CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210797Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	210797
Priority or Standard	Priority
Submit Date(s)	November 8, 2018
Received Date(s)	November 8, 2018
PDUFA Goal Date	October 8, 2019
Division/Office	DDDP/ODE III
Review Completion Date	October 8, 2019
Established/Proper Name	Afamelanotide
(Proposed) Trade Name	Scenesse
Pharmacologic Class	
Code name	
Applicant	Clinuvel, Inc.
Dosage Form(s)	Subcutaneous implant
Applicant Proposed Dosing Regimen(s)	Administer every 2 months
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Adult patients with erythropoietic protoporphyria

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OPQ = Office of Pharmaceutical Quality
OPDP = Office of Prescription Drug Promotion
OSI = Office of Scientific Investigations
OSE = Office of Surveillance and Epidemiology
DEPI = Division of Epidemiology
DMEPA = Division of Medication Error Prevention and Analysis
DRISK = Division of Risk Management

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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
EPP	erythropoietic protoporphyria
EMA	European Medicines Agency
ETASU	elements to assure safe use
EU	European Union
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICF	informed consent form
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent-to-treat
MC	multicenter
MC1R	melanocortin 1 receptor
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat

MSH	melanocyte stimulating hormone
NB-UVB	narrow-band UVB
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NOAEL	no observed adverse event level
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PASS	post-authorization safety study
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PIP	Pediatric Investigation Plan
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PPIX	protoporphyrin IX
PREA	Pediatric Research Equity Act
PRO	patient-reported outcome
PSUR	Periodic Safety Update report
PT	preferred term
Q2M	every 2 months
REMS	risk evaluation and mitigation strategy
ROC	REMS Oversight Committee
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SDN	submission document number
SGE	special government employee
SOC	system organ class
TEAE	treatment-emergent adverse event
UV	ultraviolet
VC	vehicle controlled

1. Executive Summary

1.1. Product Introduction

Scenesse® (afamelanotide) implant, 16 mg is a subcutaneous implant for which the Applicant seeks approval under Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act for the indication [redacted] (b) (4) in adults with erythropoietic protoporphyria (EPP). The active ingredient is afamelanotide, an α-melanocyte stimulating hormone (MSH) analog ([Nle4, D-Phe7]-α-MSH). Afamelanotide is a new molecular entity. Afamelanotide is not currently marketed in the United States. The proposed dose and administration is by subcutaneous implantation every 2 months.

The Agency concluded that the proposed proprietary name, Scenesse, was acceptable from both a promotional and safety perspective (Proprietary Name Review by Madhuri Patel, PharmD, Division of Medication Error Prevention and Analysis dated March 27, 2019).

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant submitted data from one adequate and well-controlled trial (Study CUV039), which provided evidence of the effectiveness of afamelanotide to increase the duration of pain-free sun exposure time in adults with erythropoietic protoporphyria (EPP). The vehicle-controlled trial assessed the primary endpoint of:

- Total number of hours spent in direct sunlight between 10:00 and 18:00 hours on days when no pain was experienced

The Applicant submitted two additional trials (Studies CUV029 and CUV030) that were supportive of the conclusions of Study CUV039:

- Study CUV029, primary endpoint: Total number of hours of direct sunlight exposure between 10:00 and 15:00 hours on days when no pain was experienced
- Study CUV030, primary endpoint: Median maximum severity score and median total severity score for all reported phototoxic reactions; post hoc endpoint: Total number of hours of direct sunlight exposure t between 10:00 and 15:00 hours on days when no pain was experienced

For Study CUV039, the p-value for the primary endpoint was close to the statistical significance level of 0.05. The Applicant conducted an analysis that excludes subjects who did not have any post-baseline efficacy data and calculated a p-value of 0.044. An analysis that includes all randomized subjects with imputation for missing data conducted by FDA has a p-value of 0.055. Although Study CUV029 had some data quality issues, afamelanotide was statistically superior to vehicle (p=0.005) for the pain-free direct sun exposure endpoint. Study CUV030 did not demonstrate statistical significance on the prespecified endpoints based on the severity of phototoxic reactions. The endpoints based on pain-free sun exposure in Study CUV030 were defined post hoc and thus not able to support efficacy for this endpoint. The borderline

statistical significance observed in Study 039 is supported by the results from Study 029. In addition, although the pain-free sun exposure endpoint in Study 030 was identified post hoc, and thus cannot be relied on to support efficacy, the results from Study 030 were very similar to those observed in Study 029 and Study 030 also provides some assurance that findings are consistent across multiple studies. The Applicant demonstrated that afamelanotide is effective for its intended use in the target population and has met the evidentiary standard required by 21 CFR 314.126(a)(b) to support approval.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Clinuvel, Inc. submitted a New Drug Application (NDA) 210797 for Scenesse (afamelanotide) implant, 16 mg [redacted] (b) (4) in erythropoietic protoporphyria (EPP) under the 505(b)(1) regulatory pathway. EPP is a rare genetic disorder affecting the heme pathway leading to the accumulation of photoactive protoporphyrin IX in tissue. Protoporphyrin IX in the skin reacts with light generating a phototoxic reaction. Patients with EPP experience intense pain upon light exposure. Management is guided by strict photoprotection (e.g., clothing, sunscreen, sun avoidance). Currently, there are no approved treatments for this disease. Treatment of EPP [redacted] (b) (4) granted orphan designation.

Scenesse is an α-melanocyte stimulating hormone (MSH) structural analogue that stimulates melanogenesis, specifically eumelanin in the epidermis. The Applicant's proposed mechanism of action for afamelanotide leading to increased pain-free sun exposure time in patients with EPP is reduced protoporphyrin IX excitation due to increased absorption of sunlight by the increased epidermal eumelanin.

Studies CUV029, CUV030, and CUV039 were multicenter, randomized, double-blind clinical trials enrolling 244 adult subjects with EPP. Twenty-six subjects randomized to vehicle in Trial CUV030 could enroll and were randomized to afamelanotide or vehicle in Study CUV039 (afa: 15, vehicle: 11); the subjects randomized to afamelanotide in Study CUV039 are all unique subjects receiving active drug. Studies CUV039 and CUV029 demonstrated the efficacy of afamelanotide implant relative to vehicle in increasing the duration of pain-free direct sun exposure. The primary endpoint in Studies CUV039 and CUV029 was the duration of direct sunlight exposure on days when no pain was experienced. Study CUV030 supported the findings of Studies CUV039 and CUV029.

