EU Risk Management Plan for SCENESSE® (afamelanotide)

RMP version to be assessed as part of this application:

RMP Version number: 10

Data lock point for this RMP: 22 June 2024

Date of final sign-off:

Rationale for submitting an updated RMP:

The change in dosing regimen involves replacing the current recommendations of a maximum of four implants per year with the recommendation of administering one implant every two months. This change is supported by a literature review and analysis of safety data collected through the post authorisation safety study (PASS).

Summary of significant changes in this RMP:

Change in dosing regimen from a maximum of four implants per year to administering one implant every two months.

Details of the currently approved RMP:

Version number: 9.16

Approved with procedure: EMA/VR/0000247271

Date of approval (opinion date): 05 June 2025

QPPV name: Meike Dahlke

QPPV signature:

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Part I: Product(s) Overview

Table Part I.1 – Product(s) Overview

Active substance(s) **(INN or common name)**	Afamelanotide (as acetate)
Pharmacotherapeutic group(s) (ATC Code)	D02BB02
Marketing Authorisation Holder	CLINUVEL (Europe) Ltd.
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	SCENESSE® 16 mg implant
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Structural analogue of the endogenous substance alpha-melanocyte-stimulating hormone (melanocortin agonist)
	Summary of mode of action: SCENESSE® (afamelanotide 16mg) is a melanocortin-1 receptor (MC1R) agonist. It is a structural analogue of the endogenous substance alpha-melanocyte-stimulating hormone (α-MSH). α-MSH is physiologically synthesised in the skin in response to ultraviolet radiation (UVR) exposure-induced cellular damage. Following damage to the skin, α-MSH selectively binds to the MC1R and mediates the synthesis, release and transfer of melanin, the brown-black pigment in the skin. SCENESSE® mimics the effects of α-MSH, activating the synthesis of melanin in skin without prior UVR exposure or cellular damage.
	Important information about its composition: not applicable
Hyperlink to the Product Information	Module 1.3.1
Indication(s) in the EEA	Current: SCENESSE® is indicated for the prevention of phototoxicity in adult patients with erythropoietic protoporphyria (EPP).
	Proposed (if applicable): Not applicable

Dosage in the EEA	Current: One SCENESSE® implant is administered every 2 months prior to expected and during increased sunlight exposure, e.g. from spring to early autumn. Three implants per year are recommended, depending on the length of protection required. The recommended maximum number of implants is four per year. The overall duration of treatment is at the specialist physician's discretion.
	Proposed (if applicable): One implant is administered every 2 months prior to expected and during increased sunlight exposure. The overall duration of treatment is at the specialist physician's discretion (see sections 4.4 and 5.1).
Pharmaceutical form(s) and strengths	Current (if applicable): SCENESSE® is formulated as a bioresorbable controlled-release implant for subcutaneous administration. It contains 16mg of afamelanotide
	Proposed (if applicable): Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

SCENESSE® (afamelanotide 16mg) is a melanocortin-1 receptor (MC1R) agonist. It is a structural analogue of the endogenous substance alpha-melanocyte-stimulating hormone (α-MSH). α-MSH is physiologically synthesised in the skin in response to ultraviolet radiation (UVR) exposure-induced cellular damage. Following damage to the skin, α-MSH selectively binds to the MC1R and mediates the synthesis, release and transfer of melanin, the brown-black pigment in the skin. Afamelanotide mimics the effects of α-MSH, activating the synthesis of melanin in the skin without prior UVR exposure or cellular damage.

Indication: Erythropoietic protoporphyria (EPP):

Afamelanotide 16mg is indicated for the prevention of phototoxicity in adult patients with erythropoietic protoporphyria (EPP). EPP is a rare genetic disorder of haem biosynthesis, caused by deficiency of the enzyme ferrochelatase. EPP is characterised by an abnormal accumulation and storage of protoporphyrin IX in erythrocytes and plasma (Lecha et al 2009). This results in cutaneous manifestations of phototoxicity (anaphylactoid reactions) and possible hepatobiliary disease in affected individuals.

Incidence and Prevalence:

EPP has been reported in patients worldwide. Table SI.1 provides national prevalence as described in the literature.

Table SI.1: Estimated prevalence of EPP in national populations*

Country	EPP prevalence as reported	Prevalence per 10,000	Reference
Europe	1:109,000	0.092	Elder et al., 2013
Denmark	1:103,774 1:76,923	No data available	Skovmose et al., 2011; Christiansen et al., 2013
Netherlands	1:75,000	0.133	Went et al., 1984
Northern Ireland	1:79,000	0.116	Todd, 1994
Slovenia	1:58,000	0.171 0.175	Kansky & Bercic, 1981;
Sweden	1: 200,000 1:180,000	0.0532 0.056	Thunell et al., 2006; Wahlin et al., 2011
United Kingdom	1:140,000 1:143,000	0.071 0.0646	Whatley et al., 2010; Holme et al., 2006
Wales	1:200,000	0.05	Elder et al., 1990; Lecha et al., 2009
Israel	1 : 639 000	0.016	Edel et al., 2019

* these are the only reports known to date

Based on numbers of EPP patients currently listed on the existing National Registers, where available, and provided by porphyria treatment centres across the European Union, CLINUVEL estimates that a maximum of [redacted] EPP patients are currently actively monitored for their condition.

Demographics of the target population:

As it is an inherited disorder, EPP will affect individuals from infancy and throughout their lives. It affects men and women equally (Holme et al., 2006) and people of all races suffer from EPP. However, X-linked dominant EPP is exceedingly rare and has only been identified in Caucasian individuals.

The target population for treatment with afamelanotide for EPP is adults greater than 18 and

less than 70 years of age. Patients over the age of 70 are not excluded from treatment but are subject to additional monitoring.

Main existing treatment options:

For patients with EPP there are limited treatment options to manage the symptoms of the disease and there is no current treatment for the disease itself other than afamelanotide. The mainstay of managing this condition was light avoidance, protective clothing and reflective sunscreens, particularly those containing zinc oxide or titanium oxide. The latter is reported as ineffective, which mostly results in patients avoiding polychromatic light and leading a withdrawn existence (Minder, 2013).

Reported past therapies include beta-carotene (Mathews Roth et al., 1974; Mathews Roth, 1986), canthaxanthin (Eales, 1978), N-acetyl cysteine, cysteine (Mathews Roth et al., 1993), antihistamines (Farr et al., 1990), conditioning of the skin by phototherapy (Collins and Ferguson, 1995), blood transfusions, and bone marrow transplantation (Wahlin and Harper, 2010). With the exception of bone marrow transplantation none of these have proven to be effective on a long-term basis (Minder et al., 2016).

Cholestyramine and bile acids such as chenodeoxycholic acid and ursodeoxycholic acid have been tried as agents to increase the biliary excretion of protoporphyrin IX and to interrupt a postulated enterohepatic circulation.

None of these therapies is currently recommended by any of the global EPP reference centres. In the absence of alternative treatment, EPP patients are subject to debilitating phototoxic reactions upon exposure to visible light.

Natural history of EPP including mortality and morbidity:

The quality of life of individuals with EPP can be severely affected over their lifetime (Holme et al., 2006; Rufener EA, 1987), due to light intolerance and the consequent "painful" cutaneous manifestations.

With EPP, excess protoporphyrin IX is formed during the maturation of erythropoietic cells in the bone marrow and is present at high levels in reticulocytes and young erythrocytes. Free protoporphyrin IX passes into the plasma where it is subsequently cleared by the liver and secreted into bile (Anstey, 2007). Bile rich in protoporphyrin IX promotes the formation of gallstones and therefore the signs and symptoms of cholelithiases can manifest in both men and women at a relatively early age. The toxic effects of protoporphyrin IX deposition in the liver can lead to potentially life-threatening hepatic dysfunction. Clinical findings suggestive of liver disease appear in approximately 20-30% of known cases of EPP, with up to 5% developing advanced liver disease. (Balwani et al., 2014; Casanova-Gonzalez et al., 2010).

Important co-morbidities:

EPP is a lifelong disease. The prognosis depends on the development and evolution of the hepatic disease (estimated to occur 20%-30% of patients in a recent review by (Balwani et al., 2014)). Since protoporphyrin IX is a lipophilic molecule that is excreted by the liver, EPP patients are at risk of cholelithiasis with obstructive episodes and chronic liver disease that may lead to potentially fatal liver failure (Lecha et al., 2009). The risk factors for liver disease have not been clearly defined, but patients with two inactivating mutations, patients with the X-ALAS variant and patients with very high levels of erythrocyte PPIX may be at increased risk (Lecha et al., 2009). There have been no reports of liver cancer in EPP patients linked to the disease, in contrast to the hepatic porphyrias, i.e. porphyrias affected by a different deficiency of the haem pathway, such as acute intermittent porphyria, variegate porphyria and

porphyria cutanea tarda, which have been linked to liver cancer (Sardh et al., 2013; Schneider-Yin et al., 2009).

Patients are made aware of the increased hepatic involvement and should report at a minimum of once per annum for a hepatic check-up.

Vitamin D deficiency and low bone mineral density have been reported in EPP patients (Allo et al., 2013; Holme et al., 2008) as is to be expected by the lack of exposure to sunlight. Studies into the impact of photodermatoses have shown that EPP has one of the largest impacts upon patient quality of life, with patients experiencing anxiety and depression around double the rate of the general population in the UK and noting the "hidden" nature of photodermatoses which may compound these effects (Rutter et al., 2019).

Part II: Module SII - Non-clinical part of the safety specification

The efficacy of afamelanotide in activating melanogenesis at a relatively low dose and in a well-tolerated and effective manner has been demonstrated in vitro and in vivo in a range of animal species. Very few safety concerns were identified in the non-clinical program with potential clinical significance.

Table SII.1: Key findings from non-clinical studies

Key safety findings (from non-clinical studies)	Relevance to human usage
Single-Dose Toxicity Prolonged, reversible, irritation at the injection site in mice and rats at high doses corresponding to at least 40 x clinical dose using an aqueous formulation; no deaths. Marked intolerance in rabbits at s.c. doses as low as [redacted].	An implant dosage form is proposed, hence animal data obtained at much higher doses using an aqueous formulation are of limited relevance. The rabbit has been shown to be uniquely intolerant to the melanocortins and these findings have no clinical relevance. The rabbit is not suitable for evaluating melanocortins.
Repeat-Dose Toxicity *Liver changes:* Seen only in female rats at the 3-month study timepoint but not at 6 months. Findings: increased AST and liver weight with no histopathological change at autopsy. *Transient changes in urine parameters:* Decrease in urine specific gravity and concurrent increases in urine pH observed at the 6 month time point only. These changes were not present at 10 months, and kidney weights and renal histopathology were normal.	Findings in one sex of rats only at 3 months and not at 6 months plus lack of effect in any dog study indicate no cause for concern. Findings are inconsistent and of doubtful clinical significance.

Key safety findings (from non-clinical studies)	Relevance to human usage
Changes in skin/hair colouring in pigmented species *Reduced body weight in dogs:* There was some body weight loss in dogs but not rats. Effects seen following [redacted] daily for 28 days but not in the 10-month study using [redacted] implant once monthly. *Inflammation of the Harderian gland in the rat*	None Findings are not marked and are associated with the secondary pharmacology of the compound. 'Decreased appetite' and 'increased appetite' have both been reported as adverse reactions under the MedDRA system organ class 'Metabolism and nutrition disorders' (see the tabulated list of adverse reactions in Section 4.8 of the SmPC). The clinical relevance of this non-clinical finding is therefore limited. No changes were observed in the dog. This orofacial gland is present in dogs and rats but not in humans, so this finding is not relevant to human safety.
Reproductive Toxicity Reproductive and developmental toxicity studies were uneventful at high subcutaneous doses of [redacted], doses that provide exposure far in excess of anticipated exposure in humans.	None. At a molecular weight of 1645.85 afamelanotide is too large to cross the placenta[1]; it is therefore not predicted to cause effects on the foetus in humans.
Genotoxicity All genotoxicity studies conducted, both *in vitro* and *in vivo*, were negative at guideline maximum concentrations/dose levels.	None
Carcinogenicity No carcinogenicity studies have been conducted. The polypeptide composition and usage (sixty day intervals between doses with 7 to 10 days of exposure per administration) of afamelanotide are such that carcinogenicity studies are not warranted. Reproductive and genotoxicity studies did not show any toxicity and there were no findings in chronic toxicity studies that suggested any carcinogenic potential. Nonclinical studies consistently showed that afamelanotide does not affect the transformation, proliferation or metastasis of human melanoma cell proliferation *in vitro*.	On the basis of the collective scientific evidence from multiple studies performed over a time period spanning decades and current scientific knowledge on the biological effects of α-MSH and its analogues, including afamelanotide, there is no scientific hypothesis or other rationale to suspect that afamelanotide has any carcinogenic potential.

