

A Study to Evaluate the Pharmacokinetics of Afamelanotide in Patients with Erythropoietic Protoporphyrria (EPP)

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

[Short Title: PK EPP Study]

Protocol No: CUV052

Final Version 1.3: 23 February 2024

EU trial number: 2023-507311-35-00

SPONSOR

CLINUVEL EUROPE LIMITED

10 Earlsfort Terrace,
Dublin 2, D02 T380
Ireland

Phone: +353 15134932

Fax +353 1901 0172

This study will be conducted in compliance with Good Clinical Practices (GCP) and ICH guidelines, and all patient study documents will be archived by CLINUVEL PHARMACEUTICALS LIMITED.

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SIGNATURES OF AGREEMENT FOR PROTOCOL AND AMENDMENTS

Protocol Title: A Study to Evaluate the Pharmacokinetics of Afamelanotide in Patients with Erythropoietic Protoporphyrria (EPP)

Protocol Final Version 1.3: 23 February 2024
Principal Investigator: I have read this protocol and agree to conduct the study as outlined herein, complying with the obligations and requirements of clinical investigators and ICH Guidelines. Name of Principal Investigators: Investigational Site Name: Investigational Site Address: Signature: _____ Date: _____
Study Director, Sponsor: Name of Sponsor Representative: [REDACTED] Title of Sponsor Representative: [REDACTED] Signature: _____ Date: _____

PROTOCOL SYNOPSIS

Name of company: CLINUVEL EUROPE LTD.	Name of finished product: SCENESSE® 16 mg implant	Name of active ingredient: Afamelanotide
Title of study: A Study to Evaluate the Pharmacokinetics of Afamelanotide in Patients with Erythropoietic Protoporphyria (EPP)		
Study number: CUV052		
Study period: 90 days		
Recruitment period goal: 2 months		
Objectives: <i>Primary objective</i> • To determine the pharmacokinetics of afamelanotide following administration of afamelanotide to adolescent and adult EPP patients. • To determine the relative comparability of the PK profiles of afamelanotide in adolescent and adult EPP patients. <i>Secondary objectives</i> • To determine the safety and tolerability of afamelanotide in adolescent and adult EPP patients. • To determine the changes in melanin density of the skin in EPP patients by reflectance spectrophotometry. • To compare the changes in melanin density in adolescent and adult EPP patients following afamelanotide treatment.		
Methodology: Twenty-eight patients will be enrolled in the study and will receive one 16 mg SCENESSE® implant. The study will recruit fourteen adolescent and fourteen adult patients. Blood samples will be collected for analysis of afamelanotide plasma concentrations at baseline (prior to implant administration) and on Day 0 [REDACTED] Melanin density will be measured on Days 0, 7, 14, 28, 60 and 90. Safety monitoring will be performed up to 90 days inclusive.		
No. of participants planned: 28 (14 adults and 14 adolescents)		
Treatment: Afamelanotide 16mg implant.		

Diagnosis and main criteria for entry:

To be eligible to enter the study, volunteers must meet the following ***inclusion criteria***:

- Fourteen EPP adult patients aged between 18 and 70 years (inclusive) and fourteen EPP adolescents aged between 12 and 17 (inclusive)
- BMI between 15 and 30 kg/m²
- >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 patients)
- Able and willing to follow the Protocol requirements, including refraining from the use of tanning products and excessive ultraviolet (UV) light exposure from the start of the study until Day 90.

Exclusion Criteria

To be eligible to enter the study, patients must not meet any of the following ***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 m²)
- Any contraindication to blood sampling
- Female who is 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 the implant administration
- Sexually active man with a partner of child-bearing potential (pre-menopausal, not surgically sterile) who is not using adequate contraceptive measures, as described above

- Any factor that may interfere with the skin reflectance measurements (e.g. excessive moles, freckles or excessively hairy skin)
- Current cigarette smokers
- History of drug abuse, licit or illicit
- Regularly drinks 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
- Has received afamelanotide in the last 60 days
- Has donated 400 mL or more of blood or had significant blood loss during the eight weeks preceding screening.

Test product:

Afamelanotide 16 mg contained in a poly(D,L-lactide-co-glycolide) implant core.

Dose:

One SCENESSE® 16 mg implant

Participants who successfully complete the study will be offered one additional commercial implant outside of the protocol.

Mode of administration:

Subcutaneous administration.

Reference therapy: None

Criteria for evaluation:Primary Endpoints:

The following pharmacokinetic (PK) parameters will be assessed as primary endpoints:

- $C_{\max}$ (maximum observed plasma concentration).
- $AUC_{(0-t)}$ (area under the plasma concentration versus time curve from zero to last observed concentration at time t).

Secondary Endpoints:

The following PK parameters will be assessed as secondary endpoints:

- $AUC_{(0-\infty)}$ (area under the plasma concentration curve extrapolated to infinite time).
- $t_{\max}$ (time to maximum observed concentration).
- $t_{1/2}$ (apparent plasma concentration half-life).
- λ_z (elimination rate constant).

Other secondary endpoints:

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

Statistical Methods (exploratory):

Plasma afamelanotide concentrations will be used to determine AUC_{0-t} , $C_{\max}$, $AUC_{0-\infty}$, $t_{\max}$, $t_{1/2}$ and λ_z for each group (adolescents from 12 to 17 years of age and adults). From these data,

descriptive statistics will be calculated for each parameter per group (group 1 adolescents and group 2 adults). The PK profiles in adults and adolescents will primarily be characterised by AUC_{0-t} and C_{max} . An analysis of covariance (ANCOVA) model will be fitted to naturally log transformed $AUC_{(0-t)}$ and C_{max} with fixed terms for group (adult or adolescent), study centre and a covariate for body weight. Estimates of geometric mean ratios (GMR) together with the corresponding 90% confidence intervals (CI) will be derived for the comparisons of Area Under the Curve ($AUC_{(0-t)}$) and C_{max} for adults versus adolescents. The point estimate and CI for the GMR will indicate the relative comparability of the PK profiles when afamelanotide is administered to adults compared to adolescents. All other PK parameters will not be subject to inferential statistical analysis and will just be summarised descriptively.

Changes from baseline for melanin density will be calculated for each anatomical site at each assessment time-point per group (adults and adolescents) and for all patients as a single group. Descriptive statistics will be calculated for each anatomical site at each time-point per group and for all patients as a single group. The time course of changes in melanin density from baseline will be determined for each patient. The melanin density per timepoint in each group will be compared.

Changes in melanin density at each time-point at each anatomical site, as well as at usually exposed sites, unexposed sites and across all sites together, in adults compared to adolescents will be assessed using ANCOVA with fixed terms for group (adult or adolescent), study centre and a covariate for baseline melanin density. From the same ANCOVA model, within group changes in melanin density at each time-point will be assessed. If the assumptions underlying ANCOVA are not upheld, then a Wilcoxon rank sum test (stratified by study centre) will be performed for comparing adults and adolescents. Within group changes will then be assessed using a Wilcoxon signed rank test.

