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Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

SCENESSE

Afamelanotide

Procedure no: EMA/PAM/0000291457

Note

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

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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	18/08/2025	18/08/2025	☐
☐	CHMP Rapporteur Assessment Report	22/09/2025	22/09/2025	☐
☐	CHMP members comments	06/10/2025	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	09/10/2025	n/a	☐
☒	CHMP adoption of conclusions:	16/10/2025	16/10/2025	☐

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1. Introduction

On 05th August 2025, the MAH submitted an interim report presenting the safety results only of a completed paediatric study for SCENESSE, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measures.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that the study 'A Study to Evaluate the Pharmacokinetics of Afamelanotide in Patients with Erythropoietic Protoporphyria (EPP)', CUV052, a phase II open-label, non-randomized, multi-centre clinical Study to evaluate the pharmacokinetics, safety and tolerability of afamelanotide, and the changes in melanin density of the skin by reflectance spectrophotometry in adults and adolescents (12 to 17 years of age) with erythropoietic protoporphyria (EPP) is part of the paediatric clinical development programme for SCENESSE. The availability and comparison of adult and adolescent pharmacokinetic data will contribute to a deeper understanding of SCENESSE and may subsequently inform future development studies by the Applicant, such as the development of the age-appropriate formulation.
A variation application consisting of the full relevant data package to support the extension of indication from adults to adolescents is expected to be submitted by the fourth quarter of 2025.

2.2. Information on the pharmaceutical formulation used in the study

Treatment was given with 16 mg afamelanotide controlled-release implant, with afamelanotide contained in a poly(D,L-lactide-co-glycolide) implant core.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted an interim report for:

- CUV052, 'A Study to Evaluate the Pharmacokinetics of Afamelanotide in Patients with Erythropoietic Protoporphyria (EPP)', a phase II open-label, non-randomized, multi-centre clinical Study to evaluate the pharmacokinetics, safety and tolerability of afamelanotide, and the changes in melanin density of the skin by reflectance spectrophotometry in adults and adolescents (12 to 17 years of age) with erythropoietic protoporphyria (EPP).

2.3.2. Clinical study

CUV052, 'A Study to Evaluate the Pharmacokinetics of Afamelanotide in Patients with Erythropoietic Protoporphyria (EPP)'

Description

The study was a phase II open-label, non-randomized, multi-centre clinical Study to evaluate the pharmacokinetics, safety and tolerability of a single afamelanotide dose, and the changes in melanin

density of the skin by reflectance spectrophotometry in adults and adolescents (12 to 17 years of age) with erythropoietic protoporphyria (EPP).

Two age cohorts were to be evaluated in the study:

- Age Cohort 1: Adults (18 to ≤ 70 years)
- Age Cohort 2: Adolescents (12 to <18 years)

Methods

A total of twenty-eight EPP patients (fourteen adolescents and fourteen adult patients) were enrolled in the study and administered a single 16 mg SCENESSE implant. Blood samples were collected for the analysis of afamelanotide plasma concentrations at baseline (prior to implant administration) and on Day 0 (4 hours and 8 hours after implant administration), Day 1 (24 hours and 32 hours), Day 2 (48 hours), Day 4 (96 hours) and Day 7 (168 hours). Melanin density was measured on Days 0, 7, 14, 28, 60 and 90. The change in melanin density was calculated across six anatomical sites (forehead, left cheek, right inside upper arm, left medial forearm, right side of abdomen (avoiding implant insertion site) and left side of sacral region/buttock) and overall (average across test sites). Safety monitoring was conducted for a duration of up to 90 days inclusive.

Study participants

Male or female participants 12 to less than 18 years of age (adolescent cohort) or 18 to 70 years of age (adult cohort) with EPP.

Inclusion Criteria

- Adult EPP patients aged between 18 and 70 years (inclusive) and EPP adolescents aged between 12 and 17 (inclusive)
- BMI between 15 and 30 kg/m^2
- >50 kg
- Agree not to use any medications (prescribed, over the counter or complementary medications) without pre-approval by the Principal Investigator during the seven days preceding the study and during the course of the study (until Day 90)
- Able to understand and sign the written Informed Consent Form (and parents or legal representative in case of adolescent participants)
- Able and willing to follow the Protocol requirements, including refraining from the use of tanning products and excessive UV light exposure from the start of the study until Day 90.