Key safety findings (from non-clinical studies)	Relevance to human usage
Gehlsen *et al.* 1992 investigated the effect of afamelanotide on the growth, metastatic behaviour and invasive potential of a variant of Cloudman S-91 murine melanoma in a mouse model and found no differences in survival time, tumour growth or size between the treatment group and control. [redacted] Jiang *et al.,* 1995 reported that afamelanotide had no effect or mildly inhibited growth of monolayer melanoma cultures. Expression of tyrosinase activity, the key enzyme in melanogenesis, was increased by afamelanotide. Hadley and Dorr, 2006 determined the effect of afamelanotide *in vitro* on the formation of human melanoma colony forming units using both fresh melanoma specimens obtained from patients and established melanoma cell lines. Normal human epidermal melanocytes were used as controls. At two different concentrations, afamelanotide was shown to have neither a stimulatory nor an inhibitory effect on either fresh melanoma samples or melanoma cell lines. Hadley and Dorr, 2006 administered afamelanotide to SCID mice inoculated with human melanoma cells and monitored tumour size for up to 9 weeks. Afamelanotide did not increase tumour growth rate compared to control (saline) nor did it convert normal melanocytes into malignant cells over the observation period. Abdel-Malek *et al.,* 2006 showed that α-MSH analogues, like afamelanotide, act as melanocortin-1 receptor (MC1R) agonists, stimulate the synthesis of tyrosinase in melanocytes, and leading to melanogenesis and a reduction in apoptosis. The authors postulated that the effects observed should contribute to the genomic stability of melanoma, thus preventing their malignant transformation. MC1R agonists could be developed to protect the skin from UV radiation-induced photodamage. [redacted]	As of 22 June 2024, [redacted] have been continuously treated with afamelanotide for [redacted] with some treated for up to [redacted]. These patients have received between [redacted]. As of 22 June 2024, [redacted] aqueous injections have been administered to [redacted] patients, and [redacted] subcutaneous implants (all strengths) have been administered to an estimated [redacted] patients and or healthy volunteers ([redacted] in clinical trials).

Key safety findings (from non-clinical studies)	Relevance to human usage
[redacted] Collectively these studies confirmed that afamelanotide does not affect tumour formation or tumour growth rate. Furthermore, current thinking supports the hypothesis and investigations that the use of physiologic α- MSH and its analogues as potential agents for prevention of melanoma (Abdel-Malek *et al.*, 2006).	
Local Tolerance Non-irritant when administered via implant	Injection site reactions, mostly mild in severity, have been observed during clinical testing. A full list is provided in Section 4.8 of the SmPC (see 'General disorders and administration site conditions' in the tabulated list of adverse reactions). These are consistent with the subcutaneous administration and are not considered to be associated with afamelanotide.
Antigenicity/Immunogenicity No indication of antigenicity or immunotoxicity	None
Dependence There is no evidence to suggest the potential for dependence.	None
General safety pharmacology <u>*Effects on the CNS:*</u> Possible CNS effects in mice at [redacted] s.c. including hunched posture, lethargy/ataxia (resolving by Day 5 post-dosing) and ptosis (resolving by 2 hours post-dosing).	Because of the high dose in animal studies this is not believed to be directly relevant to man. While it cannot be categorically excluded that some of the adverse reactions reported in the tabulated list of adverse reactions in Section 4.8 of the SmPC under the MedDRA SOC 'Nervous system

Key safety findings (from non-clinical studies)	Relevance to human usage
	disorders' (headache, dizziness, lethargy, migraine and somnolence) could potentially be linked to the observed effects on the CNS in animals, in man they were mostly mild in severity.
Effects on the CVS: No concerns, no effect on the QT interval.	None
Effects on the Respiratory System: No concerns	None
[1] Placental transfer is most relevant in man for drugs with a MW below 500 Dal (Pacifici & Nottoli, 1995; Hutson, 2011), with molecules larger than 500 Dal unlikely to cross the placenta.	

Part II: Module SIII - Clinical trial exposure

EPP is an orphan indication. The clinical development program reflects the limited number of patients and the lack of contemporary clinical trials evaluating prophylactic treatments in EPP patients. Since there is also no generally accepted pharmaceutical standard of care, with the exception of the first open-label pilot Phase II study (CUV010), the clinical development program consisted of placebo-controlled studies only. The clinical studies which support the proposed EPP indication are:

- CUV010: a pilot study using surrogate endpoints (4-month duration)
- CUV017: a multicentre, multiple crossover placebo-controlled study (12-month duration)
- CUV029: a multicentre, parallel group, placebo-controlled study (9-month duration)
- CUV030: a multicentre, parallel group, placebo-controlled study (6-month duration)
- CUV039: a multicentre, parallel group, placebo-controlled study (6-month duration)

As indicated above, afamelanotide has been evaluated in a number of dermal disorders other than EPP. These include the following indications and the relevant study numbers are contained in brackets:

- repigmentation in generalised vitiligo (CUV101, CUV102, CUV103, CUV104, CUV105)
- prevention of formation of actinic keratoses and squamous cell carcinomas in organ transplant recipients (CUV011)
- polymorphic light eruption (EP005, EP012, CUV015, CUV032)
- solar urticaria (CUV016)
- adjunctive therapy in photodynamic therapy (CUV025)
- variegate porphyria (CUV040)

A clinical trial (CUV801) has also been conducted in arterial ischaemic stroke (AIS), to evaluate the safety of afamelanotide 16mg in this population. Each patient was administered either [redacted], as per the investigator's judgement. Another clinical trial (CUV803) is ongoing to evaluate the safety of afamelanotide in aqueous solution, in which patients are being administered [redacted]

Clinical trials are also ongoing in patients with Xeroderma Pigmentosum (XP), to evaluate the safety of afamelanotide 16mg in this population (CUV156, CUV152) and with healthy volunteers (CUV151).

The SCENESSE® implant is a controlled- rather than sustained-release presentation, designed to release drug over a defined period [redacted] Afamelanotide has a short half-life [redacted] and the pharmacokinetic profile seen following administration of SCENESSE® implant is driven by the rate of release of the drug from the implant core. Binding of afamelanotide to the MC1R during this short drug release timeframe results in the secondary pharmacodynamic effect of enhanced dermal melanin for up to 60 days. Therefore, it is the limited duration of drug exposure rather than the dosing interval that is relevant to the assessment of the safety of SCENESSE®.

The CUV009 study evaluated the pharmacokinetics of [redacted] of SCENESSE® administered [redacted]. The pharmacokinetic profiles following each administration were superimposable indicating that no accumulation occurs.

To assess exposure, person-time has therefore been calculated by multiplying the number of doses by the length of time each dose is released to provide a range. The minimum number of days [redacted] is used to calculate the minimum person time, and the maximum number of days [redacted] over which the product is released, is used to calculate the maximum person time. Implant batch release specifications contain an in vitro release specification to ensure that the drug is released from the implant within a defined period.

Clinical trial data have been pooled according to dose and indication, and are provided in the tables below, limited to the indications where final study reports are available.

The tables SIII.1 to SIII.4 contain data from randomised, blinded trial population only[1]

Table SIII.1: Duration of Exposure

Duration of exposure	Subjects	[redacted]	[redacted]
Erythropoietic protoporphyria			
Cumulative up to 1 to 3 months	226	5103	7290
Adjunctive therapy in patients undergoing photodynamic therapy			
Cumulative up to 1 month	9	63	90
Polymorphic light eruption			
Cumulative up to 1 to 3 months	58	1043	1490
Vitiligo			
Cumulative up to 1 to 3 months	5	175	250
Volunteer study			

Duration of exposure	Subjects	[redacted]	[redacted]
Cumulative up to 1 month	23	161	230
Total population exposed to drug			
Cumulative up to 1 Month	32	224	320
Cumulative up to 1 to 3 months	289	6321	9030

[1]No special populations (pregnant or lactating women, nor patients with renal, hepatic or cardiac impairment) were included in the clinical trial program

Table SIII.2: Age group and gender

Age group	Gender	Subjects	[redacted]	[redacted]
Erythropoietic protoporphyria				
18-65	M	114	2604	3720
>65	M	1	21	30
19-65	F	109	2422	3460
>65	F	2	56	80
Adjunctive therapy in patients undergoing PDT				
45-65	M	7	49	70
>65	M	2	14	20
N/A	F	0	0	0
Polymorphic light eruption				
44-61	M	12	238	340
22-63	F	46	805	1150
Vitiligo				
22-65	M	5	175	250
Over 65	M	0	0	0
N/A	F	0	0	0
Volunteer studies				
20-41	M	19	133	190
28-42	F	4	28	40
Grand total				
18-65	M	157	3199	4570
>65	M	3	35	50
19-65	F	159	3255	4650
>65	F	2	56	80

Table SIII.3: Dose

Dose of exposure	Subjects	Total Number of Doses	[redacted]	[redacted]
Erythropoietic protoporphyria				
16 mg	226	729	5103	7290
20 mg	5	10	70	100
Adjunctive therapy in patients undergoing photodynamic therapy				
16 mg	9	9	63	90
Polymorphic light eruption				
16 mg	25	59	413	590
20 mg	37	90	630	900
Vitiligo				
16mg	5	25	175	250
Volunteer study				
20 mg	23	23	161	230
Total exposed population				
16 mg	265	1031	5754	8220
20 mg	65	123	861	1230

Table SIII.4: Ethnic origin

Ethnic origin	Subjects	[redacted]	[redacted]
Erythropoietic protoporphyria			
Caucasian	225[1]	5061	7230
Hispanic	1	21	30
Adjunctive therapy in patients undergoing PDT			
Caucasian	9	63	90
Polymorphic light eruption[2]			
Caucasian	28	203	290
Not determined	30	749	1070
Vitiligo			
Asian	5	175	250
Volunteer studies			
Caucasian	23	161	230
Grand Total			
Caucasian	291	5600	8000

Hispanic	1	21	30
Asian	5	175	250
Not determined	30	749	1070

[1] One CUV017 patient was reported to be of 'North African ethnicity'. Since this notation does not represent a specific ethnicity, this patient was included in the total for Caucasian.

[2] Ethnic origin and skin type of the CUV015 patients were not captured during the conduct of the study.

The tables SIII:5 to SIII.8 contain data from all clinical trial populations (including open extension).

Table SIII.5: Duration of exposure

Duration of exposure	Subjects	[redacted]	[redacted]
Erythropoietic protoporphyria			
Cumulative up to 1 to 3 months	247	5453	7790
Adjunctive therapy in patients undergoing photodynamic therapy			
Cumulative up to 1 to 3 months	9	63	90
Polymorphic light eruption			
Cumulative up to 1 to 3 months	71	1134	1620
Solar Urticaria			
Cumulative up to 1 to 3 months	5	35	50
Vitiligo			
Cumulative up to 1 to 3 months	52	1610	2300
Volunteer study			
Cumulative up to 1 month	111	770	1100
Stroke			
Cumulative up to 1 month	6	112	160
Total exposed population			
Cumulative up to 1 month	117	882	1260
Cumulative up to 1 to 3 months	390	8295	11850

Table SIII.6: Age group and gender

Age group	Gender	Subjects	[redacted]	[redacted]
Erythropoietic protoporphyria				
19-65	M	122	2716	3880
>65	M	2	42	60
18-65	F	120	2625	3750
>65	F	3	70	100
Adjunctive therapy in patients undergoing PDT				
45-65	M	7	49	70
>65	M	2	14	20
Polymorphic light eruption				
36-61	M	15	259	370
22-63	F	56	875	1250
Vitiligo				
22-65	M	27	861	1230
Over 65	M	1	28	40
18-65	F	23	693	990
Over 65	F	1	28	40
Volunteer studies				
18-49	M	99	763	1090
19-48	F	25	175	250
Stroke				
74	M	1	14	20
50-86	F	1	14	20
Over 65	F	4	84	120
Grand total				
18-65	M	270	4648	6640
>65	M	6	98	140
18-65	F	225	4382	6260
>65	F	84	182	546

Table SIII.7: Dose

Dose of exposure	Subjects	Number of Doses	[redacted]	[redacted]
Erythropoietic protoporphyria				
16 mg	242	769	5383	7690
20 mg	5	10	70	100
Adjunctive therapy in patients undergoing photodynamic therapy				
16 mg	9	9	63	90
Polymorphic light eruption				
16 mg	25	59	413	590
20 mg	50	103	721	1030
Solar Urticaria				
16 mg	5	5	35	50
Vitiligo				
16 mg	52	230	1610	2300
Stroke				
16 mg	6	16	112	160
Volunteer studies				
5 mg	6	6	42	60
10 mg	12	12	84	120
12 mg	6	6	42	60
16 mg	62	73	511	730
20 mg	38	38	266	380
40 mg	9	9	63	90
Total exposed population				
5 mg	6	6	42	60
10 mg	12	12	84	120
12 mg	6	6	42	60
16 mg	401	1161	8127	11610
20 mg	93	151	1057	1510
40 mg	9	9	63	90

Table SIII.8: Ethnic origin

Ethnic origin	Subjects	[redacted]	[redacted]
Erythropoietic protoporphyria			
Caucasian	246	5411	7730
Hispanic	1	21	30
Adjunctive therapy in patients undergoing PDT			

Caucasian	9	63	90
Polymorphic light eruption			
Caucasian	41	385	550
Not specified[1]	30	749	1070
Solar urticaria			
Caucasian	5	35	50
Pharmacodynamic assessment			
Caucasian	23	161	230
Vitiligo			
African	9	252	360
Asian	20	707	1010
Caucasian	13	406	580
Hispanic	6	133	190
Other	4	112	160
Volunteer studies			
Caucasian	110	770	1100
Stroke			
Caucasian[2]	6	112	160
Grand Total			
Caucasian	453	7343	10490
Hispanic	7	154	220
African	9	252	360
Asian	20	707	1010
Other	4	112	160
Not specified	30	749	1070

[1] Ethnic origin and skin type of the CUV015 patients were not captured during the conduct of the study.
[2] One CUV801 patient was reported to be of 'Greek ethnicity'. Since this notation does not represent a specific ethnicity, this patient was included in the total for Caucasian.