Safety data

The number of patients with TEAEs will be summarised by MedDRA preferred term and body system. TEAEs will be further summarised by intensity, seriousness, outcome and relationship to study drug. Patients who prematurely terminate treatment due to AEs related to study medication will be summarised.

STUDY FLOW CHART

Study Procedure	Study Day									
	-7 to -1	0 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 patient consent. ² PK blood samples will be taken pre-dose and at ■ 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).										

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate aminotransferase
AUC _(0-t)	Area under the plasma concentration curve from administration to last observed concentration at time t
AUC _(0-∞)	Area under the plasma concentration curve extrapolated to infinite time
BLQ	Below the Limit of Quantification
CFR	Code of Federal Regulations
CI	Confidence Interval
CK	Creatine kinase
C _{max}	Maximum plasma concentration
CRF	Case Report Form
CRP	C-Reactive Protein
CS	Clinical Specialist
DPA	Data Protection Authority
DPO	Data Protection Officer
EPP	Erythropoietic protoporphyria
FDA	Food and Drug Administration
FPI	First-patient-in
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
GMR	Geometric Mean Ratio
β-HCG	β-Human chorionic gonadotrophin
HREC	Human research ethics committee
IB	Investigator's Brochure
ICH	International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMP	Investigational Medicinal Product
ITT	Intention-to-treat
LDH	Lactic dehydrogenase
LPI	Last-patient-in
LPLV	Last-patient-last-visit
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
Mm	Millimeter
α-MSH	Alpha melanocyte stimulating hormone
NDP-α-MSH	[Nle(4), D-Phe(7)] α-melanocyte-stimulating hormone
PCV	Packed Cell Volume
PI	Principal Investigator
PK	Pharmacokinetics
PPIX	Protoporphyrin IX

RBC	Red blood cell (count)
SAE	Serious adverse event
SAP	Statistical analysis plan
SOM	Study operating manual
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{\max}$	Time until $C_{\max}$ is reached
$t_{1/2}$	Apparent plasma concentration half-life
UV	Ultraviolet
WBC	White blood cell (count)
WMA	World Medical Association
λ_z	Terminal rate constant

1.0 ETHICS

1.1 Human Research Ethics Committee (HREC)

An appropriate IRB/HREC will approve the protocol and the Participant Information and Informed Consent Form before the study is initiated. Documentation of this approval will be provided to the Sponsor and/or the Sponsor's designee. The Investigator(s) will have the following responsibilities:

- Obtain IRB/HREC approval of the protocol, informed consent documentation and any advertising material to recruit patients;
- Obtain IRB/HREC approval for any protocol amendments and informed consent documentation revisions before implementing the changes;
- Provide the IRB/HREC with any information requested before or during the study;
- Submit progress reports to the IRB/HREC, as required, during the conduct of the study;
- Request review and approval of the study as needed;
- Provide copies of all IRB/HREC re-approvals and relevant communication to the Sponsor; and,
- Notify the IRB/HREC as required of all serious and unexpected adverse events related to the study medications that occur or are reported by the Sponsor.

1.2 Ethical Conduct of the Study

This study will be conducted in accordance with the Declaration of Helsinki (see Appendix 1), its revisions (Scotland, October 2000 and incorporating Notes of Clarification - Washington, 2002 and Tokyo, 2004 and Seoul 2008) and ICH guidelines for Good Clinical Practice (GCP) governing the conduct of studies, and all applicable local regulations. The Investigator will ensure that the study is conducted in accordance with prevailing local laws and regulations. The Investigator is responsible for reporting to the Sponsor, the authorities and the IRB/HREC any modifications, safety updates, amendments, and violations of the protocol that impact on patient safety.

1.3 Participant Information and Informed Consent

Prior to any screening procedures, the Investigator will explain to each participant the nature of the study, its purpose, procedures to be performed, the necessity for withdrawal of prohibited medication, expected duration, and the benefits and risks of study participation. After this explanation and before any screening procedures are performed, the patient must voluntarily sign an informed consent statement in the presence of a witness, if applicable.

1.4 Protocol Amendments

Changes in any portion of this protocol will be documented in the form of a protocol amendment and signed by the appropriate CLINUVEL personnel and the Investigator.

Depending on the requirements of the study centre's IRB/HREC and relevant Competent Authority (where applicable), protocol amendments will either need to be submitted for approval or advised by notification. Where formal approval is required, the revision will not be implemented until approval has been obtained.

1.5 Confidentiality

All information provided to the Investigator by the Sponsor, including clinical observations at the investigative centre, are held strictly confidential and confined to the clinical personnel involved in conducting the study, under the supervision of the Investigator. This includes, but is not limited to preclinical data, protocols, Case Report Forms (CRFs) and verbal or written communications. This information is related in confidence to the IRB/HREC or other committees functioning in a similar capacity. A coded number will identify all reports, patient samples, and data published or submitted to third parties in order to maintain patient confidentiality.

All data will be obtained and held in accordance with the General Data Protection Regulation (GDPR) and all applicable regulations. Personal data to be collected for the purposes of the research are subject's health data, year of birth, age, sex, skin type, contraceptive methods used (if applicable) and results of examinations as required by the research. Personal identifiable information that will be collected are the subject's year of birth, age, sex and skin type and these will be linked with the subject's study number. Individuals from Regulatory Agencies and authorised representatives of the Sponsor, including the Clinical Specialist (CS), may need to access the subjects' confidential medical records and study data for monitoring and auditing of the study. This information will include identifiable data and will not leave the study site.

Data collected for this study will be recorded in electronic format. Only personnel authorised by the Sponsor will handle the data collected from the site. Access to the study database will be protected by password and limited to authorised individuals. The database will be locked after data cleaning and query resolution at the end of the study. In the event of a data breach, it will not be possible to identify subjects from the paper records or the study database. Confidentiality arrangements will be brought to the attention of subjects through the patient information sheet and informed consent form.

1.6 Data Protection

1.6.1 Data protection measures

The study site and study Sponsor will implement technical and organisational measures to ensure a level of security appropriate to the risk presented by data processing and transfer.

These measures will include:

- Raising awareness among data handlers
- Authentication of users
- Access management
- Incident management
- Securing of workstations/offices
- Protection of internal IT networks
- Securing of servers and websites
- Secure archiving processes
- Supervision of maintenance and data destruction
- Management of subcontractors/third parties
- Securing of exchanges with outside organisations
- Physical protection of premises
- Use of cryptographic functions

All study Sponsor personnel are required to work with a company issued account on company devices with security measures such as two-factor authentication by password and an authentication application on their devices. Employees are required to store information on company servers or on their company issued devices and access is departmentalised so that only personnel with a need to access certain information may access those specific servers. The study Sponsor employs an IT service provider that provides IT support and monitoring services including protection against potential phishing emails by filter. All office sites are secured by locks at all times with security measures in place. Policies are in place that require employees to report potential data breaches to the Data Protection Officer (DPO) and services are in place to flag if there are any unauthorised logins.

