 'Demographics of the target population' was updated to include adolescent patients ages greater than 12.
- SVII.3.2 Updated section: 'Missing Information: Safety in patients (under 18 years of age)'.
- Part II: Module SVIII – table updated

- Table Part V.1 – updated
- Table V.3.1 – updated
- II.A – updated: 'Missing information'.
- II.B – updated: 'Missing information'.

General Changes:

- Part II: Module SIII: Updated to include reference to ongoing clinical studies in patients with Xeroderma Pigmentosum (XP)
- Tables SIII.1 – SIII.4 – Updated to include data applicable to randomised, blinded trials only.
- Missing information: Long-term safety data – updated data relating to PASS study

The following Summary of safety concerns is proposed by the MAH:

List of important risks and missing information	
Important identified risks	• Change of pigmentary expressions • Allergy and hypersensitivity
Important potential risks	• Administration error
Missing information	• **Safety** in patients **(under 18 years of age)** • Off-label use in adults • Use in pregnancy and lactation • Use in the elderly • Use in patients with co-morbidities such as clinically significant renal, hepatic or cardiac impairment • Long-term safety data • Pharmacokinetic data

PART III:

No changes of the Pharmacovigilance Plan (Part III) are proposed.

The Table Part III.3: On-going and planned additional pharmacovigilance activities remains unchanged:

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
CUV-RCR-001 ongoing	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 is the assessment of the compliance with risk minimisation	Safety parameters: • Changes of pigmentary expressions • Administration site reactions • Allergy and hypersensitivity • Off-label use in paediatric patients • Off-label use in adults • Use in pregnancy	Protocol submission	Adopted by PRAC on 17/03/2016.
			Study start	6 months after Study protocol approval.
			Intermediate Reports	Reports will be submitted annually. First report (joint Disease Registry and Retrospective Chart Review

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	recommendations and the controlled access program for patients receiving SCENESSE®.	and lactation • Administration error		Report) was submitted 22/12/2016. Second report 19 December 2017 and third report 04 January 2019.
			Final report	6 years after protocol approval
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
CUV-PASS-001 **CUV-PASS-002** ongoing	EEDR gathers long term safety data and outcome endpoints in patients with EPP. The EEDR collects data from both patients and physicians	Safety parameters: • Changes of pigmentary expressions • Administration site reactions • Allergy and hypersensitivity • Administration errors • Adverse events	Protocol submission	Adopted by PRAC on 17/03/2016.
			Study start	Immediately after study protocol approval. First patient consented for treatment 22/06/2016
			Intermediate reports	Reports will be submitted annually. First report (joint Disease Registry and Retrospective Chart Review Report) was submitted 22/12/2016, second report on 19/12/17, third report on 04/01/2019 and fourth report on 15/01/2020.
Category 3 - Required additional pharmacovigilance activities				
CUV052 planned	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: • Pharmacokinetic data	Study start	Estimated to be in 2019; start date now uncertain (see above).
			Study finish	Estimated to be 6 months after study start
			Final study reports	Estimated to be quarter following study finish

Part V:

The tables in PART V.I and III were updated according to the changed list of safety concerns as proposed by the applicant:

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	**Routine risk minimisation activities**
Change of pigmentary expressions	Routine risk communication: *SmPC sections 4.4. and 4.8.* *PL section 2 and 4* Routine risk minimisation activities recommending specific clinical measures to address the risk: Advice on skin monitoring and sun protection are included in SmPC section 4.4 and in PL section 2. Other routine risk minimisation measures beyond the Product Information: Legal status: *Special medical prescription*
Allergy and hypersensitivity	Routine risk communication: *SmPC sections 4.2., 4.3. 4.8. and 6.1.* *PL sections 2 and 4* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Section 4.2. of the SmPC 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)* Other routine risk minimisation measures beyond the Product Information: Legal status: *Special medical prescription*
Administration error	Routine risk communication: *SmPC section 4.2.* *PL section 3* Routine risk minimisation activities recommending specific clinical measures to address the risk:

	SmPC section 4.2. Other routine risk minimisation measures beyond the Product Information: Legal status: *Special medical prescription*
Safety in patients **(under 18 years of age)**	Routine risk communication: *SmPC section 4.2.* *PL section 2* Routine risk minimisation activities recommending specific clinical measures to address the risk: *None* Other routine risk minimisation measures beyond the Product Information: Legal status: *Special medical prescription*
Off-label use in adults	Routine risk communication: *SmPC section 4.1.* *PL section 1* Routine risk minimisation activities recommending specific clinical measures to address the risk: *None* Other routine risk minimisation measures beyond the Product Information: Legal status: *Special medical prescription*
Use in pregnancy and lactation	Routine risk communication: *SmPC section 4.6. and 5.3.* *PL section 2* Routine risk minimisation activities recommending specific clinical measures to address the risk: *None* Other routine risk minimisation measures beyond the Product Information:

	Legal status: *Special medical prescription*
Use in the elderly (greater than 70 years of age)	Routine risk communication: *SmPC section 4.2.* *PL section 2* Routine risk minimisation activities recommending specific clinical measures to address the risk: *None* Other routine risk minimisation measures beyond the Product Information: Legal status: *Special medical prescription*
Use in patients with co-morbidities such as clinically significant renal, hepatic or cardiac impairment	Routine risk communication: *SmPC section 4.3. and 5.2.* *PL section 2* Routine risk minimisation activities recommending specific clinical measures to address the risk: *None* Other routine risk minimisation measures beyond the Product Information: Legal status: *Special medical prescription*
Long-term safety data	Routine risk communication: *SmPC section 4.4.* *PL introduction (black triangle)* Routine risk minimisation activities recommending specific clinical measures to address the risk: *None* Other routine risk minimisation measures beyond the Product Information: Legal status: *Special medical prescription*
Pharmacokinetic data	Routine risk communication:

	SmPC section 5.1. Routine risk minimisation activities recommending specific clinical measures to address the risk: *None* Other routine risk minimisation measures beyond the Product Information: Legal status: *Special medical prescription*

Table Part V.3.1.: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Change of pigmentary expressions	Routine risk minimisation measures: *SmPC section 4.8.* *SmPC section 4.4. and PL section 2 where advice is given on skin monitoring and sun protection* *PL section 2* *Special medical prescription* Additional risk minimisation measures: *Healthcare Professional Guide* *Patient guide*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *CUV-PASS-001/002* No final study report date agreed, annual reporting to the Agency *CUV-RCR-001* Final report to be expected6 years after protocol approval: March 2022
Allergy and hypersensitivity	Routine risk minimisation measures: *SmPC section 4.3. and 4.8.* *SmPC section 4.2. 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)* *PL sections 2 and 4* *Special medical prescription*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *CUV-PASS-001/002* No final study report date agreed, annual reporting to the Agency *CUV-RCR-001*

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: *Healthcare Professional Guide*	Final report to be expected 6 years after protocol approval: March 2022
Administration error	Routine risk minimisation measures: *SmPC section 4.2.* *PL section 3* *Special medical prescription* Additional risk minimisation measures: *Healthcare Professional Guide and associated training material*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *CUV-PASS-001/002* No final study report date agreed, annual reporting to the Agency *CUV-RCR-001* Final report to be expected 6 years after protocol approval: March 2022
Off-label use in adults	Routine risk minimisation measures: SmPC section 4.1. PL section 1 Special medical prescription Additional risk minimisation measures: Healthcare Professional Guide Restricted distribution	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: SCENESSE® Chart review Final report to be expected 6 years after protocol approval: March 2022
Safety in patients **(under 18 years of age)**	Routine risk minimisation measures: *SmPC section 4.2.* *PL sections 2* *Special medical prescription* Additional risk minimisation measures: *Healthcare Professional Guide* *Restricted distribution*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *CUV-RCR-001* Final report to be expected 6 years after protocol approval: March 2022

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Use in pregnancy and lactation	Routine risk minimisation measures: *SmPC section 4.6. and 5.3.* *PL section 2* *Special medical prescription* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Pregnancy Report Form* *Pregnancy Outcome and breastfeeding Report form* Additional pharmacovigilance activities: *CUV-RCR-001* Final report to be expected 6 years after protocol approval: March 2022
Use in the elderly (greater than 70 years of age)	Routine risk minimisation measures: *SmPC section 4.2.* *PL section 2* *Special medical prescription* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*
Use in patients with co-morbidities such as clinically significant renal, hepatic or cardiac impairment	Routine risk minimisation measures: *SmPC section 4.1. and 5.2.* *PL section 2* *Special medical prescription* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*
Long-term safety data	Routine risk minimisation measures: *SmPC section 4.4.* *PL introduction (black triangle)* *Special medical prescription* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Pharmacokinetic data	Routine risk minimisation measures: *SmPC section 5.1.* *Special medical prescription* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*

CHMP comment on version 9.4 of the RMP (version of the initial submission):

The "General Changes" as proposed by the applicant, are considered acceptable. Especially, the proposed update of data on long-term safety is endorsed.