The tables SIII.9 to SIII.12 are for the product in an aqueous dose form

These tables represent information from an early aqueous (immediate release) formulation of afamelanotide prior to the development of an injectable implant (controlled release) dosage form. These aqueous formulation data are relevant to this RMP as they represent a worst-case scenario for exposure to high plasma levels of afamelanotide. They do not reflect the plasma levels following the use of the controlled-release implant formulation. No special populations (pregnant or lactating women, nor patients with renal, hepatic or cardiac impairment) were included in the clinical trial program with the aqueous formulation.

A clinical trial (CUV803) is ongoing to evaluate the safety of afamelanotide [redacted], in which patients are being administered [redacted].

In the following tables the exposure data are pooled according to indication and study phase, limited to studies where final study reports are available.

Person Time on drug (days) is calculated based on the assumption that the study subject is

exposed to the drug [redacted] of a single injection for one day, so the person time for a single subject equals the sum of the number of days when an injection was administered.

Table SIII.9: Duration of exposure (volunteer studies)

Duration of exposure	Persons	Person time (days)
Cumulative up to 1 month	73	1632

Table SIII.10: Age group and gender (volunteer studies)

Age group	Gender	Persons	Person Time (Days)
18-65	M	46	952
>65	M	1	10
19-65	F	26	670
>65	F	0	0

Table SIII.11: Dose (Healthy Volunteers)

Total Exposure Dose (TED) mg	Persons	Person time (days)
Pharmacokinetic/Pharmacodynamic (Melanin density, MD)		
[redacted]	12	114
Pharmacodynamic assessment (Minimal Erythema Dose, MED)		
[redacted]	61	1519
Total exposed population		
[redacted]	73	1632

Table SIII.12: Ethnic origin (volunteer studies)

Ethnic origin	Persons	Person time (Days)
Caucasian	73	1632

Part II: Module SIV - Populations not studied in clinical trials

As described in section SII Clinical trial exposure, the majority of human drug exposure has occurred with adult Caucasian subjects with Fitzpatrick skin types I, II and III. These human populations resided in Europe, the United States of America, and Australia.

The majority of the EPP patients studied resided in Europe or the United States. The following populations have not been studied:

- Paediatric populations;
- Elderly populations greater than 70 years of age;

- Pregnant/lactating women; and
- Patients with significant co-morbidity (e.g., clinically significant renal, hepatic or cardiac impairment).

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Hypersensitivity to the active substance or any of the excipients

Reason for exclusion: Precautionary measure. It is standard medical practice for a physician to confirm the absence of allergies before administering the drug.

Is it considered to be included as missing information?: No

Rationale: There were no confirmed reports of allergy to afamelanotide or the excipient from the use of SCENESSE®. Hypersensitivity was included as an important potential risk, so was excluded as missing information

Use in the paediatric population (under 18 years of age)

Reason for exclusion: Precautionary measure. This is a standard exclusion criterion in clinical trials. The effect of afamelanotide on the children population is not known.

Is it considered to be included as missing information?: Yes

Use in the elderly (greater than 70 years of age)

Reason for exclusion: Precautionary measure. This is a standard exclusion criterion in clinical trials. The effect of afamelanotide on the elderly is not known.

Is it considered to be included as missing information?: Yes

Use in patients with co-morbidities such as clinically significant renal, hepatic or cardiac impairment

Reason for exclusion: This contraindication was included to ensure a homogeneous clinical trial population to allow accurate assessment of the safety profile. Also, the effects of treatment with afamelanotide on patients with these conditions is unknown.

Is it considered to be included as missing information?: Yes

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.1: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development

Breastfeeding women	program
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program
Population with relevant different ethnic origin	Not included in the clinical development program
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program
Paediatric population (under 18 years of age)	Not included in the clinical development program
Elderly population (greater than 70 years of age	Not included in the clinical development program
Other	Not applicable

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

Post-authorisation, all patients are accounted for in the special access schemes in Italy and Switzerland and through the European EPP Disease Registry (EEDR), except for the small number of patients for whom there was compassionate use or named patient use, or who did not consent to participate in the PASS. The calculation of treated patients is made easier because of the implementation of the controlled distribution program where there are formal drug accountability procedures.

SV.1.2 Exposure

Since the completion of the earlier (CUV010 and CUV017) EPP clinical trials, CLINUVEL has received a number of requests from physicians involved in these studies to provide SCENESSE® on a compassionate basis or under special access schemes where national legislation allowed such usage.

Sixteen patients were included in a safety extension study in [redacted] (CUV037). There were only eight adverse events reported and they were all regarded as unrelated to SCENESSE®.

From May 2010 to August 2016, treatment with SCENESSE® was available under a special access scheme in Italy pursuant to the Italian law 648/96 to satisfy the clinical demand in a rare disorder where no other effective therapy was available. [redacted] Italian patients receive the drug on multiple occasions each year. [redacted] patients (including duplication of subjects) were treated under Italian law 648/96 from 2010 to 2016.

Since May 2012, treatment with SCENESSE® has also been available to EPP patients in Switzerland under a special access scheme. [redacted] patients were treated under the Swiss scheme regime from 2012 until 22 June 2024. A total of [redacted] have received SCENESSE® through such special access schemes. Of these, [redacted] Worldwide, [redacted] patients have received SCENESSE® through special access schemes in Israel and Canada [redacted]

Marketing authorisation for the European Union was granted through the centralised procedure on 22 December 2014 and the product was first launched in the Netherlands in June 2016. Up to 22 June 2024, [redacted] enrolled in the CUV-PASS-001 and CUV-PASS-002 protocols received treatment. According the MAH's best estimates, an additional [redacted] EPP patients were treated by accredited European EPP Expert Centres (EEECs) in [redacted] outside of the PASS protocol.

A cumulative summary is presented in Table SV.1 below according to region, means of exposure (for example via PASS, special access schemes, compassionate use or named patient use), gender, age group and number of doses per year. There is certain unavoidable duplication of patient numbers in the cumulative data, as detailed in the footnotes to the table. For instance, most compassionate use patients in Switzerland subsequently received treatment under the Swiss special access scheme, and all compassionate use patients in Italy subsequently received treatment under the Italian special access scheme.

Table SV.1: Exposure table by indication, gender, age group, number of doses per year and region

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

The potential for misuse for illegal purposes is negated by both the controlled distribution of the product and the mode of administration of SCENESSE®. It is an implant that requires administration by a medical practitioner appropriately trained in the administration of the product. The use of a local anaesthetic prior to implant injection is recommended. Treatment of patients is exclusively via EPP expert centres in the relevant countries, with stocks held exclusively, a single dedicated wholesaler or the institutional pharmacies within or associated with the expert centres.

There has been no indication that afamelanotide will cause dependence and therefore illegal use in that respect is not expected.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

This section provides details of the important identified and potential risks considered by the MAH at the time of the initial marketing authorisation application. These risks were considered as having a bearing on the product's benefit-risk assessment in EPP and/or a potential public health impact, and required further characterisation or evaluation, or implementation of specific risk minimisation activities to protect patients.

The known adverse reaction profile of afamelanotide treatment identified during the afamelanotide clinical programme in EPP is described in Section 4.8 of the approved SCENESSE® SmPC (Undesirable Effects).

Because of the potential co-morbidities found in other indications studied during the clinical trial program, the potential risks highlighted in this section are limited to observations in the EPP patient population.

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Some of the adverse reactions described in Section 4.8 SCENESSE® SmPC (Undesirable Effects) approved on 22 December 2014 were not considered important for inclusion in the list of safety concerns.

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

The following ADRs have been observed with the use of SCENESSE®. However, their clinical impact on patients on the treated EPP patients in relation to the severity of their illness is considered minimal. Therefore, these ADRs are listed in section 4.8 of the SmPC but are not considered important risks:

Headache, Nausea, Upper respiratory tract infection, Decreased appetite, Dizziness, Lethargy, Somnolence, Flushing, Hot flush, Abdominal pain, Abdominal pain upper, Diarrhoea, Vomiting, Erythema, Melanocytic naevus, Pigmentation disorder, Skin discolouration, Skin, hyperpigmentation, Ephelides, Pruritus, Back pain, Implant site hypersensitivity, Implant site, reaction, Implant site pain, Implant site haematoma, Implant site erythema, Implant site irritation, Asthenia, Fatigue, Implant site discolouration, Feeling hot, Blood creatine,

phosphokinase increased, Influenza, Gastrointestinal infection, Gastroenteritis, Folliculitis, Nasopharyngitis, Haemangioma, Leukopenia, Hypercholesterolaemia, Increased appetite, Depressed mood, Insomnia, Restless leg syndrome, Hyperaesthesia, Presyncope, Post-traumatic headache, Burning sensation, Poor quality sleep, Dysgeusia, Eyelid oedema, Ocular hyperaemia, Dry eye, Presbyopia, Tinnitus, Palpitations, Tachycardia, Haematoma, Sinus congestion, Rhinitis, Nasal congestion, Lip oedema, Lip swelling, Gastroesophageal reflux disease, Gastritis, Dyspepsia, Cheilitis, Abdominal distension, Gingival pain, Abdominal discomfort, Toothache, Abdominal symptom, Bowel movement irregularity, Flatulence, Gingival discolouration, Hypoaesthesia oral Lip discolouration Tongue discoloration Rash, Rash erythematous, Rash popular, Rash pruritic, Skin irritation, Vitiligo, Acne, Eczema, Pigmentation lip, Post inflammatory pigmentation change, Seborrhoea, Skin exfoliation, Skin hypopigmentation, Hair colour changes, Hyperhidrosis, Arthralgia, Myalgia, Pain in extremity, Muscle spasm, Musculoskeletal pain, Musculoskeletal stiffness, Joint stiffness, Groin pain, Cystitis, Dysmenorrhoea, Breast tenderness, Menstruation irregular, Vaginal discharge, Libido decreased, Oedema peripheral, Oedema mucosal, Pain, Implant site oedema, Pyrexia, Chills, Injection site haematoma, Injection site irritation, Implant site hypertrophy, Implant site pruritus, Device expulsion, Hangover, Influenza like illness, Alanine aminotransferase increased, Aspartate aminotransferase increased, Liver function test abnormal, Transaminases increased, Transferrin saturation decreased, Blood cholesterol increased, Blood glucose increased, Blood iron decreased, Blood pressure diastolic increased, Blood urine present, Procedural nausea.

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

Depression, Migraine, Syncope, Diastolic hypertension, Hypertension, Menorrhagia, Fall, Wound complication.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risk: Change of pigmentary expressions ("lesions")

Risk-benefit impact:

Due to the pharmacological activation of the melanocyte through the melanocortin-1 receptor (MC1R) pathway, it is expected that pre-existent pigmentary expressions are darkened in patients after administration of SCENESSE®. Therefore, during the clinical program and post-authorisation treatment, strict skin monitoring has taken place as described in the SmPC (Section 4.4; Special warning and precautions) and in the pharmacovigilance and risk minimisation measures.

No fatalities or hospitalisations were recorded as a result of changes of pigmentary expressions. In patients who experienced pigmentation expression changes, all adverse event reports were assessed as non-serious and related to SCENESSE®.

The impact is expected to be minimal, since the pharmacological activity of afamelanotide is explained in the patient information leaflet. The SmPC and PIL contain sections on appropriate sun/UV protection and skin monitoring.

Pigmentary expressions do not represent a safety concern and the impact on public health is expected to be minimal. The mechanism of action of afamelanotide (melanogenesis), when administered systemically, is expected to result in pandermal darkening of skin, including of existing expressions where colour contrast may be more noticeable as a result of treatment. The perception that afamelanotide treatment may induce harmful lesions (i.e. skin cancers) is not supported by scientific research or more than a fifteen years of use in EPP and other indications,

including more than five years post-authorisation. Concerns that pandermal skin darkening may mask an underlying condition of pigmentation are mitigated by regular dermatological monitoring, as recommended in the SmPC. Such expressions are expected to be reported through pharmacovigilance activities. Additional information is expected to be collected via the European EPP Disease Registry.

Important Identified Risk: Administration site reactions

Risk-benefit impact:
The mechanism of site reactions following an injection with a needle of relatively large diameter consists of the vulnus (damage) of skin and subcutaneous tissue, which may be associated with leaking of blood from skin capillaries.

Some pain and discomfort at the time of administration is expected and is explained in the patient information. As detailed in the SmPC and Patient Information Leaflet, the impact can be minimised by administration of a local anaesthetic before implant administration. This should follow consultation between the doctor and the patient.

The impact on public health is expected to be minimal.

Important Potential Risk: Allergy and hypersensitivity

Risk-benefit impact:
There are various possible immunologically based pathways, which may account for the potential mechanism behind such reactions. Some examples include reactions mediated by IgE, IgG or T-cells. During clinical development hypersensitivity has been reported in [redacted] individuals treated with the active substance on one occasion each and in [redacted] individuals treated with the placebo (on one occasion each). Only one of them was attributed to afamelanotide. It is conceivable that hypersensitivity to polylactide/polyglycolide (placebo) may be experienced.

Given the unknowns surrounding this risk, it is hard to predict what the potential impact on any individual patient may be. It will be very much dependent on the actual nature and severity of the reaction and will have to be managed on a case by case basis.

The potential exists for any patient to have an allergy or be hypersensitive to afamelanotide, although unlikely based on the structure of afamelanotide (a chemically synthesised oligopeptide) and the present body of evidence. Based on the available evidence, no specific safety concern or potential impact on public safety has been identified.