The safety profile of afamelanotide implant was adequately characterized during the development program. Treatment with afamelanotide implant was not associated with an increased risk of mortality or serious adverse events. There were no deaths in the safety population. In the pooled safety analysis set (Studies CUV029, CUV030, and CUV039), serious adverse events (SAEs) occurred in 4% subjects in the afamelanotide group and 3% subjects in the vehicle group. The most common adverse reactions include implant site reactions (afa: 20% versus vehicle: 10%) and skin hyperpigmentation (afa: 4% versus vehicle: 3%). Postmarketing data submitted from the European markets did not reveal new safety signals.

The available evidence of safety and efficacy supports the approval of Scenesse (afamelanotide) implant, 16 mg to increase [redacted] (b) (4) pain-free light exposure in adults with a history of phototoxic reactions from EPP. In view of a favorable overall benefit/risk assessment, the review team recommends approval of this product.

Professional labeling, routine pharmacovigilance, and postmarketing studies are adequate to manage the risk of Scenesse in the postmarketing milieu; a Risk Evaluation and Mitigation Strategy (REMS) is not needed. Recommended postmarketing requirements and commitments under 505(o) are:

- Requirement: a thorough QT/QTc study
- Requirement: long-term safety study

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	EPP is an inherited disorder caused by a deficiency in ferrochelatase. The deficiency leads to an accumulation of protoporphyrin IX (PPIX) in red blood cells, plasma, and tissues, such as the skin. Phototoxicity is the main clinical feature of EPP, which leads to intense pain with sun exposure. The incidence of EPP is reported to be 1:75,000.	Erythropoietic protoporphyria (EPP) is an uncommon, lifelong genetic disorder resulting in pain with light exposure and leads to life-long sun avoidance that significantly impacts quality of life.
Current Treatment Options	In EPP, minimizing the phototoxic reaction via strict sun avoidance is the primary goal in disease management. There are no approved treatments for EPP, including the prevention or treatment of phototoxic reaction. Current anecdotal treatments include oral beta carotene and phototherapy. Drugs approved for the treatment of pain are typically not effective in treating pain due to phototoxic reaction of EPP.	There are currently no FDA-approved products for EPP. Current management includes daily strict photoprotection.
Benefit	Data from three trials provided evidence of the effectiveness of afamelanotide implant to increase the duration of pain-free sun exposure. The trials enrolled 244 subjects age 18 years and older with clinical diagnosis of EPP. Afamelanotide implant was superior to vehicle in Study CUV039 for the primary efficacy endpoint of duration of direct sunlight exposure between 10:00 and 18:00 hours. For Studies CUV029 and CUV030, the treatment benefit of afamelanotide implant compared to vehicle supported the findings of Trial CUV039.	Afamelanotide implant provides an effective and safe treatment option for patients with EPP.
Risk and Risk Management	Review of the safety data from clinical trials and postmarketing surveillance data from European Union did not identify safety signals. Afamelanotide implant was well tolerated in adult subjects with EPP. Labeling: Prescription labeling adequately addresses the risks associated with afamelanotide and identified during product development and postmarketing monitoring in Europe. The evaluation of the potential to prolong QT interval was not part of afamelanotide development program. Therefore, this evaluation will be included as a PMR. In addition, given that the potential of afamelanotide to affect	Prescription labeling and routine pharmacovigilance, in conjunction with the postmarketing requirements, are adequate to manage the risks of the product.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	melanogenesis, collection of additional safety information from patients on treatment with afamelanotide will be requested. The recommended PMR/PMCs are: • Postmarketing Requirement to conduct a thorough QT/QTc study • Postmarketing Requirement to conduct a voluntary registry to obtain essential long-term safety information on afamelanotide A risk evaluation and mitigation strategy (REMS) is not recommended.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

x	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	x	Clinical outcome assessment (COA) data, such as		
		x	Patient-reported outcome (PRO)	8.1
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
x	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	x	Input informed from participation in meetings with patient stakeholders		3.2
	x	Patient-focused drug development or other stakeholder meeting summary reports		3.2
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	**Patient experience data was not submitted as part of this application.**			

2. Therapeutic Context

2.1. Analysis of Condition[1]

EPP is an inherited disorder caused by a deficiency in ferrochelatase, the final enzyme in the heme biosynthetic pathway. The deficiency leads to an accumulation of protoporphyrin IX (PPIX) in red blood cells, plasma, and tissues, such as the skin. Phototoxicity is the main clinical feature of EPP and caused by light-induced excitation of PPIX. Light reaction (380 nm to 420 nm) with PPIX leads to the production of singlet oxygen and other reactive oxygen species that damage adjacent cutaneous tissue and blood vessels. With severe phototoxic reactions, erythema, edema, pruritus, blistering, and petechiae of the skin has been reported and can result in symptoms lasting days to weeks. Repeated phototoxic reactions may lead to permanent changes in the skin, such as thickening and scarring predominantly in areas of frequent sun exposure (e.g., forehead, dorsum hands, nose).

The prevalence of EPP is reported to range between 1:75,000 to 1:200,000. Individuals with EPP vary in the extent of sun exposure that results in a phototoxic reaction (seconds to hours) and is based on the degree of ferrochelatase activity. Approximately 1 to 3% of patients with EPP develop hepatic involvement, some progressing to liver failure.

2.2. Analysis of Current Treatment Options[1]

There are currently no FDA approved treatments for EPP, including treatment to increase the duration of pain-free sun exposure. In addition, there are no FDA approved treatments for the treatment or prevention of phototoxic reactions in patients with EPP or to reduce symptoms associated with phototoxic reactions. Management of EPP is focused on avoiding sun exposure (e.g., protective clothing, window treatments, sunscreen) in order to prevent the production of oxidative species in the skin that lead to cutaneous phototoxic reactions. Once a phototoxic reaction begins, treatment is focused on symptomatic relief.

The table below summarizes the treatments available to EPP patients for to increase the duration of pain-free sun exposure. Information about these treatments is based on literature reports and are considered to have had an impact on, at most, a few patients.