Exclusion Criteria

- Any personal or direct family history of melanoma
- Any significant history of allergy and/or sensitivity to any of the contents of study drug product
- Any significant history of allergy and/or sensitivity to lignocaine or other local anaesthetics if used
- Any significant illness during the four weeks before the study screening period
- Any evidence of hepatic (defined as three times standard range) or renal impairment (defined as eGFR <50 mL/min/1.73 m^2)

- Any contraindication to blood sampling
- Female who was pregnant (confirmed by positive urine β-HCG pregnancy test) or lactating
- Females of child-bearing potential (pre-menopausal, not surgically sterile) not using adequate contraceptive measures (i.e. combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable), intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomised partner) or a life-style excluding pregnancy, for up to three months after implant administration
- Sexually active man with a partner of child-bearing potential (pre-menopausal, not surgically sterile) who was not using adequate contraceptive measures, as described above
- Any factor that might have interfered with skin reflectance measurements (e.g. excessive moles, freckles or excessively hairy skin)
- Current cigarette smokers
- History of drug abuse, licit or illicit
- Regularly drank more than four standard drinks of alcohol per day (one standard drink = 300 mL beer, one glass wine, one measure spirit)
- Participation in any clinical trial during the 60 days before the study screening period
- Had received afamelanotide in the last 60 days
- Had donated 400 mL or more of blood or had significant blood loss during the eight weeks preceding screening.

Treatments

A single afamelanotide implant will be administered at baseline via subcutaneous administration.

Objectives

<u>The primary objectives of this study were to determine:</u>

- the pharmacokinetics of afamelanotide following its administration to adolescent and adult EPP participants
- The relative comparability of the PK profiles of afamelanotide between adolescent and adult EPP participants.

<u>The secondary objectives of this study were to determine:</u>

- the safety and tolerability of afamelanotide in adolescent and adult EPP participants;
- changes in melanin density of the skin using reflectance spectrophotometry;
- the comparability of changes in melanin density between adolescent and adult EPP participants following treatment with afamelanotide.

Outcomes/endpoints

Primary Efficacy Endpoint:

The primary endpoints for this study were the following PK parameters:

- C_{max}: Maximum observed plasma concentration following treatment administration, taken directly from the data without interpolation.
- $AUC_{(0-t)}$: Area under the plasma concentration versus time curve from zero (drug administration) to the last observed concentration at time t, calculated using the linear trapezoidal rule.

Secondary Efficacy Endpoints:

The secondary endpoints for this study were the following PK parameters:

- $AUC_{(0-\infty)}$: Area under the plasma concentration versus time curve from zero to infinity, calculated using the trapezoidal rule extrapolated to infinite time.
- t_{max}: Time to reach C_{max}, taken directly from the data without interpolation.
- $t_{1/2}$: Apparent plasma concentration half-life, calculated as $\ln(2)/ \lambda_z$.
- λ_z: Terminal rate constant.

Other secondary endpoints include:

- Adverse events and changes in clinical measurements from baseline.
- Changes in melanin density from baseline in adult and adolescent EPP participants.
- Comparison of melanin density in adult and adolescent EPP participants.

Safety Endpoint:

The safety and tolerability of afamelanotide was evaluated by monitoring and recording the type and incidence of treatment-emergent adverse events (TEAEs) occurring during the study period, which were listed by intensity, seriousness, outcome, and relationship to study drug. The number of participants with TEAEs were summarised by MedDRA preferred term and body system. Additional safety assessments included monitoring changes in vital signs, laboratory parameters, physical examination abnormalities and concomitant medications. TEAEs were reviewed before and after IMP administration on Day 0.

Sample size

Fourteen participants per age cohort were planned to be included.

The sample size has been selected to ensure 12 evaluable patients from each group are recruited and data are available, as per the bioequivalence guidelines.

Randomisation and blinding (masking)

Not applicable.

Statistical Methods

Statistical analyses are only planned for pharmacokinetic data and melanin density. Results for these endpoints is pending. Statistical analysis of safety data was not performed.

Results

Participant flow

The schedule of study procedures is shown below.