A contract will be in place between the study Sponsor and study Institution, detailing all data protection safeguards to be implemented by both parties.

1.6.2 Data security breach procedures

In case of a data security breach, the following measures will be implemented. The DPO will be involved in the response process.

Immediate response

- A dedicated incident response team will be assembled to assess and manage the breach.
- Affected systems will be identified and isolated to prevent further unauthorised access or data loss.

Notification

- Key internal stakeholders, including management, IT and legal teams, will be notified about the breach.
- The breach will be reported to the relevant Data Protection Authority (DPA) within 72 hours, as required by GDPR.

Assessment

- A thorough assessment will be conducted to determine the scope, nature and impact of the breach.
- The type of data that has been compromised will be identified, including personal data as covered by GDPR.

Communication

- A clear communication plan to notify affected individuals and, if necessary, the general public, will be developed.
- Affected individuals will be notified without undue delay. Information about the nature of the breach, potential risks and protective measures will be provided.

Remediation

- Vulnerabilities that led to the breach will be addressed to prevent future incidents.
- If passwords are compromised, password resets will be enforced for affected users.
- Necessary security updates and patches to systems will be applied.

Legal and compliance

- Legal advice will be sought to understand and comply with the relevant laws and regulations.
- Detailed records of the breach, investigation and response efforts will be maintained for regulatory compliance.

Post-incident review

- A post-incident review will be conducted to identify the root cause of the breach and to implement measures to prevent reoccurrence.
- The incident response plan will be reviewed and updated based on lessons learned from the breach.

Training and awareness

- Training will be provided to employees on security best practices as well as the importance of reporting incidents promptly.
- Awareness campaigns will be conducted to educate users about phishing threats and social engineering tactics.

Engage with authorities

- During the investigation, DPAs and other relevant authorities will be collaborated with.

2.0 STUDY PERSONNEL AND STUDY ADMINISTRATION

By signing the protocol, the Principal Investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor, except when required to protect the safety, rights, or welfare of patients;
2. Personally conduct or supervise the study (or investigation);
3. Inform the patients that the drug is being used for investigational purposes;
4. Ensure that the requirements relating to obtaining informed consent and HREC review and approval meet ICH-GCP guidelines and the Code of Federal Regulations (21 CFR Parts 50 and 56);
5. Report to the Sponsor any adverse events (AEs) and/or safety information that occur in the course of the study, in accordance with the protocol;
6. Read and understand the Investigator's Brochure (IB), including potential risks and safety profile of the drug;
7. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments;
8. Maintain adequate and accurate records and make those records available for inspection by the Sponsor, the Sponsor's designated representative, or any agency authorised by law;
9. Ensure that an HREC that complies with the requirements of the ICH-GCP and the Code of Federal Regulations (21 CFR Part 56) will be responsible for initial and continuing review and approval of the study;
10. Promptly report to the HREC and the Sponsor all changes in the research activity and all unanticipated problems involving risks to patients or others (to include amendments);
11. Make no changes in the research study without approval, except when necessary to eliminate hazards to the patients; and,

12. Comply with all other requirements regarding the obligations of the clinical investigators and all other pertinent requirements listed in the ICH-GCP guidelines.

3.0 INTRODUCTION AND STUDY RATIONALE

3.1 Background

As a response to exposure of the skin to ultraviolet (UV) radiation and subsequent actinic damage, an increase is seen in the secretion of alpha-melanocyte stimulating hormone (α -MSH)¹, which in turn initiates the activation, release and transfer of (eu)melanin within epidermal melanocytes. This process is called melanogenesis and is the mechanism by which skin obtains photoprotection. UV light is known to enhance production and release of α -MSH.

Afamelanotide is a potent analogue of α -MSH and an agonist of the melanocortin-1 receptor which activates the production of eumelanin in the melanocyte without preceding cellular damage as a response to UV radiation². In several clinical studies, afamelanotide was shown to stimulate eumelanin production and elicit photoprotective properties as assessed by protection against damage to the skin following exposure to controlled UV radiation.

SCENESSE[®] is a 16mg afamelanotide controlled-release implant. In December 2014, marketing authorisation for SCENESSE[®] was granted in Europe under exceptional circumstances (Article 14(8) of Regulation (EC) No 726/2004) and in Australia in October 2020 for the prevention of phototoxicity in adults with erythropoietic protoporphyria (EPP) and in October 2019 by the Food and Drug Administration (FDA) for the increase pain-free light exposure in adult patients with a history of phototoxic reactions for EPP.

Pharmacokinetic studies have been performed in healthy adults. No pharmacokinetic studies have been performed in adolescent or adult EPP patients. The objective of the proposed study is to investigate the pharmacokinetic and pharmacodynamic properties of the 16 mg afamelanotide implant in EPP patients (adults and adolescents), determining the safety and tolerability in adolescent and adult EPP patients and investigate changes in melanin density in the skin in adolescent and adult EPP patients.

3.2 Investigational Agent

Afamelanotide is a synthetic analogue of the natural melanocortin α -MSH.

The study drug is in the form of a 16mg implant for subcutaneous administration.

3.3 Study design

The proposed study CUV052 is an open label study to compare the pharmacokinetics, safety and tolerability of afamelanotide together with changes in melanin density of the skin following administration of afamelanotide to adolescent and adult EPP patients.

Twenty-eight patients will be enrolled in the study and will receive one 16 mg SCENESSE® implant. The study will recruit fourteen adolescent and fourteen adult patients who will be followed up for 90 days. After the full completion of the study (after Day 90±7), CLINUVEL will make one 16 mg SCENESSE® implant available to participants as compassionate use. It is the participants' choice to receive the additional implant. Commercial stock may be used for compassionate use as this is outside scope of the protocol.

Blood samples will be collected for analysis of afamelanotide plasma concentrations at baseline (prior to implant administration) and at [REDACTED] hours post-administration to measure afamelanotide plasma levels. The pharmacokinetic analysis will be performed at a central laboratory contracted by CLINUVEL. To analyse afamelanotide plasma concentration, a maximum of 20ml of blood will be collected from each participant at each time point mentioned above. Whole blood samples will be processed into plasma as per the laboratory manual. The samples will be stored frozen at the study site laboratory and then shipped to the central laboratory for analysis. After completion of the study, the study samples may be kept deep frozen until six months after the issue of the draft Study Report. . For further information, please refer to the CUV052 SOM.