[1] Mario Lecha, Hervé Puy and Jean-Charles Deybach. Erythropoietic protoporphyria. *Orphanet Journal of Rare Diseases* 2009, 4:19 doi:10.1186/1750-1172-4-19

Table 1. Summary of Treatment Armamentarium Relevant in Patients with Erythropoietic Protoporphyria

Product(s) Name	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues
FDA Approved Treatments			
None			
Other Treatments – Marketed, Unapproved			
B-carotene	Oral, high dose of ~180 mg or more daily	Literature reports	OTC vitamin supplement Potential for carotenemia
Cimetidine	Oral, 30-40 mg/kg/day	Literature reports	Over the counter
Colestipol	Oral, 2 gm twice daily	Literature reports	Prescription
Topical sunless tanner	Topical	Literature reports	Over the counter, aesthetic product
Phototherapy	Cutaneous exposure	Literature reports	Requires travel to site with unit, multiple times per week

OTC = over-the-counter

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The proposed product, Scenesse (afamelanotide) implant, 16 mg, is a new molecular entity and is not currently marketed in the United States.

Scenesse was granted marketing authorization in the European Union (EU) under "exceptional circumstances" on December 22, 2014. The European Medicines Agency (EMA) Summary of Product Characteristics states that Scenesse:

- Is indicated for "prevention of phototoxicity in adult patients with erythropoietic protoporphyria."
- "Should only be prescribed by specialist physicians in recognized porphyria centers and administration should be performed by a physician trained and accredited by the marketing authorization holder to administer the implant."
- Implant "is administered every 2 months prior to expected and during increased sunlight exposure, e.g., from spring to early autumn. Three implants per year are recommended, depending on the length of protection required. The recommended maximum number of implants is four per year. The overall duration of treatment is at the specialist physician's discretion."

Commercial marketing of Scenesse in European Union began June 22, 2016.

Under the IND, the Applicant has evaluated afamelanotide implant, 16 mg for the following indications:

(b) (4)

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant developed afamelanotide under IND 103131.

The Applicant submitted a request for orphan drug designation on May 16, 2008, and on July 17, 2008 was granted orphan drug designation for [Nle4, D-Phe7]-α-melanocyte stimulating hormone for "treatment of erythropoietic porphyria" (Designation #08-2632).

On December 23, 2008, the Applicant opened IND 103131 with Phase 1b study CUV028 ("Phase 1b study to confirm the pharmacokinetic and melanogenic potential of controlled-release bioresorbable implants of afamelanotide in healthy volunteers"). Teleconference with Agency held January 15, 2009 to discuss protocol deficiencies, which were adequately addressed.

On April 15, 2010, the Agency discussed via teleconference inclusion of ophthalmologist-conducted eye exams (rejected by Applicant) and dermatologist-conducted skin exam, including oral mucosa.

<u>Type C Guidance Meeting: October 27, 2010</u>
In this meeting, the Applicant sought guidance on:

- Non-clinical requested CNS effects of afamelanotide be addressed in nonclinical studies, as well as potential immunogenicity in repeat dose toxicity studies
- Clinical requested additional Phase 3 trial (Study CUV039) that incorporates clinically meaningful and agreed-upon efficacy endpoints, and a well-designed analysis plan, that are to be discussed at End of Phase 2 meeting
- Recommended that sun exposure information be documented by time of year, time during day, and length of exposure before phototoxic reaction. In addition, recommended documenting severity and duration of phototoxic reaction
- Consider treatment arm where sun avoidance is the standard of care
- Discussed blinding issue where subjects receiving afamelanotide are functionally unblinded by increased skin pigmentation
- Advised to address evaluation of QT/QTc prolongation potential of afamelanotide

(b) (4)

<u>Teleconference Meeting: March 12, 2012</u>
The Applicant requested a meeting to discuss Phase 3 trial, Study CUV039:

- Subjects who received vehicle in CUV030 would be eligible for enrollment and randomization in Study CUV039
- Functional unblinding discussed, as well as quality of patient diary information collected (capture use of protective clothing and sunscreen, and time spent in direct sunlight)

- Clinical requested photoprovocation studies as a surrogate endpoint to provide direct link between pharmacologic effect and proposed clinical benefit of photoprotection. Applicant agreed to conduct photoprovocation study at New York study site

Type C Guidance Meeting: September 30, 2015

The Applicant requested this meeting to discuss the adequacy of the afamelanotide safety and efficacy database to support an indication in EPP.

On February 24, 2016, the Agency discussed with Applicant via teleconference:

- Whether the Fast Track designation request would be appropriate
- Per EMA Pediatric Investigational Plan, no pediatric studies will be conducted until 5 years of commercial adult use. Therefore, no pediatric studies are planned
- Requested raw data for CUV010, CUV029, CUV030, CUV039, and photoprovocation studies
- Requested EMA post-marketing safety data

On April 28, 2016, the Applicant submitted a request for Fast Track designation to the IND and received Fast Track designation on June 29, 2016.

FDA Scientific Workshop on Erythropoietic Protoporphyria: October 24, 2016

The Division sponsored a Scientific Workshop on EPP that combined patients with EPP sharing their perspectives on living with EPP, an overview of the FDA's regulatory role and process, and EPP expert panel discussion on scientific aspects of clinical trial design for EPP drug development.

Pre-NDA Meeting: November 7, 2016

The Applicant requested this meeting to discuss the components of the NDA submission for afamelanotide for [redacted] (b) (4) adult patients with EPP.

On February 9, 2017, the Applicant submitted a request to waive carcinogenicity studies. Carcinogenicity waiver granted on March 10, 2017.

Rolling submission and review was requested on March 22, 2017, and was granted on May 9, 2017.

On July 25, 2017, the Applicant submitted a request for a waiver from the requirement to assess the safety and effectiveness of afamelanotide for the claimed indication in pediatric patients, which is required under the Pediatric Research Equity Act (PREA) 21 U.S.C. 355c.

On September 11, 2017, the Applicant submitted a request for review of proposed proprietary name Scenesse and was determined conditionally acceptable on December 7, 2017.