Important Potential Risk: Administration error

Risk-benefit impact:
The implant is administered by using a 14G catheter with needle. The risk of damage of the implant during the proposed administration cannot be categorically excluded but has not been reported so far. No device is supplied in the packaging. The administration procedure bears the risk for wrong insertion and/or damage to the implant. This risk is minimised by education in the approved method of administration and accreditation of all physicians administering SCENESSE®.

The impact on an individual patient cannot be quantified but the worst-case scenario following the administration of a damaged implant is a more rapid release of afamelanotide, as that in the immediate release presentation used in the early clinical studies. This would be expected to result in the same AEs as observed with SCENESSE®, but they would occur more frequently and would more often be classified as moderate or severe.

So far, there are no adverse events associated with the incorrect placement of implants, and a

mild itch and haematoma at the implant site resulted from an implant not being placed deeply enough.

The impact on public health is unknown at this time.

Important Potential Risk: Off-label use in paediatric patients

Risk-benefit impact:
It is conceivable that there may be a temptation to treat adolescents close to 18 years of age because of their closeness to the adult age threshold. Similar considerations may also apply to younger children of a larger body size. Education on the approved use to relevant medical practitioners is the preferred method of ensuring that the risk of paediatric use is minimised.

The impact on the individual patient would very much depend on the patient's age. The older the patient, the smaller the impact. Administration site reactions would be expected to represent the most immediate impact. As the drug has never been used in children, further predictions cannot be made at this time.

The impact on public health is unknown at this time.

Important Potential Risk: Off-label use in adults

Risk-benefit impact:
It is theoretically possible that there may be a temptation to treat some adult patients off-label because of the perceived benefits of afamelanotide. However, the approval procedures that have to be followed before SCENESSE® is provided, as well as the medical specialisations involved in treating EPP patients at EEECs and their patient populations make the probability of off-label use other than via an approved controlled distribution program negligible. Education of the approved use to relevant medical practitioners, as part of the overall training and accreditation of centres to administer SCENESSE®, is the preferred method of ensuring that off-label use in adults is minimised.

The impact on the individual patient would very much depend on the individual and the indication for which they would be treated. Administration site reactions would be expected to represent the most immediate impact. As the drug has been used in limited patient populations, further predictions cannot be made.

The impact on public health is unknown at this time.

Important Potential Risk: Use in pregnancy and lactation

Risk-benefit impact:
SCENESSE® is not recommended for use in pregnancy and during breastfeeding. Women of childbearing potential should use effective contraception during treatment with SCENESSE® and for a period of three months thereafter.

Available data are very limited and the impact on an individual patient and child is unknown at this time. However, so far, no adverse reactions attributable to SCENESSE® use in pregnancy have been observed.

The impact on public health is unknown at this time.

Missing information: Use in the elderly (greater than 70 years of age)

Risk-benefit impact: Patients older than 70 years of age were excluded from clinical trials, and SCENESSE® is not contraindicated in this population. Since pharmacokinetics may be different in this population and older patients usually have more concomitant diseases and concomitant medications, further data should be collected in this patient group in order to gain more knowledge of the safety profile.

Missing information: Use in patients with co-morbidities such as clinically significant renal, hepatic or cardiac impairment

Risk-benefit impact: Patients with co-morbidities such as clinically significant renal, hepatic or cardiac impairment were excluded from clinical trials, and SCENESSE® is not contraindicated in this population. Since pharmacokinetics may be different in this population and concomitant diseases and concomitant medications may have an impact on the safety profile of SCENESSE®, further data should be collected in this patient group in order to gain more knowledge of the safety profile.

Missing information: Long-term safety

Risk-benefit impact: Patients were not treated long-term in clinical trials, and treatment with SCENESSE® is not limited to a certain period of time. Since EPP is a life-long disease and treatment with SCENESSE® will be required for all of the patients' lives, further data is being presently collected in order to gain more knowledge of the long-term safety profile.

Missing information: Pharmacokinetic data

Risk-benefit impact: Several pharmacokinetic studies have been completed in healthy volunteers, but none in EPP patients. In order to evaluate whether pharmacokinetics in EPP patients is different to that in healthy volunteers, further data would be required.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

A safety signal on "allergy" was raised in September 2020 to investigate the potential causal association with SCENESSE®. An extensive review of the pharmacovigilance database and the cases of potential allergic reaction was conducted and options for the most appropriate way for establishing a definitive diagnosis were discussed. Consequently, two patients presenting with allergic symptoms, one in [redacted] and one in [redacted], were tested (skin prick test in both cases, additional histamine release test in the [redacted] patient). Test results were positive to afamelanotide. As a result, the [redacted] patient discontinued treatment with SCENESSE®. The treating physician of the [redacted] patient however, considering the significant benefits this patient has been receiving from the treatment with SCENESSE®, decided to administer another implant after pre-treatment with corticosteroids and monoclonal antibodies. Despite the pre-treatment, implantation still resulted in a generalised urticaria and treatment has since been suspended.

Based on the positive allergy test results, the causal association between the allergies and afamelanotide could be confirmed. Therefore, the important potential risk Allergy and hypersensitivity was reclassified to an important identified risk. A new signal for "anaphylactic reaction" was raised [redacted]. All reactions occurred within the recommended 30 minute observation period. [redacted] patients [redacted] presenting with symptoms were tested and the results were positive to afamelanotide for both skin prick test and the basophil activation tests (BAT). [redacted]. The important identified risk Allergy and hypersensitivity is extended to include anaphylactic reaction..

In previous RMP updates, administration site reactions, previously classified as important identified risk, were removed from the list of safety concerns as they no longer represented an important risk by the definitions of the updated GVP Module V. Off-label use in paediatric patients, off-label use in adults and use in pregnancy and lactation previously classified as important potential risks, were reclassified as missing information.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important identified risk: Change of pigmentary expressions ("lesions")

On a continuous and periodic (PSURs) basis, all safety reports are thoroughly checked to see if the PT MedDRA terms constitute a pigmentary expression, or a change of a pigmentary expression, with the results confirmed by the EU QPPV. Additionally, the following SMQs are searched periodically in the pharmacovigilance database:

- Severe cutaneous adverse reactions; and
- Skin neoplasm, malignant and unspecified.

Potential mechanisms:

The mechanism for the darkening of pre-existing pigmentary expressions is the pharmacological activity of the drug. Afamelanotide is a melanocortin agonist and increases the synthesis of dermal melanin by binding to the melanocortin 1 receptor, especially in areas of higher melanin content such as ephelides or naevi. When administered systemically, this effect is pandermal.

Evidence source(s) and strength of evidence:

1. Afamelanotide SmPC.
2. Quint et al, 2012.
3. Cyr, 2008.

Characterisation of the risk:

As listed in the SmPC:

- ephelides, melanocytic naevus, pigmentation disorder, implant site discolouration and implant site haematoma are commonly reported adverse reactions (≥1/100 to <1/10)
- pigmentation lip, hair colour changes, nail pigmentation, post inflammatory pigmentation changes, skin discolouration, skin hyperpigmentation, skin hypopigmentation and birth marks are uncommonly reported adverse reactions (≥1/1000 to <1/100)
- seborrheic keratosis, gingival discolouration, lip discolouration, tongue discolouration, tongue pigmentation, chloasma, skin depigmentation, vitiligo and yellow skin are adverse reactions reported with rare frequency (≥1/10,000 to <1/1,000)

These frequencies reflect the frequency of the adverse reactions currently captured in CLINUVEL pharmacovigilance database.

No fatalities or hospitalisations were recorded as a result of changes of pigmentary expressions. Since 22 June 2023, the DLP of the last RMP submission, CLINUVEL received [redacted]

Table SVII.3.1.: Cumulative Data On 'Changes of Pigmentary Expressions', According to Severity (Reported up to 22 June 2024)

MedDRA Preferred Term	Number of patients	Number of ADRs	Severity of Adverse Reactions			
			Mild	Moderate	Severe	UNK/Not available
Acanthoma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration site discolouration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Birth mark	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chloasma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ephelides	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gingival discolouration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hair colour changes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Implant site discolouration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lentigo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lip discolouration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Melanosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Malignant melanoma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Melanocytic naevus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metastatic malignant melanoma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nail pigmentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pigmentation disorder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pigmentation lip	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post inflammatory pigmentation change	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Seborrhoeic keratosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Skin depigmentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Skin discolouration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Skin hyperpigmentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Skin hypopigmentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tanning	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tongue discolouration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tongue pigmentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vitiligo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yellow skin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

MedDRA Preferred Term	Number of patients	Number of ADRs	Severity of Adverse Reactions			
			Mild	Moderate	Severe	UNK/Not available
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The number of patients is calculated as the number for each individual reaction. It is possible that the same patients reported more than one of the adverse reactions listed in this table.

Risk factors and risk groups:

The risk factors for the development of changes in pigmentary expressions are many and varied and largely depend on the individual's phenotype, personal medical history, family medical history and environmental factors such as previous chronic sunlight exposure.

Special caution is warranted in patients with:

- individual or family history of melanoma (inclusive of in-situ melanoma, e.g. lentigo maligna)
- suspected or confirmed susceptibility to cutaneous melanoma (CMM1, MIM #155600, synonyms: familial atypical mole-malignant melanoma syndrome, FAMMM; dysplastic naevus syndrome, DNS; B-K mole syndrome; CMM2 MIM #155601), and/or
- individual history of basal cell carcinoma, squamous cell carcinoma (inclusive of carcinoma in situ, e.g. Bowen's disease), Merkel cell carcinoma, or other malignant or premalignant skin lesions.

Preventability:

The drug activates or enhances the melanin content of pigmentary expressions through its primary pharmacological activity. It is not possible to selectively prevent the occurrence of the darkening of pigmentary expressions since this constitutionally occurs in patients.

Impact on the risk-benefit balance of the product:

The impact is expected to be minimal, since the pharmacological activity of afamelanotide is explained in the patient information leaflet.

The SmPC and PIL contain sections on appropriate sun protection and skin monitoring.

Public health impact:

Pigmentary expressions – and the darkening thereof, as most often reported from use of afamelanotide – do not represent a safety concern and the impact on public health is expected to be minimal.

Where concerns exist that any of the reported pigmentary expressions may be the result of, or precursor to other, more serious skin conditions, it is foreseen that this will be reported during and through pharmacovigilance activities. Additional information is being collected via the European EPP Disease Registry.

Important identified risk: Allergy and hypersensitivity

On a continuous and periodic (PSURs) basis all safety reports are thoroughly checked to see if the PT MedDRA terms constitute an allergy or hypersensitivity reaction, with the results confirmed by the QPPV. Additionally, the pharmacovigilance database is searched for data corresponding to the SMQ "Hypersensitivity".

Potential mechanisms:

There are various possible immunologically based pathways, which may account for the potential mechanism behind such reactions. Some examples include reactions mediated by IgE, IgG or T-cells.

Evidence source(s) and strength of evidence:

1. Afamelanotide SmPC.

2. Pichler, WJ, 2007.

3. [redacted] individual EPP patients with suspicion of allergic reactions were tested using skin prick allergy test and histamine release tests. Type I hypersensitivity to afamelanotide was confirmed for both patients.

4. Two other individual EPP patients presenting with symptoms of anaphylaxis were tested and the results were positive to afamelanotide for both skin prick test and basophil activation test (BAT).

Characterisation of the risk:

Hypersensitivity has been reported in four individuals treated with SCENESSE® during clinical studies. Hypersensitivity was also reported in [redacted] individuals treated with placebo implants [redacted]. None of these reactions were attributed to afamelanotide. It is conceivable that hypersensitivity to polylactide/polyglycolide (placebo) may be experienced.

Such reactions can be potentially serious and/or life threatening. Hospitalisation may be required in some instances and the potential for a fatal outcome cannot be excluded a priori until a much larger population has been exposed to the drug.

Since 22 June 2023, date of last RMP data lock point, CLINUVEL received [redacted] adverse reactions qualifying as allergy or hypersensitivity (SMQ) reactions experienced by [redacted] individual patients considered to be related to afamelanotide.

[redacted]

Risk factors and risk groups:

Patients with a predisposition to allergic reactions and/or a history of hyper-reactivity to proteins and/or polymers are considered at greater risk.

Preventability:

Patients are observed by healthcare professionals following injection and implantation for a period of time in accordance with the recommended observation period following any injection. As a general rule, following any intradermal or intravenous injection, observation for 30 minutes is recommended. If there has not been any reaction, the patient should be informed that it is safe to depart. If there has been a reaction, appropriate medical care should be provided.

Since SCENESSE® is administered by trained physicians in hospital settings, the best medical care will be readily available in the event of an untoward reaction.

Impact on the risk-benefit balance of the product:

The impact on the risk-benefit balance will be dependent on the actual nature and severity of the reaction and will have to be managed on a case by case basis.

Public health impact:

The potential exists for any patient to have an allergy or be hypersensitive to afamelanotide.

Based on the available evidence, hypersensitivity to afamelanotide has been confirmed as an important identified risk.

Important potential risk: Administration error

The Standardised MedDRA Query on "Medication errors" is used for the surveillance of "administration error".

Potential mechanisms:

The implant is administered using a 14G catheter with needle. The risk of damage of the implant during the proposed administration cannot be categorically excluded but has not been reported so far. No device is supplied in the packaging, however, it can be stated that the administration errors observed so far would not have been avoidable by using a custom-made device.

Evidence source(s) and strength of evidence:

To the best of the MAH's knowledge, there were no administration errors during the clinical development program and only [redacted] reports of incorrectly administered implants during commercial use.