Blood and urine samples collected for the safety monitoring at Screening, Days 14, 60 and 90 or Early Termination Visits, if applicable, will be analysed at the local laboratory and destroyed after immediately after analysis.

Melanin density will be measured on Days 0, 7, 14, 28, 60 and 90. Safety monitoring will be performed up to 90 days inclusive. Safety will be monitored throughout the study.

3.3 Conclusion and Risk/Benefit Assessment

The overall risk of this study protocol is minimal. SCENESSE® (afamelanotide 16mg) has been shown to be effective in providing systemic photoprotection in EPP and has obtained marketing authorisation in the European Union (October 2014), the United States (October 2019) and Australia (October 2020) for the treatment of adult EPP patients. The results of the clinical trials conducted by CLINUVEL, as well as of one long term observational study and the ongoing post-authorisation

pharmacovigilance activities, confirm the positive safety profile of afamelanotide in adults³⁻⁵. [REDACTED]

[REDACTED] The most common side effects found at this dose and frequency of dosing were nausea, flushing, headache, and some cases of vomiting.

In this study, the pharmacokinetics, effect on dermal melanin density and the safety of afamelanotide will be investigated in adolescent and adult patients with EPP.

4.0 STUDY OBJECTIVES

4.1 Primary Objective

- To determine the pharmacokinetics of afamelanotide following administration of afamelanotide to adolescent and adult EPP patients.
- To determine the relative comparability of the PK profiles of afamelanotide in adolescent and adult EPP patients.

4.2 Secondary Objectives

- To determine the safety and tolerability of afamelanotide in adolescent and adult EPP patients.
- To determine the changes in melanin density of the skin in EPP patients by reflectance spectrophotometry.
- To compare the changes in melanin density in adolescent and adult EPP patients following afamelanotide treatment.

5.0 INVESTIGATIONAL PLAN

5.1 Overall Design and Plan of the Study

This is a multi-centre pharmacokinetic study in EPP patients.

5.2 Selection of Study Population

Adolescent and adult EPP patients will be recruited according to an established recruitment procedure. All patients will be provided with a Study Information Sheet and Informed Consent Form and will undergo a screening evaluation that will determine eligibility for entry into the study. Fourteen adolescent and fourteen adult EPP patients will be recruited.

5.2.1 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/m²
- >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 patients)
- 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.

5.2.2 Exclusion Criteria

To be eligible to enter the study, patients must not meet any of the following **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 m²)
- Any contraindication to blood sampling
- Female who is 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 the implant administration
- Sexually active man with a partner of child-bearing potential (pre-menopausal, not surgically sterile) who is not using adequate contraceptive measures, as described above
- Any factor that may interfere with the skin reflectance measurements (e.g. excessive moles, freckles or excessively hairy skin)

- Current cigarette smokers
- History of drug abuse, licit or illicit
- Regularly drinks 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
- Has received afamelanotide in the last 60 days
- Has donated 400 mL or more of blood or had significant blood loss during the eight weeks preceding screening.

5.2.3 Recruitment Management

In this study involving up to 28 patients (14 adults and 14 adolescents aged 12 and over), the patients will be recruited through the Principal Investigator's records/database, patient association and area referrals.

The potential subjects will be provided with a Patient Information Sheet with information regarding the study. Prior to providing informed consent, the potential participants will have the opportunity to discuss the study with the investigator and/or authorised medical staff on the trial team. The patients will also be able to discuss study participation with relatives, friends, their general practitioner, or other health workers. The Screening Visit (Admission Visit) procedures for the study will only occur after the informed consent process is performed and a signed and dated Informed Consent Form has been obtained from the patient and/or the legal representative.

Please refer to the CUV052 Study Operating Manual (SOM) for a detailed description of the method for patient recruitment management.

5.2.4 Withdrawals and Replacement of Participants

A discontinuation occurs when a patient does not complete the study as required by the study protocol. Patients will be free to discontinue their participation in this trial at any time for any reason. In addition, patients may be withdrawn from the trial at the discretion of the Investigator or medically qualified nominee. A patient may withdraw for any one of, but not limited to, the following reasons:

- Informed consent withdrawn by the patient
- Patient experienced an adverse event requiring study discontinuation
- When the Investigator's or nominee's best professional judgment would indicate that it would be in the patient's best interest to be withdrawn

- Violation of inclusion/exclusion requirements.

The reasons for withdrawal or discontinuation of a patient will be recorded in the patient's CRF. If an AE is the reason for discontinuation, the event must be followed up and documented as described in the present protocol.

If the patient discontinued for any reason after the enrolment into the study, the patient will be asked to attend a study termination visit. Although this visit is voluntary, it is highly recommended that the patient attends this visit for safety monitoring. If the patient agrees to undergo the study termination visit procedures, the patient discontinuation visit described in the present protocol should be performed at the time of study discontinuation, or as soon as possible after discontinuation. These will be documented in the CRF.

Patients may not be replaced. Data compiled to the point of discontinuation will be used for 'intent to treat' analysis. These data will be analysed only against the time-points for which they were collected. Where no result has been obtained for a time-point for these parameters, the patient will not be included in the analysis of data for that time-point. Patients violating any of the inclusion and exclusion criteria will be described as protocol violators.

5.3 Study Medication

5.3.1 *Description of Study Medication*

Afamelanotide implant is a sterile biodegradable and biocompatible poly(D,L-lactide-co-glycolide) polymer implant core containing 16 mg of afamelanotide.

5.3.2 *Treatment Groups*

There is one treatment for both groups (adolescent and adult EPP patients) in this study (open-label study). As such, all patients who satisfy the inclusion/exclusion criteria will be allocated a study patient number and receive afamelanotide. Study patient number allocation will be detailed in the CUV052 SOM.

The groups consist of:

- Fourteen EPP adolescents aged 12 to 17 (inclusive)
- Fourteen EPP adult patients

Open label study: Twenty-eight (28) patients receiving afamelanotide.

5.3.2 Dosage and Administration of Study Medication

Afamelanotide implant will be administered at Baseline, as described in the CUV052 SOM.

5.3.3 Packaging and Labeling of Study Medication

The implants will be packaged in amber glass vials. The label will include information in compliance with the local regulatory requirements for clinical trials / investigational medicinal products.

5.3.4 Storage and Accountability

Study medication will be maintained in a safe and secure (locked, restricted access) location and kept at 2-8°C. The expiry or retest date for each afamelanotide vial will be printed on the label. The Investigator will agree not to supply study drug to any persons other than those enrolled in the study. Current and accurate drug receipts, inventory, accountability and dispensing records will be kept for all study drug in the Pharmacy/Investigator Site File(s), and upon study completion, a final inventory and reconciliation of all study drug will be compiled. After completion of the study, all remaining study drugs (which may include unused study drug, expired study drug or empty glass vials) will be returned to CLINUVEL or designee, as instructed by CLINUVEL. The Clinical Monitor [also referred to as CS] will provide instructions to the center for any drug-related shipments.