Table 1. Schedule of Study Procedures

Study Procedure	Study Day									
	-7 to -1	0[5]	1[5]	2[5]	4[5]	7[5]	14[5]	28±2[5]	60±7[5]	90±7 or Early Termination[1]
Informed Consent	X									
Eligibility Check	X	X								
Demography	X									
Medical & Surgical History	X									
Height, Weight & BMI Measurement	X									X
Physical Examination	X									X
Haematology, Biochemistry & Urinalysis[7]	X						X		X	X
Vital Sign Measurement	X	X					X		X	X
Pregnancy test	X[6]	X[6]					X[6]		X[6]	
Melanin Density Measurement		X				X	X	X	X	X
PK Blood Sample Collection[2]		X	X	X	X	X				
Afamelanotide Administration		X[3]								
Full Body Posterior and Anterior Photography[4]		X								X
Adverse Event Monitoring		X	X	X	X	X	X	X	X	X
Concomitant Medication Review		X	X	X	X	X	X	X	X	X

[1]Early Termination Visit procedures to be performed upon participant consent.
[2]PK blood samples will be taken pre-dose and at 4, 8, 24, 32, 48, 96 and 168 hours post-implant administration.
[3]Afamelanotide administration to occur only after all other study procedures have been completed for visit (not inclusive of post dose PK samples).
[4]Full body posterior and anterior photography undertaken using a 5 megapixel digital camera.
[5]Visits may be done at home.
[6]Serum at Screening, dipstick urine for other visits. Pregnancy test not needed for adolescents if there is no risk of pregnancy present according to the investigator.
[7]Adolescent samples to be taken always at the same time (±2 hours).

Recruitment

Adolescent and adult EPP participants were recruited through the Investigator's study team approaching potential participants with a confirmed diagnosis of EPP who were registered to the clinic's database. A total of 28 participants were screened across 3 study sites in 3 countries (Belgium, The Netherlands, Switzerland) and enrolled in the study. All participants received 1 dose of study intervention as planned; No premature study terminations.

Baseline data

Demographic and baseline characteristics for the safety population are presented below.

Table 2. Demographic and Baseline Characteristics (Safety population)

	Adults (N=14)	Adolescents (N=14)	Total (N=28)
Age (years)			
Mean	38.4	15.2	26.8
Median (min, max)	35.5 (19, 55)	16.0 (13, 17)	18.0 (13, 55)
Gender			
Male	10 (71.4%)	6 (42.9%)	16 (57.1%)
Female	4 (28.6%)	8 (57.1%)	12 (42.9%)
Fitzpatrick Skin Type			
Type I	6 (42.9%)	2 (14.3%)	8 (28.6%)
Type II	7 (50.0%)	8 (57.1%)	15 (53.6%)
Type III	1 (7.1%)	4 (28.6%)	5 (17.9%)
Height (cm)			
Mean	173.69	169.89	171.79
Median (min, max)	174.25 (158.0, 191.0)	168.00 (158.5, 186.0)	169.00 (158.0, 191.0)
Weight (kg)			
Mean	68.53	60.55	64.54
Median (min, max)	64.30 (55.0, 92.5)	58.15 (50.4, 79.0)	61.20 (50.4, 92.5)
BMI (kg/m^2)			
Mean	22.71	21.10	21.91
Median (min, max)	21.05 (17.7, 28.6)	20.31 (16.7, 27.7)	20.98 (16.7, 28.6)

The majority of the adult participants enrolled in this study were male (71.4%) and half of the adult participants were assessed as Fitzpatrick skin type II (50%). The mean age of the adolescent participants enrolled in this study was 15.2 years (median: 16.0, minimum: 13, maximum: 17) and the majority were female (57.1%). Over half of the adolescent participants enrolled in this study were assessed as Fitzpatrick skin type II (57.1%).

Number analysed

The safety population included all 28 participants (14 adolescents and 14 adult EPP patients) who received a single SCENESSE implant.

Efficacy and PK results

Pharmacokinetic results and melanin density results are pending. The Applicant remarks that full efficacy results, including melanin density (a pharmacodynamic measure), are expected to be available by January 2026.

Safety results

Adverse Events

A total of 53 TEAEs were reported among 23 participants (82.1%).

Table 3. Incidence and Frequency of Treatment Emergent Adverse Events by MedDRA System Organ Class and Preferred Term - Safety Population