Characterisation of the risk:

Since marketing authorisation [redacted] administration errors were reported, which represents [redacted] of all SCENESSE® administrations.

[redacted] administration errors corresponded to reports of SCENESSE® being administered at an incorrect site, as per SmPC, by [redacted] physician and were not associated with any adverse reactions.

[redacted] administration error was a report of SCENESSE® implant not having been administered deep enough. It was recorded in the medical records that the position of the implant was subsequently adjusted with a sterile glove and cloth. The administration error was associated with a non-serious adverse reaction (verbatim "mild itch and hematoma at the place of implant") assessed as mild in severity and reported as resolved. It was not considered that any further action by CLINUVEL was warranted in relation to this isolated instance.

Another administration error was a report of SCENESSE® implant being found outside of the skin two days after administration. [redacted]
The administration error was not associated with any adverse reactions, but the patient did not recall any pigmentation or improvement of sun tolerance following the implant. The administration error was assessed as mild in severity and the outcome was reported as unknown.

[redacted] reports refer to accidental puncture of blood vessels. The implants were subsequently administered [redacted]

In clinical trials afamelanotide has been administered as an immediate release aqueous formulation at a [redacted] that is seen following administration of SCENESSE®. [redacted]

The nature and severity of adverse events following the aqueous formulation is likely to [redacted]

At this time, no other administration errors have been reported.

Risk factors and risk groups:

There are no known risk groups or risk factors.

Preventability:

The application procedure bears the risk for wrong insertion and/or damage of the implant. This risk is minimised by education in the approved method of administration and accreditation of all physicians administering SCENESSE®.

Impact on the risk-benefit balance of the product:

The impact on an individual patient cannot be quantified but the worst-case scenario following the administration of a damaged implant is a more rapid release of afamelanotide, as that in the immediate release presentation used in the early clinical studies. This would be expected to result in the same AEs as observed with SCENESSE®, but they would occur more frequently and would more often be classified as moderate or severe.

As indicated above, there were no adverse events associated with the incorrect placement of implants in seven patients, and a mild itch and haematoma at the implant site resulted from an implant not being placed deeply enough.

Public health impact:

Unknown.

SVII.3.2. Presentation of the missing information

Missing information: Off-label use in paediatric patients

Evidence source:

Presently, there are limited clinical data on the use of afamelanotide in paediatric patients. Therefore, outcomes and their seriousness, severity and nature of risk are not known.

[redacted] patients [redacted] have been treated with SCENESSE®. A total of [redacted] were reported by [redacted]. All reactions were assessed as non-serious, with [redacted] classified as mild in severity. The severity of the other reactions [redacted] The demographics for the EPP patients treated are tabulated below.

Gender	Age	Body Weight (kg)	Height (cm)	Initiated

				SCENESSE® Treatment
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

However, data on low body weight patients treated under the post-authorisation safety study 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.

[redacted] patients with body weight [redacted] have been enrolled and treated under the PASS at [redacted] EPP expert centres in Europe. Age range 18-66 years, [redacted]

The profile of adverse events reported by [redacted]

	[redacted]	[redacted]
At least one TEAE:	[redacted]	[redacted]
At least one TEAE assessed as related to treatment:	[redacted]	[redacted]
At least one serious TEAE:	[redacted]	[redacted]
At least one serious TEAE assessed as related:	[redacted]	[redacted]

A total of [redacted] serious adverse events were reported by [redacted]

[redacted]

[redacted]

Population in need of further characterisation:

It is conceivable that there may be a temptation to treat adolescents close to 18 years of age because of their closeness to the adult age threshold. Similar considerations may also apply to younger children of a larger body size.

Missing information: Off-label use in adult patients

Evidence source:

Presently, there are no clinical data to assess the potential use of afamelanotide in an off-label indication in adults in a post-authorisation setting. Therefore, outcomes and their seriousness, severity and nature of risk are not known.

[redacted] In each case, the MAH was approached by the treating physicians and agreed to supply the drug product. All required authorisations (e.g. ethics approval) were obtained. These instances are therefore not considered representative of unauthorised off-label use of drug product commercially supplied for use in EPP. Frequency of off-label use other than via approved compassionate use or special access programs is estimated to be zero. There were no adverse reaction reports associated with programs. Based on this, it is considered that there is insufficient knowledge to determine whether the safety profile in off-label use would differ from that characterised so far.

During the commercial distribution the MAH received information regarding administration site other than the indicated iliac crest: a patient enrolled in the PASS in [redacted] who had an implant administered to the lower left of the abdomen at the patient's request; a patient enrolled in the PASS in the [redacted] whose implant was placed left oblique from naval; three patients enrolled in the PASS in the [redacted] whose implant was placed right under the naval; [redacted] whose implants were administered in the [redacted] Instances of change in dosing frequency were also reported: [redacted]

Anticipated risk/consequence of missing information:

It is theoretically possible that there may be a temptation to treat some adult patients off-label because of the perceived benefits of afamelanotide. However, the approval procedures that have to be followed before SCENESSE® is distributed and administered, as well as the medical specialisations involved in treating EPP patients at EEECs and their patient populations make

the probability of off-label use other than via an approved controlled distribution program negligible.

The anticipated risk would very much depend on the individual and the indication for which they would be treated. Administration site reactions would be expected to represent the most immediate impact. As the drug has been used in limited patient populations, further predictions cannot be made.

Missing information: Use in pregnancy and lactation

Evidence source:

Presently, there are very limited clinical data on the use of afamelanotide in pregnancy and no data on use in lactation. Therefore, outcomes and their seriousness, severity and nature of risk are not known.

To date there have been [redacted] reports of pregnancy [redacted] in sexual partners of recipients) during the clinical development or compassionate use programs, expanded access program and the PASS in which pregnancy was reported to CLINUVEL within one month to three years after the last administration of afamelanotide. Out of the [redacted] reports, [redacted] reports were considered as exposure during pregnancy. A [redacted] patient reported pregnancy in partner approximately 30 days after administration of the last implant. The baby was delivered by natural birth on [redacted] and no adverse reaction was reported. Another male patient reported pregnancy in partner in the same month of receiving SCENESSE®. The baby was delivered on [redacted] and no adverse reaction was reported.

Another case of pregnancy in partner was reported where pregnancy was detected 25 days after the last implant administration. No adverse events were reported, and the baby was delivered by natural birth on [redacted].

[redacted] The outcome of the pregnancy of partner resulted in a preterm caesarean section (because of the placenta being too small). The newborn was dependent on intensive care after birth due to dyspnoea. The pregnancy in the patient's partner was detected seven days after the patient had received the last SCENESSE® implant and conception must have occurred prior to the implant administration. Therefore, an effect of SCENESSE® on the unborn baby and any causal relationship with the reported events (Small size placenta, Premature baby, Dyspnoea, Low birth weight and Body height decreased) were excluded.

[redacted] and the baby was delivered by natural birth on [redacted]. In the other case, the pregnancy was detected one day after the partner received SCENESSE® treatment. The outcome of pregnancy remains unknown.

Pregnancy was detected in a [redacted]. No adverse events or reactions were reported. The baby was delivered by caesarean, with no birth defects. Another female EPP patient discovered her pregnancy approximately six weeks after the last administration date. The patient experienced several adverse events during pregnancy. The baby was delivered via caesarean section (breech position and insufficient dilatation during contractions) on [redacted]

One additional report refers to the partner of a male patient. The date of pregnancy detection was not reported. The patient's partner developed Group B Streptococcus infection and was treated with antibiotics every 4 hours during labour. The baby was born via natural delivery on [redacted] During the pregnancy, the patient's partner had also experienced PTs "malaise",

"vomiting" and "somnolence". The reporter mentioned that breastfeeding started late due to stress. The outcome of pregnancy was reported as live birth, normal. The child experienced gastrooesophageal reflux disease. A separate child case was created to capture the events gastrooesophageal reflux disease and exposure via breast milk.

A female patient, whose pregnancy was detected 43 days after the administration of the last SCENESSE® implant, experienced gestational diabetes and insulin resistance. The outcome of the pregnancy was not reported.

Another female patient's pregnancy was detected 10 days after the administration of the last SCENESSE® implant. The estimated delivery date was in [redacted] The outcome of the pregnancy was not reported.

Pregnancy in a female patient was detected 96 days after the administration of the last SCENESSE® implant. The patient experienced HELLP syndrome which was assessed as not serious and not related. The baby was delivered via caesarean section at 31 weeks with no birth defects. A separate child case was created to capture premature birth.

Pregnancy in partner of a male EPP patient was detected 44 days after the administration of the SCENESSE® implant. The baby was delivered via caesarean section on [redacted]

[redacted]

There have been no adverse consequences or spontaneous abortions in these patients attributed to afamelanotide, and all are being followed up. To the best of the MAH's knowledge, there have been no instances of breastfeeding by a mother receiving treatment with afamelanotide.

Population in need of further characterisation:

The at-risk groups are women of childbearing potential not using adequate contraception and women who are breastfeeding.

Missing information: Use in the elderly >70 years of age

Evidence source:

There are no controlled trials of SCENESSE® administration in the elderly.

Upon analysis of cumulative data on use in the elderly (patients > 70 years), no new significant safety information has been identified. [redacted] all the reported ADRs are listed in the current SmPC for SCENESSE® and do not indicate a difference in safety profile in the elderly as compared to a younger population.

Population in need of further characterisation:

Patients >70 years of age

Missing information: Use in patients with co- morbidities such as clinically significant renal, hepatic or cardiac impairment

Evidence source:

There are no controlled trials of SCENESSE® administration in patients with co-morbidities such as clinically significant renal, hepatic or cardiac impairment.

There is no data available from use of SCENESSE® in patients with other, potentially serious

illnesses, such as patients who suffer from liver, kidney or heart disease. There is an increased risk of adverse reactions in these patients.

Population in need of further characterisation:

Patients with concomitant liver, kidney or heart disease.

Missing information: Long-term safety data

Evidence source:

Since the first patient treatment in the PASS was carried out in June 2016, long-term safety data have now become available.

There have been patients who have received longer term treatment when treatment within more than one setting is considered (for example compassionate use, Expanded Access programs and the EEDR). During the reporting period of PSUR #13 (period from 23 June 2022 to 22 June 2023), CLINUVEL has received [redacted] reports of adverse reactions from [redacted] patients receiving long-term (>24 months) treatment under the PASS. These reports were mainly received from the Rotterdam (PASS-001) and Dusseldorf (PASS-002) sites. Most reports received were non-serious, apart from one report (PT "Hepatic enzyme increased") which was assessed as serious due to hospitalisation and the outcome of which was reported as not covered.

Most of the reported reactions are consistent with the safety profile outlined in the SmPC and have also been reported during short-term use. Out of all the related reactions as assessed by CLINUVEL, [redacted] reactions, reported by [redacted] individual patients were assessed as unlisted as per the SmPC (PTs: Bronchitis, Chest pain, Condition aggravated, Dyspnoea, Face oedema, Hyperaesthesia Illness, Implant site discharge, Implant site injury, Malabsorption from administration site, Polyneuropathy, Rhinorrhoea, Sensitive skin, Vascular injury and Vertigo). The new information has not identified any new safety issues in relation to the long-term use of SCENESSE®.

As per the PASS intermediate report #8 submitted in January 2024, safety data of a minimum of two years has been evaluated for [redacted] EPP patients enrolled in the PASS study; three years of data were available and analysed for [redacted] patients plus four, five, six and seven years of data for [redacted] patients respectively. The clinical benefits described in the PASS intermediate report #8 and the limited number of reports of problems with effectiveness leading to discontinuation of treatment with SCENESSE® together with the lack of any safety issue identified up to DLP, support the lack of a change in the benefit-risk profile and safe use of up to four consecutive implants.

Population in need of further characterisation:

Patients treated for more than six years.

Missing information: Pharmacokinetic data

Evidence source:

Limited dose-finding studies have been conducted and the pharmacokinetics of afamelanotide or any of its metabolites have not been fully characterised, especially in EPP patients.

As previously explained, the MAH was unable to identify suitable study site(s) willing and able to conduct the CUV052 study as per the synopsis which had been provided in the RMP v8.1. Despite this, the MAH remained committed to conducting a pharmacokinetic study and continued discussions with expert physicians at EEECs to agree on a feasible protocol. The revised synopsis is included in appendix 6 of the RMP.

[redacted]

Anticipated risk/consequence of the missing information:

Distribution, metabolism or excretion are not described. Data of possible interactions or effects in special populations, e.g. patients with hepatic or renal impairment are not available.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

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

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

- Pregnancy Report form.

Specific adverse reaction follow-up questionnaires for Use in pregnancy and lactation:

There are three different questionnaires in place: Pregnancy Report form, and Pregnancy Outcome and Breastfeeding Report form. The purpose of this questionnaires is to obtain structured information on the missing information Use in pregnancy and lactation. The main objective is to evaluate, if there have been any harmful consequences for the mother or for the baby related to the reported use of SCENESSE® during pregnancy or lactation. These questionnaires are also used to gain more information about the use of SCENESSE® during

pregnancy in line with the recommendations of the guideline on 'The Exposure to Medicinal Products During Pregnancy: Need for Post-Authorisation Data' (EMEA/CHMP/313666/2005).

The questionnaires are targeted specific forms provided in English language.

- Allergy and Hypersensitivity Questionnaire

Specific adverse reaction follow-up questionnaire for cases of allergy and hypersensitivity:

The purpose of this questionnaire is to collect information about severe allergic and/or anaphylactic reactions that may be experienced by a patient treated by SCENESSE®. Information about the severity, whether the reaction is local or generalised or the type of hypersensitivity experienced allow a better characterisation of the reaction and therefore facilitate the diagnostic and prevent the risk of complications or re-occurrence.