5.3.5 Compliance

Data related to the administration of the study drug will be recorded on the CRF.

5.4 Prior and Concomitant Therapy

5.4.1 Prior Therapy

All patients will be instructed to report to the Investigator any treatments, prescribed medicines, over-the-counter medications, dietary supplements or nutraceuticals that are being used. Use of any other prior and concomitant therapy which may interfere with the objective of the study within seven days prior to the Screening period, will need to be recorded.

5.4.2 Concomitant Therapy

The Investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the study and these will be fully documented in the patients' medical records and CRF. In the event that a patient has taken a medication which has not been pre-approved, the

Investigator will make a decision to continue or discontinue the patient, based on whether the medication may interfere with the objectives of the study.

For complete information, during the study, contraceptive therapy must not be changed.

5.4.3 Description of Study Days

Screening Period (up to Day -7)

The Screening Visit will only occur after the informed consent process is performed and a signed and dated informed consent form has been obtained from the patient.

The Investigator will assess eligibility for the study after the following procedures are performed and information collected:

- Inclusion and exclusion criteria review
- Complete medical and surgical history review
- Demographic information, including sex, year of birth, age
- Height, weight and BMI measurement
- General physical examination
- Vital signs
- Blood and urine specimen collection for clinical laboratory evaluations (haematology, serum chemistry and urinalysis)
- Serum β -HCG pregnancy test for females of child-bearing potential.

Study Period

Day 0

The Investigator will re-assess patient's eligibility for study participation by confirming that all inclusion and exclusion criteria are still fully met. After patient's eligibility has been confirmed by the Investigator (in collaboration with the Principal Investigator), the following procedures will be performed:

- Vital signs
- Blood sample collection for PK measurement prior to implant administration
- Pregnancy test (urine dipstick) for female of child-bearing potential only
- Melanin density measurement
- Full body posterior and anterior photography

- AE review (before and after the implant administration)
- Concomitant medication review
- Afamelanotide implant administration (after all other evaluations have been completed).
- Blood samples collected for PK analysis at [REDACTED] after the implant administration.

[REDACTED]

The following procedures will be performed:

- AE review
- Concomitant medication review
- PK samples will be taken [REDACTED] after the implant administration on Day 0

[REDACTED]

The following procedures will be performed:

- AE review
- Concomitant medication review
- PK samples will be taken [REDACTED] after the implant administration on Day 0

[REDACTED]

The following procedures will be performed:

- AE review
- Concomitant medication review
- PK sample will be taken [REDACTED] after the implant administration on Day 0

[REDACTED]

The following procedures will be performed:

- Melanin density measurement
- AE review
- Concomitant medication review
- PK sample will be taken [REDACTED] after the implant administration on Day 0

Day 14

The following procedures will be performed:

- Blood and urine specimen collection for clinical laboratory evaluations (haematology, serum chemistry and urinalysis)
- Vital signs
- Pregnancy test (urine dipstick) for female of child-bearing potential only
- Melanin density measurement
- AE review
- Concomitant medication review

Day 28

The following procedures will be performed:

- Melanin density measurement
- AE review
- Concomitant medication review

Day 60

The following procedures will be performed:

- Blood and urine specimen collection for clinical laboratory evaluations (haematology, serum chemistry and urinalysis)
- Vital signs
- Pregnancy test (urine dipstick) for female of child-bearing potential only
- Melanin density measurement
- AE review
- Concomitant medication review

Day 90 (or Early Termination)

The following procedures will be performed. For an Early termination visit, the following procedure will only be performed if agreed by participants:

- Height and weight measurement

- Physical examination
- Blood and urine specimen collection for clinical laboratory evaluations (haematology, serum chemistry and urinalysis)
- Vital signs
- Melanin density measurement
- Full body posterior and anterior photography
- AE review
- Concomitant medication review

5.4.4 Study Procedures Flowchart

Please refer to the section Study Flow Chart of the protocol.

5.4.5 Methods of Assessment

5.4.5.1 Pharmacokinetic Samples

Afamelanotide concentrations will be measured in plasma using a validated assay. Procedures for blood sampling are outlined in the CUV052 SOM as per the central laboratory guidance.

5.4.5.2 Melanin Density

Melanin Density will be measured on Days 0, 7, 14, 28, 60 and 90 or Early Termination Visit if applicable, using a spectrophotometer according to a standardised procedure outlined in the CUV052 SOM. Six different anatomical sites will be assessed: 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.

5.4.5.3 Safety Variables

A blood and urine sample will be taken for safety monitoring at Screening, Days 14, 60 and 90 or Early Termination Visit, if applicable.

The following laboratory tests will be performed using a local laboratory:

Biochemistry

Sodium	Albumin	Total Cholesterol
Potassium	Protein	Total Triglycerides
Chloride	Total Bilirubin	Protoporphyrin IX (PPIX)
Bicarbonate	Gamma Glutamyl Transferase (GGT)	Testosterone*
Glucose	Alkaline Phosphatase (ALP)	Estrogen*
Urea	Alanine Aminotransferase (ALT)	IGF-1*
Creatinine	Aspartate Aminotransferase (AST)	*Only participants <18 years old
Glomerular Filtration Rate	Lactate Dehydrogenase (LDH)	
Phosphate	Creatine Kinase (CK)	
Total Calcium	C-Reactive Protein (CRP)	

Haematology

Haemoglobin	Neutrophils
Red Blood Cell Count (RBC)	Lymphocytes
White Blood Cell Count (WBC)	Monocytes
Packed Cell Volume (PCV)	Eosinophils
Platelets	Basophils

Urinalysis

Protein	Glucose
Blood	Ketones
Bilirubin	pH
Specific Gravity	Nitrites
Urobilinogen	

For females of childbearing potential, a pregnancy test will be performed on the serum sample collected at Screening Visit and with a urine dipstick on Days 0, 14 and 60 or at Early Discontinuation Visit. Pregnancy testing not needed for adolescents if there is no risk of pregnancy present according to the investigator. The Investigator will sign and date all laboratory reports and review all laboratory test results. The Investigator will evaluate the clinical significance of all values outside the reference range and will document within the laboratory report as well as in the patient's CRF. If a laboratory value is outside the reference range and felt to represent a clinically significant change from the baseline value, this will be reported as an AE in the patient's medical notes and on the adverse event CRF page. An assessment of this AE will be made by the Investigator, in particular regarding the relationship of the event to the study drug and event expectation (expected/unexpected).

General Physical Examination

A general physical examination will be performed at Screening Visit and on Day 90 or Early Discontinuation Visit. Any changes from baseline examination will be evaluated and noted on the CRF, as well as in the patient's medical notes.