System Organ Class Preferred Term	Statistic	Adults (N=14)	Adolescents (N=14)	Total (N=28)
Any AE	n (%) e	12 (85.7%) 24	11 (78.6%) 29	23 (82.1%) 53
Blood and lymphatic system disorders	n (%) e	1 (7.1%) 1	1 (7.1%) 1	2 (7.1%) 2
Anaemia	n (%) e	1 (7.1%) 1	0	1 (3.6%) 1
Thrombocytopenia	n (%) e	0	1 (7.1%) 1	1 (3.6%) 1
Gastrointestinal disorders	n (%) e	4 (28.6%) 4	5 (35.7%) 5	9 (32.1%) 9
Diarrhoea	n (%) e	2 (14.3%) 2	1 (7.1%) 1	3 (10.7%) 3
Dyspepsia	n (%) e	0	1 (7.1%) 1	1 (3.6%) 1
Irritable bowel syndrome	n (%) e	0	1 (7.1%) 1	1 (3.6%) 1
Nausea	n (%) e	2 (14.3%) 2	2 (14.3%) 2	4 (14.3%) 4
General disorders and administration site conditions	n (%) e	6 (42.9%) 7	3 (21.4%) 3	9 (32.1%) 10
Application site erythema	n (%) e	1 (7.1%) 1	0	1 (3.6%) 1
Implant site haematoma	n (%) e	1 (7.1%) 1	1 (7.1%) 1	2 (7.1%) 2
Implant site pain	n (%) e	0	1 (7.1%) 1	1 (3.6%) 1
Influenza like illness	n (%) e	4 (28.6%) 5	0	4 (14.3%) 5
Pyrexia	n (%) e	0	1 (7.1%) 1	1 (3.6%) 1
Immune system disorders	n (%) e	1 (7.1%) 1	0	1 (3.6%) 1
Seasonal allergy	n (%) e	1 (7.1%) 1	0	1 (3.6%) 1
Infections and infestations	n (%) e	3 (21.4%) 3	4 (28.6%) 4	7 (25.0%) 7
Gastroenteritis	n (%) e	0	1 (7.1%) 1	1 (3.6%) 1
Gastroenteritis viral	n (%) e	1 (7.1%) 1	0	1 (3.6%) 1
Nasopharyngitis	n (%) e	1 (7.1%) 1	0	1 (3.6%) 1
Respiratory tract infection	n (%) e	0	1 (7.1%) 1	1 (3.6%) 1
Rhinitis	n (%) e	1 (7.1%) 1	2 (14.3%) 2	3 (10.7%) 3
Injury, poisoning and procedural complications	n (%) e	0	2 (14.3%) 2	2 (7.1%) 2
Road traffic accident	n (%) e	0	1 (7.1%) 1	1 (3.6%) 1
Skin abrasion	n (%) e	0	1 (7.1%) 1	1 (3.6%) 1
Investigations	n (%) e	1 (7.1%) 2	0	1 (3.6%) 2
Alanine Aminotransferase increased	n (%) e	1 (7.1%) 1	0	1 (3.6%) 1
Aspartate aminotransferase increased	n (%) e	1 (7.1%) 1	0	1 (3.6%) 1

Footnotes:
N=number of patients in analysis population, n=number of patients, e=number of events,
%=100x(n/N).

Most Frequently Reported Adverse Events

The most frequently reported TEAEs by PT across both groups were:

- Headache [seven TEAEs reported by six participants, 21.4% (three adults, (21.4% of all adults) and three adolescents, (21.4% of all adolescents)]
- Photosensitivity reaction [six TEAEs in three participants, 10.7% (three adolescents, 21.4%)]
- Influenza like illness [five TEAEs in four participants, 14.3% (four adults, 28.6%)]
- Nausea [four TEAEs in four participants, 14.3% (two adults, 14.3% and two adolescents, 14.3%)]

- Diarrhoea [three TEAEs in three participants, 10.7% (two adults, 14.3% and one adolescent 7.1%)]
- Rhinitis [three TEAEs in three participants, 10.7% (one adult, 7.1% and two adolescents, 14.3%)]

The only other events that were reported by more than one participant were Implant site haematoma (7.1%, one adult and one adolescent, one event each), and Migraine (7.1%, two adolescent participants, one event each).

The TEAEs most frequently reported by **adult participants** were, by PT:

- Influenza like illness [five TEAEs in four adults (28.6%)]
- Headache [four events in three adults (21.4%)]
- Diarrhoea [two events in two adults (14.3%)]
- Nausea [two events in two adults (14.3%)]

The TEAEs most frequently reported by **adolescent participants** were, by PT:

- Photosensitivity reaction [six events in three adolescents (21.4%)]
- Headache [three events in three adolescents (21.4%)]
- Nausea [two events in two adolescents (14.3%)]
- Rhinitis [two events in two adolescents (14.3%)]
- Migraine [two events in two adolescents (14.3%)]

AEs Related to Study Intervention

Photosensitivity reaction is an expected event in EPP patients. None of these photosensitivity reactions were assessed as related to treatment.

Out of the 53 reported AEs, 23 events in 15 participants (53.6%) were considered treatment related. This included eight adults (57.1% of adults) who reported a total of 14 related TEAEs and seven adolescents (50.0% of adolescents) who reported a total of nine related TEAEs.