The respective forms are provided in Annex 4 of this RMP.

III.2 Additional pharmacovigilance activities

❖ CUV-PASS-001 summary

Study short name and title: **CUV-PASS-001 EPP Disease Registry**

Rationale and study objectives:

In December 2014, marketing authorisation for SCENESSE® was granted in Europe under exceptional circumstances (Article 14(8) of Regulation (EC) No 726/2004). The establishment of a Disease Registry was imposed as a specific obligation with data to be collected from both EPP patients and physicians.

Analyses comparing long term safety data and outcome endpoints in EPP patients receiving treatment with SCENESSE® (Treated Group) and those not receiving SCENESSE® (Untreated Group) or having discontinued treatment with SCENESSE® (Discontinued Group) are to be undertaken.

Primary objectives

- Gather long-term safety data of SCENESSE®
- Evaluate compliance with the risk minimisation measures

Secondary objectives

- Evaluate adherence with the controlled distribution program
- Generate data to contribute to knowledge about clinical benefits and to add data on potential clinical effectiveness of SCENESSE®

Study design:

This is a non-interventional post-authorisation study to be conducted in EPP patients eligible for treatment with SCENESSE®. Those participating in the registry study but electing not to receive SCENESSE® will act as controls. In the absence of alternative treatment for EPP, a comparator group consisting of untreated patients (Untreated Group) will be included.

Study population:

Adult patients with erythropoietic protoporphyria (EPP): eligibility for treatment will be based on a positive diagnosis for EPP and the lack of any contraindications for treatment with SCENESSE®, as described in the approved SmPC. Both treated and untreated patients will be enrolled in the study.

Milestones:

Protocol adopted by PRAC on 17 March 2016

Study start immediately after study protocol approval. First patient consented for treatment 22 June 2016

Intermediate reports will be submitted annually. First report (joint Disease Registry and Retrospective Chart Review Report) was submitted on 22 December 2016, second report on 19 December 2017, third report on 04 January 2019, fourth report on 15 January 2020, fifth report on 05 January 2021, sixth report on 05 January 2022, seventh report on 09 January 2023, eighth report on 10 January 2024 and ninth report on 09 January 2025.

- **CUV-PASS-002 summary**

Study short name and title: **CUV-PASS-002 EPP Disease Registry**

Rationale and study objectives:

In December 2014, marketing authorisation for SCENESSE® was granted in Europe under exceptional circumstances (Article 14(8) of Regulation (EC) No 726/2004). The establishment of a Disease Registry was imposed as a specific obligation with data to be collected from both EPP patients and physicians.

Analyses comparing long term safety data and outcome endpoints in EPP patients receiving treatment with SCENESSE® (Treated Group) and those not receiving SCENESSE® (Untreated Group) or having discontinued treatment with SCENESSE® (Discontinued Group) are to be undertaken.

This specific version of the protocol is to cover countries such as Germany where it is not possible to enter patients treated off-label in a disease registry study.

Primary objectives

- Gather long-term safety data of SCENESSE®
- Evaluate compliance with the risk minimisation measures

Secondary objectives

- Evaluate adherence with the controlled distribution program
- Generate data to contribute to knowledge about clinical benefits and to add data on potential clinical effectiveness of SCENESSE®

Study design:

This is a non-interventional post-authorisation study to be conducted in EPP patients eligible for treatment with SCENESSE®. Those participating in the registry study but electing not to receive SCENESSE® will act as controls. In the absence of alternative treatment for EPP, a comparator group consisting of untreated patients (Untreated Group) will be included.

Study population:

Adult patients with erythropoietic protoporphyria (EPP): eligibility for treatment will be based on a positive diagnosis for EPP and the lack of any contraindications for treatment with SCENESSE®, as described in the approved SmPC. Both treated and untreated patients will be enrolled in the study.

Milestones:

Protocol adopted by PRAC on 17 March 2016; an amended protocol version of 28 June 2022 adopted by PRAC in 2022.

Study start immediately after study protocol approval. First patient consented for treatment 22 June 2016.

Intermediate reports will be submitted annually. First report (joint Disease Registry and Retrospective Chart Review Report) was submitted on 22 December 2016, on second report 19 December 2017, third report on 04 January 2019, fourth report on 15 January 2020, fifth report on 05 January 2021, sixth report on 05 January 2022, seventh report on 09 January 2023, eighth report on 10 January 2024 and ninth report on 09 January 2025.

- **CUV052 summary**

Study short name and title: **CUV052 Pharmacokinetic Study**

Rationale and study objectives:

Primary objective

- To determine the pharmacokinetics of afamelanotide in adolescent and adult EPP patients following administration of one SCENESSE® implant
- To determine the relative comparability of the pharmacokinetic profiles of afamelanotide in adolescent and adult EPP patients

Secondary objectives

- To confirm the safety and tolerability of afamelanotide in adolescent and adult subjects with EPP

[redacted]

Study design:

This is a multi-centre, open-label pharmacokinetic study in adolescent and adult subjects with EPP.

Study population:

[redacted]

Milestones:

[redacted]

III.3 Summary Table of additional Pharmacovigilance activities

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

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
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, fourth report on 15/01/2020, fifth report 05 Jan 2021, sixth report 05 Jan 2022, seventh report 09 Jan 2023, eighth report 10 Jan 2024 and ninth report on 09 Jan 2025.
Category 3 - Required additional pharmacovigilance activities				
CUV052 ongoing	SCENESSE® PK profile in 14 adolescent and 14 adult EPP patients after administration of one SCENESSE® 16mg implant Determine the relative comparability of the PK profiles in adolescent and	Safety parameters: • Pharmacokinetic data	Study start	First subject enrolled [redacted]
			Study finish	Estimated to be end November 2024
			Final study reports	Estimated to be Q1 2025

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	adult EPP patients.			

Part IV: Plans for post-authorisation efficacy studies

Not applicable.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

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: *Advices 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, including anaphylactic reaction	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: *SmPC section 4.2 & 4.4, where advice is given to monitor the patient for 30 minutes and to have appropriate medical treatment readily available to prevent and/or treat anaphylactic reactions sufficiently. If a serious hypersensitivity reaction occurs, appropriate medical treatment should be initiated, the implant should be removed if needed and further treatment with SCENESSE should be discontinued.* 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*
Off-label use in paediatric patients	Routine risk communication: *SmPC sections 4.1., 4.2. and 4.4.* *PL sections 1 and 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 5.2.* 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*

V.2. Additional Risk Minimisation Measures

Healthcare Professional Guide associated with Healthcare professional training material:

Objectives:

Educational material for physicians and relevant healthcare professionals with associated training and accreditation conducted by CLINUVEL on the use and administration of SCENESSE® and the risks of off-label use, change of pigmentary expressions, administration site reactions, allergy and hypersensitivity, including anaphylactic reaction.

The educational material package includes:

- Summary of product characteristics,
- Face to face training material,
- Educational video,
- Registry information sheet

Rationale for the additional risk minimisation activity:

To train healthcare professionals how to administer SCENESSE® correctly and to make them aware of the risks and missing information outlined in the Risk Management Plan.

Target audience and planned distribution path:

The SCENESSE® SmPC and an animated video on the administration technique will be made available to physicians and relevant healthcare professionals who will undergo training. Formal training is conducted by CLINUVEL staff incorporating a discussion on the need for additional monitoring and the RMP.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Successful completion of the training will be evaluated at the time of the training by CLINUVEL staff. Particular attention will be made on assessing that the physicians and relevant healthcare professionals clearly understand the training provided by CLINUVEL, in particular the method of administration instructions, are aware of all contraindications, special warnings and precautions for use, and the undesirable effects listed in the SmPC. At the time of the monitoring visits, compliance with the training provided by CLINUVEL is checked. Deviation reports will be raised, and corrective actions should be put in place (if applicable) if noncompliance with training requirements is identified. During routine pharmacovigilance activity, the rate of administration

error is monitored. An increase of errors i.e. occurring in more than 5% of all administrations will trigger a re-assessment of the training. Additional assessment tools may be organised, depending on the local requirements.
Accreditation of physicians and relevant healthcare professionals will be renewed every two years upon confirmation that the staff have actively been involved in the treatment and/ or management of patients during the accreditation period.

The need for re-training and accreditation before the above-mentioned timelines will occur in the event that noncompliance with the training and educational material previously delivered is identified.

Healthcare professionals' training records will be maintained by CLINUVEL.

Controlled distribution

Objectives:

Control distribution to EEECs participating in the EEDR.

Rationale for the additional risk minimisation activity:

To ensure appropriate administration of SCENESSE® by trained healthcare professionals to only EPP patients and minimise the risk of administration errors.

Target audience and planned distribution path:

Each order for SCENESSE® is placed by the EEEC directly with CLINUVEL. The order, if initiated by a physician and/or institutional pharmacist not previously trained and accredited, will trigger CLINUVEL evaluating the healthcare professionals and associated institution on their ability to treat EPP patients with SCENESSE® under the RMP. If confirmed, training and accreditation of the physician and/or institutional pharmacist and/ or any relevant healthcare professionals will be conducted by CLINUVEL. Completion of the training and accreditation activities is required prior to processing of the SCENESSE® order.

CLINUVEL instructs the sole EU distributor [redacted] to ship the ordered amount of implants directly to the EEEC only after the physician and any relevant healthcare professionals have completed training and accreditation.

It is recognised that some EPP patients may not consent to participate in the EEDR. If this is the case, physicians may treat such patients provided they agree to provide any safety-related information that may occur to the patient while treated with SCENESSE®. There is also the possibility that physicians may wish to treat patients with SCENESSE® outside the scope of the approved indication of the SmPC. In this situation, physicians are required to obtain explicit written consent from CLINUVEL and the necessary approvals from relevant competent authorities (including regulatory and ethics, where applicable) before supply of SCENESSE® can be considered.

Plans to evaluate the effectiveness of the interventions and criteria for success:

SCENESSE® is only distributed to centres which have received formal accreditation and training by CLINUVEL's staff. Off-label reports are reviewed on a routine and periodic (PSURs) basis; Off-label use should not occur without explicit written consent from

CLINUVEL and the necessary approvals from relevant competent authorities, including regulatory and ethics, where applicable.

Patient Guide

Objectives:

Educational materials for patients to address the risk of "change of pigmentary expressions" and sun safety, which are not imposed in the Annex II of the EPAR but are offered by the MAH for use in all countries where SCENESSE® is distributed.

Rationale for the additional risk minimisation activity:

To make patients aware of the important identified risk "change of pigmentary expressions" and to educate them on sun/UV safety.

Target audience and planned distribution path:

The educational material is offered to the patients via the respective EEEC.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Not applicable, as these educational materials is not imposed in the Annex II of the EPAR.

V.3 Summary of risk minimisation measures

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
Allergy and hypersensitivity, including anaphylactic reaction	Routine risk minimisation measures: *SmPC section 4.3., 4.8 and 6.1.* *SmPC section 4.2 & 4.4, where advice is given to monitor the patient for 30 minutes and to have appropriate medical*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *AE-specific follow-up questionnaire* Additional pharmacovigilance

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	treatment readily available to prevent and/or treat anaphylactic reactions sufficiently. If a serious hypersensitivity reaction occurs, appropriate medical treatment should be initiated, the implant should be removed if needed and further treatment with SCENESSE should be discontinued. *PL sections 2 and 4* *Special medical prescription* Additional risk minimisation measures: *Healthcare Professional Guide*	activities: *CUV-PASS-001/002* No final study report date agreed, annual reporting to the Agency
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
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
Off-label use in paediatric	Routine risk minimisation	Routine pharmacovigilance activities beyond adverse

Safety concern	Risk minimisation measures	Pharmacovigilance activities
patients	measures: *SmPC section 4.1., 4.2. and 4.4.* *PL sections 1 and 2* *Special medical prescription* Additional risk minimisation measures: *Healthcare Professional Guide* *Restricted distribution*	reactions reporting and signal detection: *None*
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*
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.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	PL introduction (black triangle) *Special medical prescription* Additional risk minimisation measures: *None*	detection: *None* Additional pharmacovigilance activities: *None*
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*

Part VI: Summary of the risk management plan

This is a summary of the risk management plan (RMP) for SCENESSE®. The RMP details important risks of SCENESSE®, how these risks can be minimised, and how more information will be obtained about SCENESSE®'s risks and uncertainties (missing information).

SCENESSE®'s summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how SCENESSE® should be used.

This summary of the RMP for SCENESSE® should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of SCENESSE®'s RMP.

I. The medicine and what it is used for

SCENESSE® is authorised for EPP (see SmPC for the full indication). It contains afamelanotide as the active substance and it is given as a controlled release injectable implant.