Weight, Height and BMI

Weight in kilograms and height in centimetres will be recorded at Screening and Day 90 or Early Discontinuation Visit.

Vital Signs Measurements

Vital signs (blood pressure, temperature and pulse rate) will be recorded at Screening Visit and on Days 0, 14, 60 and 90 or Early Discontinuation Visit in a standardised manner, i.e. after the patient has rested in a sitting position for five minutes.

Adverse Events

An AE is defined as any untoward medical event (clinical or laboratory) experienced by a patient during the course of a clinical trial, whether or not it is related to the investigational product. An AE may be a symptom, sign, or abnormal finding or test result. Whenever possible, the Investigator will group together into a single term, signs and symptoms that constitute a single diagnosis. For example, cough, rhinitis, and sneezing might be grouped together as "upper respiratory tract infection."

The Investigator will monitor each patient closely for the development of AEs, and any adverse experience spontaneously reported by or elicited from the patient itself or observed by the Investigators (physician or study staff) will be recorded in the patient's medical notes and on the appropriate AE page log of the CRF, when applicable. Reporting of AEs by participants will be elicited by nonspecific questions such as "Have you noticed any problems?" or "Do you feel different in any way?". Participants will be encouraged to report AEs at their onset. The study period during which all AEs (including serious adverse events (SAEs) must be reported begins after written informed consent has been obtained and ends at least three months after the date of the last injection administration, depending on the Investigator's medical judgement. For patients who are removed from therapy because of disease progression or toxicity, AEs will be reported for a minimum period of an additional three months after the cessation of therapy. It is the responsibility of any member of the study site staff to immediately report any suspected AE to the Principal Investigator. The Investigator will assess the AE(s) in the patient's medical notes and provide the date and time of

onset, severity, seriousness, action taken, outcome, date of resolution (or comment that the event is still continuing), relationship to study medication and event expectation.

If a laboratory value is outside the normal range, the physician must comment on the findings in the laboratory report. For any clinical laboratory abnormality, the Investigator will make a judgment as to clinical significance. All clinically significant laboratory abnormalities will be recorded as an AE in the patient's medical notes and on the AE page log of the CRF.

All AEs will be followed up in accordance with GCP. AEs will be graded for severity as defined below:

- **Mild** - The AE is transient and easily tolerated by the patient. Specific action is optional.
- **Moderate** - The AE causes the patient discomfort and interrupts the patient's usual activities.
- **Severe** - The AE causes considerable interference with the patient's usual activities and may be incapacitating or life-threatening.

Outcome of the event must be described as one of the following:

- Recovered without sequelae;
- Recovered with sequelae;
- Not recovered;

The Investigator will be asked to document his/her opinion of the relationship of the event to the study drug as follows:

- **Related** - There are facts or arguments to suggest a causal relationship, i.e. there is a reasonable possibility of a causal relationship between the drug and the AE(s);
- **Not Related** - There is not a reasonable possibility that the AE(s) is/are related to the drug – alternative aetiology, diagnosis, or explanations for the AE(s) exist, or the time from suspect drug intake make a relationship improbable.

Serious Adverse Events

A SAE is any AE occurring at any dose that results in any of the following outcomes:

- Death (due to any cause);
- Is life-threatening;

- Requires inpatient hospitalisation or a prolongation of an existing hospitalisation;
- Results in a persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect;
- Important medical events that may not be immediately life threatening, result in death or require hospitalisation but may be considered a SAE when, based upon appropriate medical judgment, they may jeopardise the patient or may require medical or surgical intervention to prevent one of the outcomes listed in the definition above.

Serious Adverse Reaction (SAR)

- An AE that occurs in a clinical trial subject, which is assessed by the sponsor and/or investigator as being serious and as having a reasonable possibility of a causal relationship with the Investigational Medicinal Product (IMP). A SAR can result in any of the outcomes listed above.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

An AE that occurs in a clinical trial subject, which is assessed by the sponsor and/or investigator as being unexpected (according to the applicable product information), serious and as having a reasonable possibility of a causal relationship with the Investigational Medicinal Product (IMP). A SUSAR can result in any of the outcomes listed above.

SUSARs will be reported electronically through Eudravigilance by the CLINUVEL. Fatal or life-threatening SUSARs will be reported as soon as possible but no later than seven days after the sponsor becomes aware of the reaction. CLINUVEL will submit a completed report within an additional eight days. Non-fatal or non-life threatening SUSARs will be reported as soon as possible but no later than 15 days after CLINUVEL become aware of the reaction. The sponsor should promptly notify all concerned investigators/institutions of findings that could adversely affect the safety of the subjects.

Reporting: Any SAE, including death due to any cause, which occurs during this study, has to be reported by telephone to CLINUVEL **within 24 hours** of knowledge by the Investigator. If the Investigator becomes aware of an SAE with a suspected causal relationship to the study drug that occurs after the end of the clinical trial, the Investigator shall, without undue delay, report the SAE to the sponsor.

In addition to this initial report, a SAE form will be completed and sent via facsimile or email to CLINUVEL. All SAEs require initial notification and a written SAE report within 24 hours of knowledge by the Investigator. In addition, all SAEs will be recorded on the patient's medical notes and on the Adverse Events page of the CRF.

Please refer to the CUV052 Safety Management Plan for a detailed description of the procedure.

The responsible Investigator will determine whether the seriousness of the event warrants removal of any patient from the study. The Investigator will institute appropriate diagnostic and therapeutic measures and keep the patient under observation for as long as is medically indicated.

In this study, any pre-arranged (i.e. prior providing written Informed Consent) elective surgery will be excluded as an AE.

5.5 Data Quality Assurance

5.5.1 Data Collection, Monitoring and Auditing

The Investigator and institution will provide direct access to source data/documents and will permit trial-related monitoring, auditing, review by the IRB/ HREC, and regulatory agency inspections. The Sponsor and/or its designee will monitor the study in accordance with GCP. The CS is qualified by training and experience to oversee the conduct of the study. His/her responsibilities include study monitoring (review accuracy and completeness of records, source document checks), evaluation of study data (drug accountability, communication, and written records), monitoring of centre facilities to ensure continued adequacy and adverse event monitoring. The CS maintains regular contact with the investigational centre, through email and telephone contacts and on-site visits to ensure that the investigational plan and regulations governing the conduct of clinical trials are followed. These contacts are also to ensure that timely and accurate data will be submitted, that problems with inconsistent and incomplete data are addressed, and that the centre facilities and management continue to be adequate for this study. Any questions regarding these matters are addressed with the CS.

The CS will evaluate and summarise the results of each visit in written reports, identify any repeat data problems with the Investigator, and specify recommendations for the resolution of noted deficiencies.