Part I (as well as Part II: Module SI) should be updated according to the approved indication as result of the ongoing variation. (OC)

The proposal of the MAH to add a new safety concern "Use in adolescent patients (12 to under 18 years of age)" as missing information is not comprehensible for the assessor. This additional safety concern should be deleted. (OC) As there are still very limited data in adolescent patients as well as in paediatric patients, this should be reflected as one missing information in the RMP. However, the current missing information "Off-label use in paediatric patients under 18 years of age" should be renamed as "Safety in patients under 18 years of age". All relevant sections should be updated accordingly. (OC)

The MAH points out, that four adolescent patients with EPP were treated under the PASS (CUV-PASS-001). However, according to the study protocol the population to be included in CUV-PASS-001 are adult patients only. The MAH should comment, why inclusion criteria of the PASS are not met. (OC)

In addition, Table SV.1 of the RMP only mentions two EPP patients < 18 year-old exposed to Scenesse. The MAH is asked to clarify. (OC)

In Part V.3 only the Chart Review CUV-RCR-001 is listed as additional pharmacovigilance activity to address the missing information "Off-label use in paediatric patients 12 to under 18 years of age" resp. "Use in adolescent patients". However, in Part VI.II.B the Category 1 PASS CUV-PASS-001/002 is additionally listed as additional pharmacovigilance activity to address the missing information "Off-label use in paediatric patients 12 to under 18 years of age" resp. "Use in adolescent patients" As this PASS is intended for adult patients only, it should be deleted from Part VI.II.B. The MAH is reminded, that the table in Part VI.II.B should use text/table from Part V.3 and should not contain different measures/activities. Part VI.II.B should be revised accordingly (OC).

In Part V.3 (and corresponding Part VI.II.B) CUV-RCR-001 is listed as additional pharmacovigilance activity to address the missing information "Use in adolescent patients (12 to under 18 years of age)". It would have been possible to include patients under 18 years of age in the Category 1 PASS CUV-RCR-001. Up to the date of submission of the last Annual Reassessment, no patients have been included in CUV-RCR-001. The MAH is asked to explain why the adolescent patients treated where not included in the Retrospective Chart Review (OC).

The submitted RMP, version 9.4, is not approvable.

CHMP comment on version 9.5 of the RMP:

The "General Changes" as proposed by the applicant, are considered acceptable. Especially, the proposed update of data on long-term safety is endorsed.

Part I (as well as Part II: Module SI) has been updated in accordance with the applied indication in the ongoing variation. Depending on the outcome of the ongoing variation, the MAH is requested to update Part I (as well as Part II: Module SI) and the Educational Material, if applicable (**OC**).

The proposal of the MAH to add a new safety concern "Use in adolescent patients (12 to under 18 years of age)" has been deleted as requested. As there are still very limited data in adolescent patients as well as in paediatric patients, the missing information 'Off-label use in paediatric patients under 18 years of age' has been renamed to "Safety in patients (under 18 years of age)". However, the brackets in "Safety in patients (under 18 years of age)" should be deleted for reasons of comprehensibility (**OC**).

In addition, Table SV.1 of the RMP only mentions two EPP patients < 18 year-old exposed to Scenesse. Therefore, Part II SV should be updated with the most recent data (**OC**).

The submitted RMP, version 9.5, is not approvable.

3.1. Overall conclusion on the RMP

☒ The changes to the RMP could be acceptable provided an updated RMP and satisfactory responses to the request for supplementary information in Annex 1 are submitted.

4. Changes to the Product Information

Please refer to Attachment 1, which includes all agreed changes to the Product Information.

4.1.1. User consultation

No new user test or bridging report has been submitted since the information given in the PL only slightly differs from the approved PL in regard to the paediatric information included. This is acceptable.

4.1.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Scenesse is included in the additional monitoring list and no changes are warranted on that respect.

5. Benefit-Risk Balance

5.1. Therapeutic Context

5.1.1. Disease or condition

The following extension of indication is applied:

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

5.1.2. Available therapies and unmet medical need

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, 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 adolescents patients with EPP.

5.1.3. Main clinical studies

The MAH did not perform any clinical studies in patients under 18 years of age. The claim on efficacy in patients younger than 18 years of age currently purely relies on studies conducted in adults, which were part of the initial marketing authorization.

5.2. Favourable effects

Based on the studies conducted in adults, 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). Phototoxicity as measured by photoprovocation testing in 21 adult patients was delayed. In addition, improvement of the quality of life in the adult study participants over the course of the treatment phase with Scenesse were reported.