Table 4. Incidence of Treatment Related Adverse Events by MedDRA System Organ Class, Preferred Term and Severity - Safety Population

	Adults (N=14)			Adolescents (N=14)		
System Organ Class Preferred Term	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Any Treatment Related AE	8 (57.1%)	0	0	7 (50.0%)	0	0
Gastrointestinal disorders	4 (28.6%)	0	0	3 (21.4%)	0	0
Diarrhoea	2 (14.3%)	0	0	1 (7.1%)	0	0
Nausea	2 (14.3%)	0	0	2 (14.3%)	0	0
General disorders and administration site conditions	4 (28.6%)	0	0	2 (14.3%)	0	0
Implant site haematoma	1 (7.1%)	0	0	1 (7.1%)	0	0
Implant site pain	0	0	0	1 (7.1%)	0	0
Influenza like illness	3 (21.4%)	0	0	0	0	0
Infections and infestations	1 (7.1%)	0	0	1 (7.1%)	0	0
Gastroenteritis viral	1 (7.1%)	0	0	0	0	0
Rhinitis	0	0	0	1 (7.1%)	0	0
Nervous system disorders	3 (21.4%)	0	0	3 (21.4%)	0	0
Headache	3 (21.4%)	0	0	3 (21.4%)	0	0

Footnotes:
N=number of patients in analysis population, n=number of patients, %=100x(n/N).
Patients are summarised once for each event according to the maximum severity.

Drug-related Serious Adverse Events

None of the reported AEs were assessed as severe. The maximum severity of any AE was moderate. No SAEs were reported in either adolescent or adult participants. All related AEs were assessed as mild in severity. There were no reports of moderate or severe TEAEs related to study treatment.

Discontinuations and Interruptions Due to Adverse Events

There were no discontinuations and interruptions due to adverse events. This was a single-dose study.

Clinical Laboratory Evaluation, Vital Signs and Other Observations Related to Safety

All 28 participants had at least one biochemistry result (excluding PPIX results) outside of the normal range, however, these were assessed by the Investigator as not clinically significant apart from results in four participants during the study, none of which were assessed as related to study treatment. Abnormal urinalysis results observed throughout the study were assessed in 24 participants by the Investigator as not clinically significant, except for one case of haematuria that was assessed as not related to study treatment.

Abnormal values for blood pressure, heart rate, and temperature were observed in 16 participants at various timepoints during the study. However, only one of these abnormalities was assessed as clinically significant by the Investigator. This assessment was given to a blood pressure value at the Screening visit.

None of the reported abnormalities in vital signs and physical examination findings were SAEs or AEs leading to discontinuation.

2.3.3. Discussion on clinical aspects

The submitted study (CUV052) was a phase II open-label, non-randomized, multi-centre clinical Study to evaluate the pharmacokinetics, safety and tolerability of afamelanotide, and the changes in melanin density of the skin by reflectance spectrophotometry in adults and adolescents (12 to 17 years of age)

with erythropoietic protoporphyria (EPP). Twenty-eight participants were enrolled, 14 adolescents and 14 adults.

Efficacy & Pharmacokinetics

Pharmacokinetic results and melanin density results are pending. The Applicant remarks that full efficacy results, including melanin density (a pharmacodynamic measure), are expected to be available by January 2026.

Safety

The safety of SCENESSE was generally comparable between adolescent and adult EPP patients. Reported adverse events were in line with the known safety profile when SCENESSE is used in adults. No new safety concerns were noted. However, the significance of the findings is limited by the small number of participants in the safety population.

3. Rapporteur's overall conclusion and recommendation

The Applicant has submitted the interim report presenting only the safety data of a completed paediatric study for SCENESSE, a phase II open-label, non-randomized, multi-centre clinical study to evaluate the pharmacokinetics, safety and tolerability of afamelanotide, and the changes in melanin density of the skin by reflectance spectrophotometry in adolescents (12 to 17 years of age) and adults with erythropoietic protoporphyria (EPP) (CUV052).

No major concerns with regards to safety were noted. Although the safety population was very limited.

Pharmacokinetic results and melanin density results from study CUV052 are pending.

No claims or proposals for updates of the product information are made in this submission.

Once the full dataset from study CUV052 is available, including pharmacokinetic results and melanin density results, prompt submission of a type 2 variation for assessment of the data would be expected.

The benefit-risk balance for the approved indications remains favourable.

☒ **Fulfilled**