Standardised CRF will be provided for each eligible patient in this study only. Patients who provide written informed consent will be identified by a screening number for the purpose of screening. All screening results will be recorded in patient's medical notes and the assigned screening number will be entered on to screening logs, which will be made available for monitoring by CLINUVEL. If a patient fails screening tests (and is therefore declared ineligible to participate), the patient will end their involvement in the study, but may be reviewed at a later date for re-consent and re-screening if considered suitable by the Principal Investigator. This outcome would also be noted on screening logs against the patient's screening number. If the patient successfully satisfies all screening tests and is therefore considered eligible to enter the study, a participant number will be allocated to the eligible patient, which will be used to track the patient for the rest of their involvement in the study. This outcome would also be noted on screening logs. The patient randomisation number will be recorded on all pertinent study related documentation. The patient randomisation number will consist of the assigned centre number and a patient number in sequential order at that study site. CRFs will be completed and available for review and retrieval by the CS, representatives of CLINUVEL, or its delegated representative.

All clinical information requested in the protocol will be recorded on the CRF following GCP.

Before the study starts, the local Laboratory will provide a list of reference ranges for all laboratory tests to be undertaken, current laboratory accreditation/certification and details of the method used for quality control. These will be held by the Investigator and a copy sent to the CS.

Data Management will be sent relevant details e.g. reference ranges. Any change in the laboratory, its procedures, reference ranges etc. during the study must be notified promptly to the CS. The CS will inform Data Management of these changes.

The CS and Investigator will review all CRFs to ensure accuracy, completeness, and compliance with the protocol.

CLINUVEL EUROPE LIMITED, as well as the entities of the CLINUVEL group (based in the United Kingdom, the United States of America, Switzerland, Singapore, Monaco and Australia) will be able to make use of the data associated with the samples. Persons acting on behalf of CLINUVEL EUROPE LIMITED (such as the vendor for data management and statistics, central laboratory) will also be able to make use of the data associated with the samples.

5.5.2 Database Management and Quality Control

The study will be monitored by the CS, and/or representatives of CLINUVEL, or its delegated representative, as frequently as is necessary to determine that data recording and protocol adherence are satisfactory. The CRFs and related source documents will be reviewed in detail by the representatives at each Study Visit, and identified discrepancies will be resolved.

Detailed procedures for data entry, data coding, cleaning and electronic data transfer will be provided in a Data Management Plan.

5.6 Statistical Methods and Determination of Sample Size

5.6.1 Statistical and Analytical Plans

Details of the statistical analysis methods for the pharmacokinetic and pharmacodynamic endpoints are given in Sections 5.7.3 and 5.7.4. A formal statistical analysis plan (SAP) will be prepared prior to completion of the study and before data analysis is undertaken.

5.6.2 Safety Assessment

Assessment of safety will be based on examination of adverse event data and the change from baseline in clinical measurements, including clinical laboratory evaluations, vital signs and physical examination results.

5.6.3 Pharmacokinetic Assessment

The plasma concentrations of afamelanotide will be used for calculation of at least the following pharmacokinetic parameters derived by non-compartmental methods using actual blood sampling times (relative to the corresponding administration time) for patient data:

Primary Endpoints:

- $AUC_{(0-t)}$: 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.
- C_{max} : Maximum observed plasma concentration following treatment administration, taken directly from the data without interpolation.

Secondary Endpoints:

- $AUC_{(0-\infty)}$: 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.
- λ_z : Terminal rate constant.
- $t_{1/2}$: Apparent plasma concentration half-life, calculated as $\ln(2)/\lambda_z$.

Other Secondary Endpoints:

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

From these data, descriptive statistics will be calculated for each parameter per group. The PK profiles in adults and adolescents will primarily be characterised by AUC_{0-t} and C_{max} . An analysis of covariance (ANCOVA) model will be fitted to naturally log transformed $AUC_{(0-t)}$ and C_{max} with a fixed terms for group (adult or adolescent), study centre and a covariate for body weight. Estimates of geometric mean ratios (GMR) together with the corresponding 90% confidence intervals (CI) will be derived for the comparisons of $AUC_{(0-t)}$ and C_{max} for adults versus adolescents. The point estimate and CI for the GMR will indicate the relative comparability of the PK profiles when afamelanotide is administered to adults compared to adolescents. All other PK parameters will not be subject to inferential statistical analysis and will just be summarised descriptively. Descriptive statistics will be calculated for the plasma concentrations of afamelanotide at each nominal blood sampling time point for each group.

5.6.4 Pharmacodynamic Assessment

Changes in melanin density from baseline at each time-point at each anatomical site, as well as at usually exposed sites, unexposed sites and across all sites together, in adults compared to adolescents will be assessed using ANCOVA with fixed terms for group (adult or adolescent), study centre and a covariate for baseline melanin density. From the same ANCOVA model, within group changes in melanin density at each time-point will be assessed. If the assumptions underlying ANCOVA are not upheld, then a Wilcoxon rank sum test (stratified by study centre) will be performed for comparing adults and adolescents. Within group changes will then be assessed using a Wilcoxon signed rank test.

5.6.5 Sample Size

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, and it is not based on any statistical reasoning but is thought to be sufficient to achieve the objectives of the study.

5.6.6 Analysis Plan

A statistical and analytical plan will be prepared prior to commencing the study, detailing all pharmacokinetic and statistical analysis methods.

The clinical report will be produced in two stages. Stage one will include all pharmacokinetics data up to and including [REDACTED] Stage two will then add all remaining data to Day 90.

5.6.6.1 Safety Population

The Safety Population will include all enrolled patients who receive a dose of afamelanotide. This population will be used for baseline and safety summaries.

5.6.6.2 PK Population

The PK Population will include all patients who receive a dose of afamelanotide, do not have any major protocol deviations that would affect the evaluation of PK data, and who have sufficient plasma concentration measurements to enable calculation of $AUC_{(0-t)}$ and C_{max} . This population will be used for the analysis of the PK parameters.

5.6.6.3 Intent to Treat Population

The Intent to Treat (ITT) Population will include all enrolled patients who receive a dose of afamelanotide and who have a measurement of melanin density. This population will be used for the analysis of changes in melanin density.

5.6.6.4 Handling of Missing Data

All available data from patients will be included in the analysis according to the ITT principle. In this single dose study, if patients do not have sufficient plasma concentration measurements to enable calculation of $AUC_{(0-t)}$ and C_{max} , they will be excluded from analysis. Plasma concentrations recorded as below the limit of quantification (BLQ) prior to the first measurable concentration will be assigned a value of zero, otherwise they will be set to missing. Derivations of the PK parameters will be based

only on non-missing data and actual times of blood sampling. The assessment of melanin density will be based on observed data (no imputation for missing values).