On June 19, 2018, the Applicant submitted a request for orphan drug exclusivity in the "treatment of erythropoietic protoporphyria (EPP), [redacted] (b) (4)

The Applicant submitted the fourth and final component of the NDA via the rolling review process on November 8, 2018. The Applicant was notified of priority review status and acceptance of NDA filing on January 7, 2019 and January 9, 2019 respectively.

On May 10, 2019, the Applicant submitted information regarding the administration device for afamelanotide implant triggering a major amendment to the priority review application. On May 31, 2019, the Applicant was notified of the new action date for afamelanotide implant, October 6, 2019.

4. Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The overall quality of the clinical information contained in this submission was adequate. The sites selected for inspection by Office of Scientific Investigations were based on numbers of enrolled subjects, high number of protocol deviations, and prior inspectional history. The Clinical Inspection Summary (see table below) included the following results (Review by Cheryl Grandinetti, Pharm.D., dated April 17, 2019):

Table 2. Site Inspection Results

Site Number, Name, and Address	Protocol ID	Number of Subjects	Classification	Inspection Dates
Site #2 Herbert Bonkovsky, M.D. Carolinas Medical Center Liver-Biliary-Pancreatic Center 1300 Scott Avenue Charlotte, NC 28204	CUV039	14	NAI	Jan 16, 2019 – Jan 18, 2019
Site #6 Joseph Bloomer, M.D. UAB Gastroenterology Hepatology 1918 University Blvd, MCLM 295 Birmingham, AL 35294	CUV039	12	NAI	Jan 14, 2019 – Jan 18, 2019
Site #7 Charles Parker, M.D. University of Utah Williams Bldg., Clinical Trials Office 295 Chipeta Way Salt Lake City, UT 84112	CUV039	12	VAI	Jan 14, 2019 – Jan 18, 2019

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable
Source: Modified from OSI Review.

Based on the results of the inspections, Dr. Grandinetti concluded that the conduct of the trials appears to be adequate and the data generated by these sites appears to be acceptable to support the use of this product for the proposed indication. Refer to the Clinical Inspection

Summary by Dr. Grandinetti dated April 17, 2019, for a brief review of the data to support this conclusion.

4.2. Product Quality

The Applicant, CLINUVEL, Inc, has submitted this 505(b)(1) new drug application (NDA) for Scenesse (afamelanotide) implant,16 mg. Scenesse is indicated for pain-free (b) (4) exposure in adult patients with erythropoietic protoporphyria (EPP). Scenesse is to be subcutaneously administered to the patient by a healthcare professional who is proficient in the subcutaneous implantation procedure and has completed training prior to administration.

- The applicant of this 505(b)(1) NDA has provided sufficient CMC information to assure the identity, purity, strength, and quality of the drug substance, afamelanotide, and the drug product, Scenesse (afamelanotide) implant,16 mg.
- Labels/labeling issues have been satisfactorily addressed.
- The Office of Process and Facility has made an overall "Acceptable" recommendation regarding the facilities involved in this NDA.
- The claim for categorical exclusion of the environmental assessment is granted.

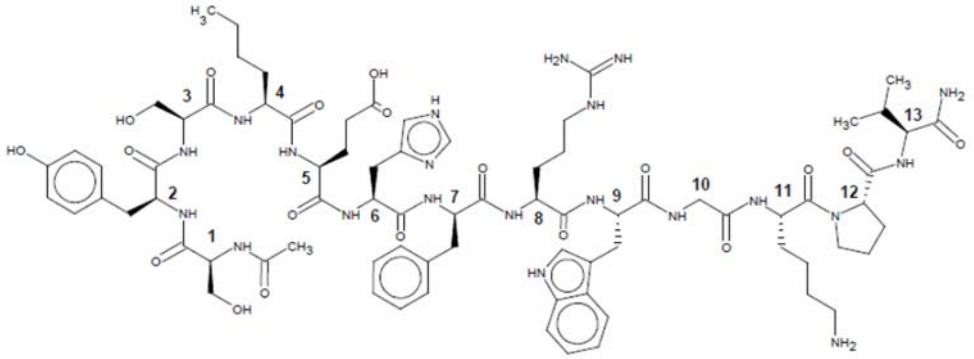
Therefore, from the OPQ perspective, this NDA is recommended for **APPROVAL** with expiration dating period of 48 months.

Drug Substance

Afamelanotide is a 13-amino acid linear peptide synthesized and isolated as its acetate salt and has been classified as a new molecular entity. Afamelanotide is a structure analogue of the endogenous compound α-melanocyte stimulating hormone (α-MSH) and acts as a melanocortin-1 receptor (MC1R) agonist increasing the level of eumelanin that provides photoprotection through different mechanisms.

Afamelanotide (free base) has the chemical name of N-acetyl-L-serinyl-L-tyrosyl-L-seryl-L-norleucyl-L-glutamyl-L-histidinyl-D-phenylalanyl-L-arginyl-L-tryptophanyl-glycyl-L-lysyl-L-prolyl-L-valinamide, the molecular formula of $C_{78}H_{111}N_{21}O_{19}$, the molecular weight of 1646.85 g/mol, and the molecular structure below:

Figure 1. Molecular Structure of Afamelanotide



Source: Module 3.2.S.1.2 Structure

Afamelanotide acetate has the molecular formula of $C_{78}H_{111}N_{21}O_{19} \bullet xCH_3COOH$ with average x (b) (4) and the average molecular weight of (b) (4) g/mol.

Afamelanotide acetate is manufactured by (b) (4) in accordance to current good manufacturing practices (cGMP) requirements and tested against an adequate specification that assures the identity, strength, purity and quality of the drug substance at release and throughout its proposed retest date of (b) (4) months. The information regarding the manufacture of afamelanotide acetate is provided in DMF (b) (4) which has been reviewed and found to be adequate to support this NDA.

Drug Product

The drug product, Scenesse (afamelanotide) implant, 16 mg is a white to off-white, sterile, biodegradable solid implant intended for subcutaneous administration. Since the implant is biodegradable, there will be no need for the removal of the implant from the patients.