Further information about the evaluation of the benefits of SCENESSE® can be found in the medicine's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/scenesse

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of SCENESSE®, together with measures to minimise such risks and the proposed studies for learning more about the risks of SCENESSE®, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of SCENESSE®, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of SCENESSE® is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of SCENESSE® are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of SCENESSE®. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	• Change of pigmentary expressions • Allergy and hypersensitivity, including anaphylactic reaction
Important potential risks	• Administration error
Missing information	• Off-label use in paediatric patients • 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

II.B Summary of important risks

Important identified risk: Change of pigmentary expressions	
Evidence for linking the risk to the medicine	SCENESSE® increases the level of melanin pigment in the skin and makes the skin darker. When taking SCENESSE® the contrast in the colour of already darker skin areas (e.g. ephelides, sun spots etc, collectively 'pigmentary expressions') and the surrounding skin can become more intense. It is important to monitor these areas to make sure that any change observed is only a result of the drug's normal activity and that is does not mask a skin condition. Any darkening of pigmentary expressions induced by SCENESSE® is reversible.
Risk factors and risk groups	The risk factors for the development of changes in pigmentary expressions are many and varied and largely depend on the individual's phenotype, personal medical history, family medical history and environmental factors such as previous

	chronic sunlight exposure. Special caution is warranted in patients with: • individual or family history of melanoma (cancer that develops from the pigment-containing cells known as melanocytes) • suspected or confirmed susceptibility to melanoma (see above) of the skin, and/or • individual history of basal cell carcinoma (cancer that grows on parts of your skin that get a lot of sun), squamous cell carcinoma (second most common form of skin cancer), or other malignant or premalignant skin lesions.
Risk minimisation measures	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* *PIL section 2* *Special medical prescription* Additional risk minimisation measures: *Healthcare Professional Guide* *Patient guide*
Additional pharmacovigilance activities	*CUV-PASS-001/002* See section II.C of this summary for an overview of the post-authorisation development plan.
Important identified risk: Allergy and hypersensitivity including anaphylactic reaction	
Evidence for linking the risk to the medicine	The body's immune system helps to fight infections by recognising unknown substances. However, sometimes the immune system can also respond to medicines and this reaction is known as an allergy or hypersensitivity. SCENESSE® is a new drug which has only been tested in a limited number of patients. As with any drug, there is a possibility that some patients may experience an allergic reaction to the drug or any of its components.
Risk factors and risk groups	Patients with a predisposition to allergic reactions and/or a history of hyper-reactivity to proteins and/or polymers are considered at greater risk.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.3., 4.8 and 6.1.*

	SmPC section 4.2 & 4.4, where advice is given to monitor the patient for 30 minutes and to have appropriate medical treatment readily available to prevent and/or treat anaphylactic reactions sufficiently. If a serious hypersensitivity reaction occurs, appropriate medical treatment should be initiated, the implant should be removed if needed and further treatment with SCENESSE should be discontinued. *PL sections 2 and 4* *Special medical prescription* Additional risk minimisation measures *Healthcare Professional Guide*
Additional pharmacovigilance activities	*CUV-PASS-001/002* See section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Administration error	
Evidence for linking the risk to the medicine	The implant is administered using a catheter needle; the risk of damage to the implant during the administration can on theoretical grounds not be excluded. The route of administration poses a risk for patients with respect to non-maintenance of sterile conditions in clinical practice and also with respect to application site reactions.
Risk factors and risk groups	There are no known risk groups or risk factors.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.2.* *PIL section 3* *Special medical prescription* Additional risk minimisation measures: *Healthcare Professional Guide and associated training material*
Additional pharmacovigilance activities	*CUV-PASS-001/002* See section II.C of this summary for an overview of the post-authorisation development plan.
Missing information: Off-label use in paediatric patients	
Evidence for linking the risk to the medicine	SCENESSE® has never been fully evaluated in children. Children up to 17 years of age suffering from EPP must not be administered SCENESSE® as safety and efficacy in children have not been demonstrated.
Risk factors and risk groups	It is conceivable that there may be a temptation to treat adolescents close to 18 years of age may because of their

	closeness to the adult age threshold. Similar considerations may also apply to younger children of a larger body size.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.1., 4.2. and 4.4.* *PIL sections 1 and 2* *Special medical prescription* Additional risk minimisation measures: *Healthcare Professional Guide* *Restricted distribution*
Additional pharmacovigilance activities	*CUV-PASS-001/002* See section II.C of this summary for an overview of the post-authorisation development plan.
Missing information: Off-label use in adults	
Evidence for linking the risk to the medicine	SCENESSE® has never been fully evaluated in conditions other than EPP. SCENESSE® should not be used in other patient populations as safety and efficacy in these patients have not been demonstrated.
Risk factors and risk groups	It is theoretically possible that there may be a temptation to treat some adult patients off-label because of the perceived benefits of afamelanotide. However, the approval procedures that have to be followed before SCENESSE® is provided, as well as the medical specialisations involved in treating EPP patients at EEECs and their patient populations make the probability of off-label use other than via an approved controlled distribution program negligible.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.1.* *PIL section 1* *Special medical prescription* Additional risk minimisation measures: *Healthcare Professional Guide* *Restricted distribution*
Additional pharmacovigilance activities	*CUV-PASS-001/002* See section II.C of this summary for an overview of the post-authorisation development plan.
Missing information: Use in pregnancy and lactation	
Evidence for linking the risk to the medicine	SCENESSE® has never been fully evaluated in conditions other than EPP. SCENESSE® should not be used in other patient populations as safety and efficacy in these patients have not

	been demonstrated.
Risk factors and risk groups	The at-risk groups are women of child bearing potential not using adequate contraception and women who are breastfeeding.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.6. and 5.3.* *PIL section 2* *Special medical prescription* Additional risk minimisation measures: *No risk minimisation measures*
Additional pharmacovigilance activities	*CUV-PASS-001/002* See section II.C of this summary for an overview of the post-authorisation development plan.
Missing information: Use in the elderly greater than 70 years of age	
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.2.* *PIL section 2* *Special medical prescription* Additional risk minimisation measures: *No risk minimisation measures*
Missing information: Use in patients with co- morbidities such as clinically significant renal, hepatic or cardiac impairment	
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.1. and 5.2.* *PIL section 2* *Special medical prescription* Additional risk minimisation measures: *No risk minimisation measures*
Missing information: Long-term safety data	

Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.4.* *PIL introduction (black triangle)* *Special medical prescription* Additional risk minimisation measures: *No risk minimisation measures*
Missing information: Pharmacokinetic data	
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 5.1.* *Special medical prescription* Additional risk minimisation measures: *No risk minimisation measures*

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

The following studies are conditions of the marketing authorisation:

Study short name: CUV-PASS-001 and -002 EPP Disease Registry

Purpose of the study: Analyses comparing long term safety data and outcome endpoints in EPP patients receiving treatment with SCENESSE® (Treated Group) and those not receiving SCENESSE® (Untreated Group) or having discontinued treatment with SCENESSE® (Discontinued Group) are to be undertaken.

Primary objectives

- Gather long-term safety data of SCENESSE®
- Evaluate compliance with the risk minimisation measures

Secondary objectives

- Evaluate adherence with the controlled distribution program
- Generate data to contribute to knowledge about clinical benefits and to add data on potential clinical effectiveness of SCENESSE®

II.C.2 Other studies in post-authorisation development plan

Study short name CUV052 Pharmacokinetic EPP Study

Rationale and study objectives:

Purpose of the study: To collect data on distribution, metabolism and excretion of SCENESSE®

Primary objective

- To determine the pharmacokinetics of afamelanotide in adolescent and adult EPP patients following administration of one SCENESSE® implant

- To determine the relative comparability of the pharmacokinetic profiles of afamelanotide in adolescent and adult EPP patients

Secondary objectives

- To confirm the safety and tolerability of afamelanotide in [redacted] adult subjects with EPP

[redacted]

Part VII: Annexes

Annex 1 – EudraVigilance Interface

Available in electronic format only

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Table 1 Annex 2: Planned and on-going studies

Study	Summary of objectives	Safety concerns addressed	Protocol link Milestones
A Post-Authorisation Disease Registry Safety Study to Generate Data on the Long-Term Safety and Effectiveness of SCENESSE® (Afamelanotide 16mg) in Patients with Erythropoietic Protoporphyria (EPP) CUV-PASS-001 Category 2	EEDR gathers long term safety data and effectiveness outcomes in patients with EPP. The EEDR collects data from both patients and physicians	Changes of pigmentary expressions Allergy and hypersensitivity Administration errors Long term safety data	Link to protocol Interim results: Reports are submitted annually. First report (joint Disease Registry and Retrospective Chart Review Report) submitted 22 Dec 2016; Second report 19 Dec 2017; Third report 04 Jan 2019; Fourth report 15 Jan 2020; Fifth report 05 Jan 2021; Sixth report 05 Jan 2022; Seventh report 09 Jan 2023; Eighth report 10 Jan 2024; Ninth report 09 Jan 2025 Final study report submission: No final study report date agreed, annual reporting to the Agency
A Post-Authorisation Disease Registry Safety Study to Generate Data on the Long-Term Safety and Effectiveness of SCENESSE® (Afamelanotide 16mg) in Patients with Erythropoietic Protoporphyria (EPP) CUV-PASS-002 Category 2	The disease registry non-interventional post-authorisation safety study (EEDR) gathers long term safety data and effectiveness outcomes in patients with EPP. The EEDR collects data from both patients and physicians (Protocol version for countries where patients treated off-label cannot be included in the disease registry)	Changes of pigmentary expressions Allergy and hypersensitivity Administration errors Long term safety data	Link to protocol Interim results: Reports are submitted annually. First report (joint Disease Registry and Retrospective Chart Review Report) submitted 22 Dec 2016; Second report 19 Dec 2017; Third report 04 Jan 2019; Fourth report 15 Jan 2020. Fifth report 05 Jan 2021; Sixth report 05 Jan 2022; Seventh report 09 Jan

Study	Summary of objectives	Safety concerns addressed	Protocol link Milestones
			2023 Eighth report 10 Jan 2024; Ninth report 09 Jan 2025 Final study report submission: No final study report date agreed, annual reporting to the Agency
A Study to evaluate the Pharmacokinetics of Afamelanotide in Patients with Erythropoietic Protoporphyria (EPP) CUV052 Category 3	Pharmacokinetics profile in 14 adolescent and 14 adult EPP patients after administration of one SCENESSE® implant. Determine the relative comparability of the pharmacokinetics profile in adolescent and adult EPP patients .	Pharmacokinetics data	Link to protocol Interim results: Not applicable Final study report submission: Not applicable

Table 2 Annex 2: Completed studies

Not applicable.

Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

Part A: Requested protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP:

Not applicable.

Part B: Requested amendments of previously approved protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP:

Not applicable.

Part C: Previously agreed protocols for on-going studies and final protocols not reviewed by the competent authority

Approved protocols:

CUV-PASS 001 Version 8 was endorsed by consensus by PRAC on 17 March 2016 (EMA Procedure Reference Number: EMEA/H/C/PSP/0022.1A.1), Version 9.4 was endorsed by consensus by PRAC on 07 July 2022 (EMA Procedure Reference Number EMEA/H/C/PSA/S/0076.2).

CUV-PASS 002 Version 4 was endorsed by consensus by PRAC on 17 March 2016 (EMA Procedure Reference Number: EMEA/H/C/PSP/0033.1), Version 5.5 was endorsed by consensus by PRAC on 18 July 2022 (EMA Procedure Reference Number EMEA/H/C/PSA/S/0076.2).

Annex 4 - Specific adverse drug reaction follow-up forms

Pregnancy report form

Pregnancy outcome and breastfeeding report form

Allergy and Hypersensitivity Questionnaire

Annex 5 - Protocols for proposed and on-going studies in RMP part IV

Not applicable.

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Approved key messages of the additional risk minimisation measures

Prior to the use of SCENESSE® in each Member State, the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational and controlled access programmes, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational and controlled distribution programmes are aimed at ensuring appropriate administration of SCENESSE® by trained healthcare professionals who are experienced in treating only EPP patients and minimising the risk of administration errors.

The MAH shall ensure that in each Member State where SCENESSE® is marketed, all healthcare professionals and patients who are expected to use SCENESSE® are provided with the following educational package and trained:

- Physician educational material
- Patient information pack

❖ **Physician and healthcare professional educational material**:

- Summary of product characteristics,
- Face to face training material,
- Educational video,
- Registry information sheet.

The face to face training material, including the educational video, shall contain the following key messages:

- Demonstration of the correct application technique, highlighting the measures needed to ensure the implant is not damaged during use.
- The importance of maintaining aseptic conditions.
- Methods to prevent or minimise application errors and application site reactions

Registry information sheet shall contain the following key messages:

- The importance of recruiting and entering patients in the EU Registry,
- How to access and use the EU Registry.
- Other:
  - Successful completion of the training will be evaluated at the time of the training by CLINUVEL staff. Particular attention will be made on assessing that the physicians and relevant healthcare professionals clearly understand the training provided by CLINUVEL, in particular the method of administration instructions, all contraindications, special warnings and precautions for use, and the undesirable effects listed in the SmPC. Additional assessment tools may be organised, depending on the local requirements.
  - Accreditation of physicians and relevant healthcare professionals is renewed every two years upon confirmation that the staff have actively been involved in the treatment and/or management of patients during the accreditation period.

- The need for re-training and accreditation before the above-mentioned timelines will occur in the event that noncompliance with the training and educational material previously delivered is identified.
- Healthcare professionals' training records are maintained by CLINUVEL.
- Educational material will be revised following any changes requiring regulatory action (e.g. submission of a variation), where applicable.

Controlled distribution to European EPP Expert Centres (EEECs):

A list of all EEECs specialising in the treatment of porphyrias and known to CLINUVEL is presented in **Table A6-1**. It is expected that initial demand for SCENESSE® will be limited to these centres, however, further requests from additional centres cannot be excluded. CLINUVEL will consider adding additional centres and/or physicians to the list after evaluation of their ability to treat EPP patients with SCENESSE® and/ or training and accreditation of all relevant healthcare professionals at the new centre. Distribution to new centres will be limited to those whose ability to treat EPP patients with SCENESSE® under the RMP has been evaluated and have undergone training and accreditation by CLINUVEL.