5.7 Early Termination of the Study

The study may be terminated early if the Sponsor, Investigator or CS discovers conditions arising during the course of the study which indicate that the clinical investigation should be halted. The study may then be terminated after appropriate consultation and discussion.

Conditions that may warrant study termination include, but are not limited to, the discovery of a significant, unexpected, and unacceptable risk to the participants, failure of the Investigator to enroll participants at an acceptable rate, insufficient adherence to the protocol requirements, completion of study objectives or at the discretion of the Sponsor.

6.0 STUDY REPORT, PUBLICATION POLICY & ARCHIVING OF STUDY DOCUMENTATION

Investigators are required to maintain all study documentation, including copies of CRFs, Informed Consents, and adequate records for the receipt and disposition of study medications, for a period of 25 years following study close-out.

The Investigator will ensure to make all study data accessible to the CS, Sponsor, or other authorised representatives of the Sponsor and Regulatory Agencies during the conduct of the study as well as during the archiving period. A file for each patient will be maintained that includes the signed Informed Consent form and copies of all source documentation related to that patient. The Investigator will ensure the availability of the source documents from which the information on the CRF is derived (conform industry standards, patient details will be pseudonymised).

All information provided to the Investigator dealing with this study drug or the methodologies used in the protocol, as well as information obtained during the course of the study will be regarded as strictly confidential and proprietary to the Sponsor ("Proprietary Information"). The Investigator agrees not to disclose any information supplied by the Sponsor in any way without written permission as outlined in the Confidentiality section of this protocol. For the purposes of this section, "Investigator" includes, but is not limited to, the PI and/or his/her agents, designees, sub-investigators, or other individuals involved in the running, administration, or collection/handling of patients/data for this study.

Any formal presentation or publication of data from this trial will be considered as a joint publication by the Investigators and the appropriate personnel at CLINUVEL. It is mandatory that the first publication is based on data analysed as stipulated in the SAP, and not by the Investigators themselves. Participating Investigators agree not to present data before the full, initial publication, unless formally agreed to by all other Investigators and CLINUVEL.

CLINUVEL must receive copies of any intended communication in advance of publication, at least 30 working days for an abstract or oral presentation and 45 working days for a journal submission. CLINUVEL will review the communications for accuracy, thus avoiding potential discrepancies with submissions to the health authorities, verify that confidential information is not inadvertently divulged, and provide any relevant supplementary information.

7.0 STUDY TIMETABLE

- Projected starting date (first-patient-in [FPI]) [REDACTED]
- Projected number of patients 28
- Projected completion of patient accrual (last-patient-in [LPI]) [REDACTED]
- Projected patient study end date (last-patient-last-visit [LPLV]) [REDACTED]

8.0 AMENDMENTS AND UPDATES

Amendment or Update Number	Date	Section of Study Protocol	Amendment or Update	Reason
Original	18 September 2023	NA	NA	NA
V 1.1	2 October 2023	Study Flow Chart Pregnancy requirements	Day 2 was missing Adolescents not to test if not necessary	Typo Improve patients experience as adolescents
V1.2	23 January 2024	Inclusion/exclusion criteria Dose Section 6.7.3. pharmacokinetic Assessment Throughout Safety Variables Early Termination Visit Study Design Study Rationale	Update of contraception measurements Update BMI Addition of the optional implant after the study Addition of other secondary endpoints in main text Addition of data protection considerations Recruitment management updated Addition of SAR and SUSAR and update on reporting Early Termination optional Update of storage and Use of Biological Samples Clarification that no EPP PK studies have been performed to date	EC/RA request Align with expectations for children EC/RA request To match synopsis EC/RA request EC/RA request EC/RA request EC/RA request EC/RA request
V1.3	23 February 2024	Study Design Study Design Timelines	Additional information regarding storage of blood samples collected for pharmacokinetic analysis. Addition of information regarding store and destruction of blood and urine samples collected for routine safety assessments. Updated timelines to reflect the course of the study	Align with central laboratory procedures EC/RA request Update in timelines

9.0 REFERENCES

1. Bolognia, J., Murray, M. & Pawelek, J. UVB-Induced Melanogenesis May Be Mediated Through the MSH-Receptor System. *J. Invest. Dermatol.* **92**, 651–656 (1989).
2. Castrucci, A. M., Hadley, M. E., Sawyer, T. K. & Hruby, V. J. Enzymological studies of melanotropins. *Comp. Biochem. Physiol. B* **78**, 519–524 (1984).
3. Biolcati, G. *et al.* Long-term observational study of afamelanotide in 115 patients with erythropoietic protoporphyria. *Br. J. Dermatol.* **172**, 1601–1612 (2015).
4. Langendonk, J. G. *et al.* Afamelanotide for Erythropoietic Protoporphyria. *N. Engl. J. Med.* **373**, 48–59 (2015).
5. Minder, E. I. Afamelanotide. *Drugs Future* **35**, 365 (2010).

10.0 APPENDICES

APPENDIX 1: DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient’s best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician’s knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the

physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be performed only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be performed only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

APPENDIX 2: ELEMENTS OF INFORMED CONSENT DOCUMENTATION

In seeking informed consent, the following information shall be provided to each patient:

1. A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the patient's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;
2. A description of any reasonably foreseeable risks or discomforts to the patient;
3. A description of any benefits to the patient or to others which may reasonably be expected from the research;
4. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the patient;
5. A statement describing the extent, if any, to which confidentiality of records identifying the patient will be maintained; and,
6. An explanation of whom to contact for answers to pertinent questions about the research and participants' rights. It is the Sponsor's policy to reimburse an institution or Investigator for expenditures for the medical treatment of normal and patient volunteers who are injured as a direct result of their participation in the Sponsor's protocol as long as the Investigator has complied with the provisions of the protocol. Therefore, the consent form should reflect this in its explanation of the institution's policy. Further details on whom the volunteer should contact in case of injury should also be included.
7. An explanation of whom to contact for answers to pertinent questions about the research and research patient's rights and whom to contact in the event of a research-related injury to the patient.
8. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the patient is otherwise entitled, and that the patient may discontinue participation at any time without penalty or the loss of benefits to which the patient is otherwise entitled.

When appropriate, one or more of the following elements of information shall also be provided to each patient (required under ICH):

1. A statement that the particular treatment or procedure may involve risks to the patient (or to the embryo or foetus, if the patient is or may become pregnant) which are currently unforeseeable;
2. Anticipated circumstances under which the patient's participation may be terminated by the Investigator without regard to the patient's consent;
3. Any additional costs to the patient that may result from participation in the research;
4. The consequences of a patient's decision to withdraw from the research and the procedures for the orderly termination of participation by the patient;
5. A statement that significant new findings that develop during the course of the research which may relate to the patient's willingness to continue participation will be provided to the patient; and,
6. The approximate number of participants involved in the study.