Each implant is approximately 1.7 cm in length and 1.45 mm in diameter consisting of 16 mg of afamelanotide equivalent to 18 mg of afamelanotide acetate as the active ingredient, and 15.3 to 19.5 mg of biodegradable/bioresorbable copolymers, poly (DL-lactide-co-glycolide) as inactive ingredients. The implants are individually packaged in Type I amber glass vials sealed with rubber stoppers with aluminum overseal. (b) (4)

(b) (4)

The drug product is also manufactured by (b) (4) CLINUVEL, Inc., in accordance to cGMP requirements and tested according to a specification that includes testing and acceptance criteria for all physical and chemical attributes essential for assuring the identity, strength, purity, and quality of the drug product at release and throughout its proposed expiration dating period of 48 months.

4.3. Devices and Companion Diagnostic Issues

Scenesse implants are not supplied (copackaged) with the device for subcutaneous administration. The implants should be administered using a separately marketed surgical device, the SFM Cannula for subcutaneous implant/pellet administration. For information on the surgical device for drug product implantation, refer to review by Peter Petrochenko, PhD, CDRH.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Afamelanotide is an agonist of the melanocortin-1 receptor (MC1-R). It is a 13 amino acid synthetic peptide and a structural analogue of the endogenous hormone α-melanocyte stimulating hormone (α-MSH). Afamelanotide has a greater resistance to degradation by serum or proteolytic enzymes than α-MSH, which results in a longer half-life. Afamelanotide was 100 to 1000 times more active than natural α-MSH in bioassays. Afamelanotide's primary pharmacological activity results in increased synthesis, release and transfer of eumelanin through stimulation of the MC1-R, which is expected to confer photoprotection against DNA damaging effects of sun exposure by its ability to quench reactive oxygen radicals

Afamelanotide has been evaluated in nonclinical toxicity studies. Overall, the results from the conducted nonclinical studies did not highlight any significant toxicity signal of concern associated with the proposed use of afamelanotide. Although no stand-alone safety pharmacology studies have been conducted with afamelanotide, signs of systemic toxicity, cardiovascular, respiratory, autonomic and central nervous systems were monitored via daily clinical observations for up to 13 weeks in rats and dogs and no adverse effects on these systems were noted at dose levels in great excess of that to be used clinically. A functional battery of neurobehavioral tests did not show treatment-related toxicity in rats subcutaneously treated with doses up to 20 mg/kg/day afamelanotide for 13 weeks. There were no treatment-related effects on blood pressure in dogs subcutaneously receiving 15 mg/kg/day afamelanotide for 28 days. There were no treatment-related effects on ECG measurements in dogs subcutaneously receiving implants containing 100 mg afamelanotide once every 15 days for 13 weeks.

Afamelanotide toxicity after repeat dose administration has been assessed in rats and dogs and these nonclinical studies did not identify any particular toxicity of concern. In chronic repeat dose studies using the afamelanotide implant (6 months in rats and 10 months in dogs), the no observed adverse effect level (NOAEL) was 32 mg (approximately 64 mg/kg) once every 2 months in rats and 16 mg (approximately 1.6 mg/kg) once every 2 months in dogs, which was approximately 39 and 3.3 times the recommended human dose (16 mg given to a 60 kg patient once every 2 months), based on a body surface area comparison. There were no treatment-related adverse effects in Black Hooded rats following subcutaneous treatment with implants containing 16 mg afamelanotide once every month for 6 months, in the presence or absence of narrow-band ultraviolet B (NB-UVB) light.

There was no indication of genetic toxicity with afamelanotide in a battery of genetic toxicology studies. Afamelanotide was negative in the Ames test, in vitro mouse lymphoma assay, and in vivo mouse bone marrow micronucleus assay. No carcinogenicity studies are required for this NDA with the proposed indication and treatment regimen [Afamelanotide implant (16 mg) is administered subcutaneously once every 2 months in adult patients with erythropoietic porphyria (EPP) with a maximum of (b) (4) implants per year administered to each patient].

There were no treatment-related parental toxicity or effects on fertility and reproductive performance in rats treated subcutaneously with doses up to 20 mg/kg/day afamelanotide (at least 12 times the recommended human dose, based on a body surface area comparison). An embryo-fetal developmental study could not be conducted in rabbits with afamelanotide because rabbits were remarkably intolerant to afamelanotide administration. Therefore, embryo-fetal developmental toxicity studies were conducted in *Sprague Dawley (*SD) rats and in a pigmented strain of rats, the Lister Hooded rats. There were no treatment-related effects on embryo-fetal development or pre-/post-natal development in rats at subcutaneous doses up to 20 mg/kg/day afamelanotide.

Potential safety signals were noted in the nonclinical studies conducted to support the use of afamelanotide implant in EPP patients. Transient signs of central nervous system (CNS) and respiratory system toxicity, including hunched posture, lethargy, ataxia, ptosis, decreased respiratory rate, and/or labored breathing, were seen in rats and mice treated subcutaneously with single doses of ≥500 mg/kg afamelanotide. These effects may have been due to the moribund state of the animals at extremely high doses of afamelanotide. In repeated-dose toxicity studies, the relevant finding included increased skin pigmentation in dogs and rats, which is consistent with afamelanotide's pharmacological activity. This effect was observed at exposure levels significantly greater than human exposure. Inflammation was observed in the Harderian gland in rats treated with afamelanotide, which is not considered relevant to human safety since the Harderian gland is not present in humans.

The pigmentary function of the skin can be considered to be fully developed by the end of the first year of life in humans. It can therefore be postulated that the primary pharmacological effect of afamelanotide is expected to be the same in children as it is in adults. The pharmacologic target of afamelanotide (MC1 receptor) is the same in children as it is in adults with respect to function and expression. None of the toxicity signals noted in animal studies pose a significant safety concern for use of afamelanotide implant in adult and/or pediatric subjects. The Applicant does not currently intend to use afamelanotide implant in pediatric patients in the US. The Applicant was granted a waiver request for conduct of a juvenile animal study with afamelanotide implant under IND 103131. No juvenile animal study is required for this NDA.

(b) (4)

Scenesse has been tested in the chronic toxicity studies in rats and dogs, which can further support the safety of the two excipients. From a Pharmacology/Toxicology perspective, there is no safety concern for the two excipients in this NDA.

This NDA is approvable from a pharmacology/toxicology perspective. There is no recommended nonclinical PMC/PMR for this NDA.