Each order for SCENESSE® is placed by the EEEC directly with CLINUVEL. The order, if initiated by a physician and/or institutional pharmacist not previously trained and accredited, will trigger CLINUVEL evaluating the healthcare professionals and associated institution as to their ability to treat EPP patients with SCENESSE® under the RMP. If confirmed, training and accreditation of the physician and/or institutional pharmacist and/ or any relevant health care professionals will be conducted by CLINUVEL. Completion of the training and accreditation activities is required prior to processing of the SCENESSE® order.

CLINUVEL instructs the sole EU distributor [redacted] to ship the ordered amount of implants directly to the EEEC only after the physician and any relevant health care professionals have completed training and accreditation.

SCENESSE® is indicated for the prevention of phototoxicity in adult patients with EPP. Through the controlled distribution strategy and additional risk minimisation activities, it is intended that all adult EPP patients treated with SCENESSE® will consent to participate in the EEDR.

It is recognised that some EPP patients may not consent to participate in the EEDR. If this is the case, physicians may treat such patients provided they agree to provide any safety-related information that may occur to the patient while treated with SCENESSE®. There is also the possibility that physicians may wish to treat patients with SCENESSE® outside the scope of the approved indication of the SmPC. In this situation, physicians are required to obtain explicit written consent from CLINUVEL and the necessary approvals from relevant competent authorities (including regulatory and ethics, where applicable) before supply of SCENESSE® can be considered.

Table A6-1 List of Porphyria Treatment Centres known to CLINUVEL

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted] Expert Centre or EEEC)
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	[redacted]	[redacted]
	[redacted]	[redacted]

The patient information pack:

- Patient information leaflet
- A patient guide

Patient guide:

Educational materials for patients to address the risk of "change of pigmentary expressions" and sun safety, which are not imposed in the Annex II of the EPAR, but are offered by the MAH for use in all countries where SCENESSE® is used are made available to patients:

- Ultraviolet Radiation and Sun Safety (leaflet and poster): this is aimed at reinforcing the need to be vigilant in the sun, so that patients do not become too complacent with regards to sun exposure when using the drug. Although this is extremely unlikely, as sun avoidance has been consistently observed during all EPP clinical trials, it cannot be excluded that patients may be willing to risk a higher level of sun exposure post-approval.
- Know your skin: a guide to spotting skin cancer (leaflet): this is aimed at encouraging patients to actively monitor any changes to pigmentary expressions to the skin. It is not a substitute for the active monitoring of changes to pigmentary expressions required of doctors in the SmPC.

Annex 7 - Other supporting data (including referenced material)

Available long-term safety data from the extension safety study CUV037 and from expanded access program in Italy and Switzerland have been included in Module 2.7.4 (Summary of Clinical Safety).

Literature references:

Wensink, D. (2019, September). Clinical effectiveness of afamelanotide in patients with erythropoietic protoporphyria: An observational study. Presented at the SSIEM Annual Symposium, Rotterdam.

Minder, A. (2019, August). ON LONG-TERM AFAMELANOTIDE TREATMENT SWISS RESIDENTS WITH ERYTHROPOIETIC PROTOPORPHYRIA. Presented at the ICPP 2019, Milan.

Minder, E. I. (2019, August). Erythropoietic protoporphyria (EPP) Experience with Scenesse 2006-2018, Swiss Cohort. Presentation presented at the Light and Life 2019, Barcelona, Spain.

Minder, E. I., Barman-Aksoezen, J., & Schneider-Yin, X. (2017). Pharmacokinetics and Pharmacodynamics of Afamelanotide and its Clinical Use in Treating Dermatologic Disorders. Clinical Pharmacokinetics, 56(8), 815–823.

Neumann, N. J. (2018). Afamelanotid. Internistische Praxis, 59(1), 155–159.

Annex 8 – Summary of changes to the risk management plan over time

Version	Approval date Procedure	Change
5.0	11 Dec 2014 Marketing Authorisation Application Procedure	<u>General changes</u> This version of the RMP was initially signed off on 21 Oct 2014 prior to CHMP positive opinion granted on 23 Oct 2014. Minor updates were received from the EMA on 22 Oct 2014, with confirmation that the document was acceptable. Further minor comments were received on 30 Oct 2014 and on 05 Nov 2014 with a specific request not to update the RMP version after incorporation of the Agency's comments and inclusion of the final agreed SmPC. The same version of the RMP (with the EMA changes implemented and final SmPC inserted in Annex 2) was signed off on 10 Nov 2014 and was submitted to the EMA on request from the Agency for a final check prior to submission of the final eCTD sequence. Minor comments (typos correction) were received back from the EMA on 27 Nov 2014 and implemented without updating the version number.
6.0[1], 7.0, 7.1, 8.0	10 Jan 2017, 07 Jun 2017, 12 Oct 2017 EMEA/H/C/2548/II/0018	<u>General changes</u> This version of the RMP has been updated to reflect new information gained from when the product was launched in Jun 2016 to the end of the reporting interval of the most recent PSUR (22 Jun 2017). • QPPV details were updated • Regulatory status was updated • Part II Module SIII - update on exposure data • Part II Module SIV - update on patient exposure • Part II Module SV - update on distribution and the establishment of the disease registry, update on patient exposure and findings from PSUR • Part II Module SVII – updated to incorporate new information concerning post-launch activities, updated safety information • Part VI - amendments to the pharmacokinetic study project deadlines, update to overview of

[1] This version of the RMP is version 7.1. The submission for RMP Version 7.0 (submitted in EMEA/H/C/002548/IB/0014 Sequence 0043) was not approvable according to PRAC, with further changes requested.

Version	Approval date Procedure	Change
		disease epidemiology <u>Editorial changes</u> • Part II Module SI • Part II Module SIII • Part II Module SV - editorial changes to reflect the launch of SCENESSE® • Part II Module SVII • Part III • Part IV – minor editorial changes to reflect that the product has been launched • Part V • Part VI <u>Safety concerns</u> n.a. <u>Pharmacovigilance Plan</u> • Part III - amendments to the pharmacokinetic study project deadlines <u>Post-authorisation efficacy plan</u> • Part IV – update in table of post-authorisation efficacy studies to describe PASS as a study with outcome endpoints <u>Risk minimisation measures</u> • Part V – additional text to reflect post-launch activities. Updates to reflect evaluation of effectiveness of RMMs <u>Annexes</u> • Annex 2 – minor changes to SmPC and Package Leaflet (as notified) • Annex 3 – updated licensing status • Annex 4 – tabulation of clinical trial status updated • Annex 6 – approved synopses of PASS and retrospective chart review protocols, current synopsis for study CUV052 added, minor administrative clarifications • Annex 7 – current version of adverse event follow up form included • Annex 9 – Annual report (intermediate report 1) on SCENESSE® EPP Disease Registry and

Version	Approval date Procedure	Change
		Retrospective Chart Review Studies added [according to previous template] • Annex 10 – details of actual rather than proposed Risk Minimisation Measures included. Updates to training and accreditation section and to controlled distribution section to reflect current processes [according to previous template] • Annex 11 – a tabulation of approved materials related to additional risk minimisation measures has replaced to mock ups of proposed materials [according to previous template]
8.1	01 Feb 2018 EMEA/H/C/2548/II/0018	<u>General changes</u> • Table SII.1 – update of exposure numbers to reflect revised methodology of counting previously treatment naïve patients and correct error • Tables SIV.1.1 & SV.2.1 – amended to correct inconsistencies on patient exposure • SVII.3.1 – revision of MedDRA terms and removal of tables incorporating interval data • Minor amends to reflect reviewer's feedback on RMP version 8.0 dated 21 December 2017 <u>Editorial changes</u> • Part II – editorial amendments for consistency with SmPC <u>Safety concerns</u> n.a. <u>Pharmacovigilance Plan</u> n.a. <u>Post-authorisation efficacy plan</u> n.a. <u>Risk minimisation measures</u> n.a. <u>Annexes</u> n.a.
9.0	<Approval date>	<u>General changes:</u>

Version	Approval date Procedure	Change

	<Procedure>	• Change of the MAH from CLINUVEL (UK) LTD to CLINUVEL EUROPE LIMITED
		• Update of the template as per GVP module V
		• Reclassification of the risks:
		  • Important identified risk "administration site reactions" removed from the list of safety concerns
		  • Important potential risks: Off-label use in paediatric patients, Off-label use in adults, Use in pregnancy and lactation reclassified as missing information
		• Safety data updated to reflect new information gained from February 2018 (RMP v8.1) to the end of the reporting interval of the most recent PSUR (22 Jun 2019).
		• Change of the Product distributor from [redacted]

9.1		<u>General changes:</u> • Reclassification of the risks: • Important potential risk Allergy and hypersensitivity reclassified as important identified risk • Safety data updated to reflect new information gained from August 2020 (RMP v9.0) to 25 March 2022
9.3		<u>General changes to reflect reviewer's feedback on RMP ver 9.1:</u> • Part III.2 – revision to CUV-RCR-001 summary • Annex 2 – revision to Table 1 relating to CUV-RCR-001
9.4		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.

Version	Approval date Procedure	Change
		• Part II: Module SI 'Demographics of the target population' was updated to include adolescent patients ages greater than 12. • SVII.2 – new section: 'Use in adolescent patients' • SVII.3.2 updated. New section: 'Missing Information: use in adolescent patients (12 to less than 18 years of age)'. Updated section: 'Missing Information: Off-label use in paediatric patients'. • Part II: Module SVIII – table updated • Part II: Module SIV – table updated • Table Part V.1 – updated • Table V.3.1 – updated • II.A – updated: 'Missing information'. • II.B – updated: 'Missing information'. <u>General Changes:</u> • 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
9.5		<u>Revised changes to reflect reviewer's feedback on RMP as part of EMEA/H/C/002548/II/0044:</u> • SVII.2 – new section: 'Use in patients under 18 years of age' • SVII.3.2 updated. Updated section: 'Missing Information: Safety in patients under 18 years of age'. • Part II: Module SVIII – table updated • Part II: Module SIV – table updated • Table Part V.1 – updated • Table V.3.1 – updated • II.A – updated: 'Missing information'. • II.B – updated: 'Missing information'. <u>General Changes:</u>

Version	Approval date Procedure	Change
		• 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
9.6		Change in the pharmacovigilance plan to terminate an obligation to conduct a retrospective chart review (RCR) study [redacted] comprehensive scientific data on long-term safety and outcome endpoints is already being generated through the specific obligation of PASS study. Part II: Module SII- Table SII.1 Part II: Module SIII – Clinical trial exposure and table SIII.5, SIII.7 and SIII.8 updated Part II: Module SV – SV.1.2 and Table SV.1 updated Part II: Module SVII- SVII.3.1, Table SVII.3.1, SVII.3.2 updated Part III: III.2, III.3 updated Part V: V.2 and table V.3.1 updated Part VI: II.B, II.C.1 updated Part VIII: Annexes: Table 1 Annex 2, Annex 3 part C, Annex 6, Table A6-1 updated
9.7		Revised changes to reflect reviewer's feedback on RMP as part of EMEA/H/C/002548/II/0044
9.8		The change in dosing regimen involves replacing the current recommendations of a maximum of four implants per year with the recommendation of administering one implant every two months. This change is supported by a literature review and analysis of safety data collected through the postauthorisation safety study (PASS). Part I Product Overview, Table 1.1 revised to change the recommendation of dose regimen
9.9, 9.10, 9.11		Revised changes to reflect reviewer's feedback on RMP as part of EMEA/H/C/002548/II/0049
9.12		Changes made to the Category 3 pharmacokinetic study CUV052 protocol to facilitate enrolment and to

Version	Approval date Procedure	Change
		provide updated timelines for CUV052. Part II: Module SII- Nonclinical part of the safety specification- Table SII.1- key findings from non-clinical studies updated. Part II: Module SIII- Clinical trial exposure updated. Part II- Module SIV- Populations not studied in clinical trials updated. Part II- Module SV-SV.1.2 Exposure Updated SVII.2 – New safety concerns and reclassification with a submission of an updated RMP updated. S.VII.3.1 Presentation if important identified risks and important potential risks updated. SVII.3.2 Missing information: Pharmacokinetic data updated with CUV052 protocol information Part III.2 Additional pharmacovigilance activities updated with CUV052 protocol information Table Part III.3: On-going and planned additional pharmacovigilance activities updated to include timelines for CUV052 II.C.2 Other studies in post-authorisation development plan update of primary and secondary objectives of CUV052 Table 1 Annex 2: Planned and on-going studies updated
9.13		Revised changes to reflect reviewer's feedback on RMP as part of EMEA/H/C/002548/II/0052
9.14		Revised changes to reflect reviewer's feedback on RMP as part of EMEA/H/C/002548/II/0052
9.15		To include "anaphylactic reactions" under the current important identified risk "Allergy & Hypersensitivity". Addition of Follow up questionnaire on Allergy and Hypersensitivity as routine RMM
9.16		Upon approval of Version 9.12, it was taken as base and incorporated changes related to "anaphylactic reactions" under the current important identified risk "Allergy & Hypersensitivity". Also incorporates revised changes to reflect reviewer's feedback on RMP as part of EMEA/H/C/002548/II/0056. Addition of Follow up questionnaire on Allergy and

Version	Approval date Procedure	Change
		Hypersensitivity as routine RMM