5.3. Uncertainties and limitations about favourable effects

The marketing authorization in adults relies on the results from the sole pivotal trial CUV039. In addition, the two measures used to assess the effects of treatment are subjective self-assessment of symptoms and phototesting. Subjective self-assessment is prone to a placebo effect.

Due to the very limited amount of objectifiable data available and in the absence of alternative data, data collection via "diaries" was used post-marketing. It still remains difficult to interpret them due to confounding and high variability between subjects. Careful interpretation of this adult data may at best possibly show positive trends for this treatment option for EPP patients.

No efficacy data in patients under 18 years of age is available. In addition, no pharmacokinetic data have been provided that would allow extrapolation of clinical efficacy in adolescents from efficacy data generated in adults.

Moreover, no age appropriate prolonged release formulation for the adolescent population has been developed so far and it is unknown whether the proposed dosing scheme, same as in adults, will yield similar efficacy.

5.4. Unfavourable effects

In the EU the product has been marketed in June 2016 under the provisions of the post-authorisation commitments made to EMA (disease registry study (CUV-PASS- 001/CUV-PASS-002) and the retrospective chart review study (CUV-RCR-001)). There has now been over six years of post-authorisation experience in treating adult EPP patients with SCENESSE, but there are very limited safety data on adolescents treated with SCENESSE. Up to now, six EPP-patients (four of them with a body weight of at least 73 kg) were treated in the scope of a PASS. Demographic data of the other 2 patients was not provided. No data from younger patients are available.

To evaluate the possible impact of treating adolescent EPP patients with a body weight of 60 kg or more, the MAH extracted data for patients under 60 kg (low bodyweight patients) from the database and compared with data from all patients. Based on the comparison of TEAEs reported in the total population of patients in the PASS and the subset of low bodyweight patients in the PASS, the MAH considers safety data to be adequate to demonstrate that the use of SCENESSE in adolescent patients of body weight 60 kg and above.

5.5. Uncertainties and limitations about unfavourable effects

Apart from six adolescent EPP patients no safety data in EPP patients under 18 years of age are available. The number of six adolescent EPP patients is too low to allow any conclusion including whether the safety profile is similar to adults. Information on demographics and other parameters is lacking, not even the age of the two further patients was provided, thus no conclusions can be drawn.

In addition, no pharmacokinetic data have been provided that would allow extrapolation of clinical safety in adolescents from safety data generated in adults.

Moreover, adolescents differ in many other ways from adults (e.g. height, weight, BMI, hormones) which may directly affect distribution of the drug and TEAEs.

Differences in safety of adolescents and adults were not to full extent discussed.

Moreover, no age appropriate prolonged release formulation resp. age appropriate device for a paediatric population has been developed so far. An argumentation that the implant and also the dosage scheme are suitable in adolescent patients missing. Procedures used as practical examples for use of 14G needles in children (such as biopsies, needlescopic appendectomy) are not suitable as no implant is administered to resp. left in the adolescent patients. It is unknown whether the proposed dosing scheme and the implant used, which are same as in adults, will yield similar safety.

5.6. Benefit-risk assessment and discussion

5.6.1. Importance of favourable and unfavourable effects

The MAH did not perform any clinical studies in patients under 18 years of age. Recently (in January 2023) the PDCO agreed to modify timelines of the PIP (EMEA-000737-PIP02-11-M02), timelines for clinical studies in the paediatric population were postponed. Even if the necessity of a treatment option

in patients younger than 18 years of age for this rare disease (EPP) is recognised, a decision on extension of indication must be based on (scientific) data from the respective age and patient group. However, neither clinical (study) data nor pharmacokinetic data have been provided for this age group that would allow extrapolation of clinical efficacy in adolescents from efficacy data generated in adults.

In addition, no age appropriate prolonged release formulation resp. age appropriate device for a paediatric population has been developed so far.

The paediatric safety database spans six adolescent patients only. An adequate discussion of the safety profile in the adolescent population and whether the dosage applied for is comparable to that established in adults is still lacking.

5.6.2. Balance of benefits and risks

The justification for the extension of the indication provided by the MAH is primarily based on the unmet medical need in younger patients. Although the unmet medical need in patients under 18 is recognised, no sufficient data were presented by the MAH to justify an extension of the indication to adolescent patients.

5.6.3. Additional considerations on the benefit-risk balance

N/A

5.7. Conclusions

The overall B/R of Scenesse in patients aged 12-17 years is negative.