5.2. Referenced NDAs, BLAs, DMFs

Most of the pivotal nonclinical studies have been reviewed under IND 103131. Summary pharmacology/toxicology information on these studies is provided in this review. The code names used for Scenesse (afamelanotide) implant are CUV1647, Melanotan, Melanotan-1 (MT-1), [Nle^4, D-Phe^7]-α-MSH, and EPT1647.

5.3. Pharmacology

Melanin is produced as a result of exposure to ultraviolet (UV) light or sunlight when alpha-melanocyte stimulating hormone (α-MSH) interacts with melanocyte cells in the skin. It is mediated through attachment to and activation of melanocortin 1 receptors (MC1-Rs). Afamelanotide, a synthetic analogue of α-MSH, was 100 to 1000 times more active than natural α-MSH in bioassays, had a longer duration in the body, and had potent melanogenic activity inducing increased pigmentation of the skin. The increase in melanin synthesis following afamelanotide treatment is expected to confer photoprotection against DNA damaging effects of sun exposure by its ability to quench reactive oxygen radicals.

No stand-alone safety pharmacology studies have been conducted with afamelanotide. In acute subcutaneous toxicity studies in mice and rats, transient signs of systemic toxicity, including hunched posture, lethargy, ataxia, ptosis, decreased respiratory rate, and/or labored breathing, were noted at doses of ≥500 mg/kg afamelanotide. Signs of systemic toxicity, cardiovascular, respiratory, autonomic and central nervous systems were also monitored via daily clinical observations for up to 13 weeks in rats and dogs and no adverse effects on these systems were noted with doses up to 20 mg/kg/day afamelanotide. A functional battery of neurobehavioral tests did not show treatment-related toxicity in rats subcutaneously treated with doses up to 20 mg/kg/day afamelanotide for 13 weeks. There were no treatment-related effects on blood pressure in dogs subcutaneously receiving 15 mg/kg/day afamelanotide for 28 days. There were no treatment-related effects on ECG measurements in dogs subcutaneously receiving implants containing 100 mg afamelanotide once every 15 days for 13 weeks.

5.4. ADME/PK

5.4.1. A 30-day Pharmacokinetic Study of Release of CUV1647 From 10- and 16-mg Bioresorbable Implants in Rats (PC1307)

Each Sprague Dawley rat received a 10 or 16 mg bioresorbable implant subcutaneously. Both implants had similar release profiles with over 85% of afamelanotide released from the implants by Day 5 and 97% to 99% released by Day 30.

5.4.2. Repeated Dose Chronic Toxicity Study in PVG/C Arc Black Hooded Rats Treated With Afamelanotide 16 mg Implant and Narrow-Band Ultraviolet B (NB-UVB) Light Irradiation: Main Study (b) (4) 1266.B)

Rats received 16 mg afamelanotide implants subcutaneously once every 4 weeks for 24 weeks (6 doses total), in the presence or absence of NB-UVB light (3 times per week). Plasma concentrations of afamelanotide at 1 hour after the first implantation were 187.1±141.6 and 109.0±54.5 ng/mL in non-irradiated males and females, respectively, and 98.5±57.4 and 93.2±52.4 ng/mL in irradiated males and females, respectively. Plasma concentrations of afamelanotide at 1 hour after the last implantation were 64.6±12.5 and 117.4±49.2 ng/mL in non-irradiated males and females, respectively, and 66.5±51.1 and 140.9±80.8 ng/mL in irradiated males and females, respectively.

5.4.3. Ninety Day Repeated Dose Subcutaneous Toxicity Study in the Rat (1564/003)

Rats received 0.2, 2, or 20 mg/kg/day afamelanotide subcutaneously once daily for 90 days. Toxicokinetic (TK) analysis was performed on Days 1 and 90. Afamelanotide AUC levels could not be determined on Day 1 for the 0.2 and 2 mg/kg/day doses, because there were insufficient data points.

Table 3. Toxicokinetic Parameters for Afamelanotide in the 90-Day Study in Rats

Dose level		T_{max} (hr)		C_{max} (ng/mL)		$AUC_{0\text{-}24hr}$ (ng·hr/mL)	
(mg/kg/day)	Day	Males	Females	Males	Females	Males	Females
0.2	1	0.5	0.5	0.5	2.5	---	---
2	1	0.5	0.5	42.0	49.5	---	---
20	1	1.0	0.5	493.8	271.5	333	546
0.2	90	0.5	0.5	11.7	4.8	8	4
2	90	0.5	0.5	78.70	110.0	117	61
20	90	3.0	0.5	924.8	1098.9	4563	2549

5.4.4. A 10-Month Subcutaneous Toxicity Study of Afamelanotide Implants in Dogs With 1-Month Recovery (1822-001)

Plasma concentrations of afamelanotide were 9.92±7.46, 11.79±5.83, and 14.99±6.94 ng/mL at 8 hours after the first dosing and 6.06±1.10, 15.99±4.57, and 13.00±4.51 ng/mL at 8 hours after the last dosing in dogs following subcutaneous treatment with implants at 16 mg or 32 mg afamelanotide once every 2 months, or at 32 mg afamelanotide once every month, respectively.

5.4.5. Reproductive Toxicology Studies

No TK analysis was conducted in the fertility and early impanation study in the rat (1564/011), embryofetal development study in the SD rat (1564/007), and pre- and post-natal development study in the rat (1564/010). In the embryofetal development study in Lister Hooded rats (10/070-105P), blood samples were collected only at approximately 30 minutes after first and last dose administration [Gestation Day (GD) 6 and GD 17] from animals subcutaneously treated with vehicle or 20 mg/kg/day afamelanotide. No afamelanotide was detected in the

samples from the vehicle-treated animals. Plasma concentrations of afamelanotide were estimated to be greater than the lower limit of quantification (2.00 ng/mL) in the animals treated at 20 mg/kg/day and calculation of AUC levels was not possible in this study.

5.5. Toxicology

5.5.1. General Toxicology

Afamelanotide has been evaluated in nonclinical toxicity studies. Overall, the results from the conducted nonclinical studies did not highlight any significant toxicity signal of concern associated with the proposed use of afamelanotide. In chronic repeat dose studies using the afamelanotide implant (6 months in rats and 10 months in dogs), the NOAELs were 32 mg (approximately 64 mg/kg) once every 2 months in rats and 16 mg (approximately 1.6 mg/kg) once every 2 months in dogs.

5.5.1.1. 26-Week Subcutaneous Implantation Toxicity Study With a 4-Week Recovery Period in Lister Hooded Rats (10/070-218P)

Key study findings:

- There were no treatment-related effects on mortality, clinical signs, neurobehavioral assessment, body weights, food consumption, ophthalmoscopy, hematology, clinical chemistry, urinalysis, organ weights, and macroscopic findings, following subcutaneous treatment with implants at 16 mg or 32 mg afamelanotide once every 2 months, or at 32 mg afamelanotide once every month.
- Minimal to mild tubular degeneration/atrophy and/or mononuclear cell infiltrate in the Harderian gland were noted in the Main Study and Recovery animals treated at 32 mg once every month. A reversible, slightly higher incidence of increased skin pigmentation of mild severity in pigmented skin areas was noted in the Main Study animals treated at 32 mg once every month at necropsy.
- The NOAEL was 32 mg afamelanotide (approximately 64 mg/kg) once every 2 months.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 4. Study 10/070-218P Methods

Dose and frequency of dosing:	0 (Placebo) and 32 mg (HD) once every month (7 doses); 16 mg (LD) and 32 mg (MD) once every 2 months (4 doses)
Route of administration:	Subcutaneous (implant)
Formulation/vehicle:	Clinical formulation
Species/strain:	Lister hooded rats (HsdOla:LH)
Number/sex/group:	30/sex/group (see the following table)
Age:	Approximately 7 weeks at first dosing
Satellite groups/unique design:	See the following table. Main study animals were sacrificed on Day 209 (4 weeks after the last implant on Day 181). Recovery animals underwent necropsy on Day 237.
Deviation from study protocol affecting interpretation of results:	No

HD = high dose; LD = low dose; MD = mid dose

Table 5. Study Design for the 26-Week Study in Lister Hooded Rats

Group no./ Designation	Dose (mg afamelanotide /animal/occasion)	Main		Recovery		Satellite (blood collection for measurements of afamelanotide concentration in plasma)	
		Male	Female	Male	Female	Day 1, 8h post implantation, terminal bleed	
						Male	Female
1/Placebo	0	20	20	10	10	5	5
2/Low dose	16	20	20	-	-	5	5
3/Mid dose	32	20	20	-	-	-	-
4/High dose	32	20	20	10	10	5	5

Table 6. Observations and Results: Changes From Control

Parameters	Major Findings
Mortality	No treatment-related changes
Clinical signs	No treatment-related changes
Body weights	No treatment-related changes
Ophthalmoscopy	No treatment-related changes
Hematology	No treatment-related changes
Clinical chemistry	No treatment-related changes
Urinalysis	No treatment-related changes
Gross pathology	No treatment-related changes
Organ weights	No treatment-related changes
Histopathology Adequate battery: Yes	Minimal to mild tubular degeneration/atrophy and/or mononuclear cell infiltrate in the Harderian gland in the Main Study HD and Recovery animals. A reversible, slightly higher incidence of increased skin pigmentation of mild severity in pigmented skin areas in the HD animals at necropsy.
Neurological assessment	No treatment-related changes

LD: low dose; MD: mid dose; HD: high dose.

5.5.1.2. Repeated Dose Chronic Toxicity Study in PVG/cArc Black Hooded Rats Treated With Afamelanotide 16 Mg Implant and Narrow-Band Ultraviolet B (NB-UVB) Light Irradiation: Main Study (b) (4) 1266.B)

Key study findings:

- There were no treatment-related effects on mortality, clinical signs, irradiated skin sites, body weights, food consumption, ophthalmoscopy, hematology, clinical chemistry, urinalysis, organ weights, and macroscopic findings, following subcutaneous treatment with implants at 16 mg afamelanotide once every 4 weeks for 6 months, in the presence or absence of NB-UVB light.
- The NOAEL was 16 mg afamelanotide (approximately 48 mg/kg) once every 4 weeks, in the presence or absence of NB-UVB light.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes, OECD

Table 7. Study (b) (4) 1266.B Methods

Dose and freque dosing:	0 (placebo) and 16 mg once every 4 weeks (6 doses)
Route of administration:	Subcutaneous (implant)
Formulation/vehicle:	Clinical formulation
Species/strain:	PVG/cArc black hooded rats
Number/sex/group:	20/sex/group (see the following table)
Age:	Approximately 7 to 10 weeks
Satellite groups/unique design:	Rats were or were not irradiated with NB-UVB three times per week at a dose corresponding to 37.5% of the minimal erythemal dose (MED) over a 24-week period (see the following table). Rats were sacrificed after 24-week treatment or 4 weeks after the final implantation.
Deviation from study protocol affecting interpretation of results:	No

Table 8. Treatment Groups for Study (b) (4) 1266.B

Group No	Number of animals/sex	Unique animal number	Dose Administered 6 times, once every 4 weeks	Exposure Dose (mJ/cm^2) 3 times a week
1	20 males 20 females	R5172-R5191 R5192-R5211	Placebo implant	0
2	20 males	R5212-R5231	Placebo implant	75
	20 females	R5232-R5251	Placebo implant	28
3	20 males 20 females	R5252-R5271 R5272-R5291	16 mg afamelanotide implant	0
4	20 males	R5292-R5311	16 mg afamelanotide implant	75
	20 females	R5312-R5331	16 mg afamelanotide implant	28

Table 9. Observations and Results: Changes From Control

Parameters	Major Findings
Mortality	No treatment-related changes
Clinical signs and skin irritation	No treatment-related changes
Body weights	No treatment-related changes
Food consumption	No treatment-related changes
Ophthalmoscopy	No treatment-related changes
Hematology	No treatment-related changes
Clinical chemistry	No treatment-related changes
Urinalysis	No treatment-related changes
Gross pathology	No treatment-related changes
Organ weights	No treatment-related changes
Histopathology*	No treatment-related changes

* Only skin and lymph nodes were examined

5.5.1.3. A 10-month subcutaneous toxicity study of afamelanotide implants in dogs with 1-month recovery (1822-001)

Key study findings:

- There were no treatment-related effects on mortality, body weights, food consumption, neurobehavioral examinations, ECG, blood pressure, hematology, clinical chemistry, organ weights, macroscopic and microscopic findings, following subcutaneous treatment with implants at 16 mg or 32 mg afamelanotide once every 2 months, or at 32 mg afamelanotide once every month.
- Transient decreases in urine specific gravity and concurrent increases in urine pH were noted at the 6-month interval in animals treated at 32 mg afamelanotide once every month or every 2 months. Changes in hair color and coat appearance were noted in all afamelanotide-treated groups.
- The NOAEL was 16 mg afamelanotide (approximately 1.6 mg/kg) once every 2 months.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 10. Study 1822-001 Methods

Dose and frequency of dosing:	0 (vehicle), 16, and 32 mg once every 2 months; 32 mg once every month
Route of administration:	Subcutaneous (implant)
Formulation/vehicle:	Clinical formulation
Species/strain:	Beagle dogs
Number/sex/group:	4 or 7/sex/group (see the following table)
Age:	Approximately 5.5 to 6.5 months
Satellite groups/unique design:	See the following table
Deviation from study protocol affecting interpretation of results:	No

Table 11. Study Design for the 10-Month Study in Dogs

Table A. Group Assignments				
Group Number	Treatment	Number of Implants	Number of Animals[a,b]	
			Male	Female
1	0 mg (Placebo)	1	7	7
2	16 mg	1	4	4
3	32 mg Bi-monthly	2	4	4
4	32 mg Monthly	2	7	7

[a] Four animals/sex/group were euthanized on Day 301
[b] Three animals/sex at 0 mg (Placebo) and 32 mg Monthly were maintained for a 30 day recovery period and were euthanized on Day 330 (± 3 days)

Table 12. Observations and Results: Changes From Control

Parameters	Major Findings
Mortality	No deaths
Clinical signs	Changes in hair color and coat appearance in all afamelanotide-treated groups
Body weights	No treatment-related changes
Food consumption	No treatment-related changes
ECG	No treatment-related changes
Hematology	No treatment-related changes
Clinical chemistry	No treatment-related changes
Urinalysis	Transient decreases in urine specific gravity and concurrent increases in urine pH at the 6-month interval in the 32 mg monthly and 32 mg bi-monthly groups (both sexes)
Gross Pathology	No treatment-related changes
Organ Weights	No treatment-related changes
Histopathology Adequate battery: Yes	No treatment-related changes
Neurobehavioral examinations	No treatment-related changes
Indirect blood pressure	No treatment-related changes

5.5.2. General Toxicology - Additional Studies

5.5.2.1. Melanotan: Ninety-Day Repeated Dose Subcutaneous Toxicity Study in the Rat (1564/003)

Four groups of 10 male and 10 female SD rats received 0 (vehicle, 0.9% saline), 0.2, 2, or 20 mg/kg afamelanotide subcutaneously once daily for 90 days. There were no treatment-related effects on mortality, clinical signs, functional behavior, body weights, food consumption, organ weights, and gross pathology. A decreased blood potassium level was observed in both male and female animals treated with afamelanotide. A lower incidence of agglomeration of secretion in the Harderian gland and a higher incidence of focal chronic inflammatory cell infiltrates were observed in both male and female animals treated at 20 mg/kg/day. Female but not male rats treated at 20 mg/kg/day showed a significant but relatively small decrease in total protein and increase in AST levels. A statistically significant increase in monocyte count and a higher incidence and generally greater severity of subcutaneous inflammatory cell infiltrates at

the injection site were found in only male rats treated at 20 mg/kg/day. The NOAEL was considered to be 2 mg/kg/day afamelanotide in this study.

5.5.2.2. Melanotan: 13-Week Subcutaneous Implant Toxicity Study in Dogs (246984)

Subcutaneous administration of Melanotan (afamelanotide) to dogs by slow release implants containing 20 or 100 mg afamelanotide every 15 or 30 days for 13 weeks did not cause treatment-related effects on mortality, food consumption, ophthalmoscopy, ECG, hematology, clinical chemistry, urinalysis, and organ weights. Darkened skin below non-white colored fur areas was observed from Day 12 in all animals receiving 20 or 100 mg afamelanotide, except one male and one female. The hair appeared dense and soft from Day 60 for all treated animals including both animals not showing signs of darkened skin. A decrease in weight gain was observed from Week 4 in males receiving 100 mg afamelanotide implants; overall body weight gain in these males was significantly lower than the controls (27%) at the end of study. Histopathological examination of skin from the implantation site or ears of treated animals showed increased incidences and severity of follicular pigmentation and follicular hyperplasia. The NOAEL in this study was 100 mg afamelanotide in females and 20 mg afamelanotide in males receiving implants once every 15 days.

5.5.3. Genetic Toxicology

5.5.3.1. Melanotan: Reverse Mutation Assay "Ames Test" Using *Salmonella* Typhimurium (1564/004)

<u>In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)</u>

Key study findings:

- No significant increases in the frequency of revertant colonies were observed for any strains, with or without metabolic activation, at any dose of Melanotan (afamelanotide)
- Afamelanotide was not mutagenic in the Ames test

GLP compliance: Yes

Test system: *Salmonella* Typhimurium strains TA1535, TA1537, TA102, TA98, and TA100; up to 5000 µg/plate; +/- S9

Study is valid: Yes

5.5.3.2. Melanotan: L5178Y TK+/- Mouse Lymphoma Assay (1564/005)

<u>In Vitro Assays in Mammalian Cells</u>

Key study findings:

- Afamelanotide did not induce a statistically significant or dose-related increase in the mutant frequency, at any dose level, either with or without metabolic activation
- Afamelanotide was not mutagenic to L5178Y cells

GLP compliance: Yes

Test system: Mouse lymphoma cells; up to 5000 µg/mL; +/- S9

Study is valid: Yes

5.5.3.3. Micronucleus Test Of Melanotan, Lot No. 037827 in the Arc(S) Mouse (b) (4) 342.B)

<u>In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)</u>

Key study findings:

- Mice treated with afamelanotide did not reveal an increase in the incidence of micronucleated polychromatic erythrocytes (MPCEs) when compared with the vehicle control group at 24- and 48-hour sampling times.
- Afamelanotide was not clastogenic

GLP compliance: Yes

Test system: Mouse, bone marrow micronuclei; single subcutaneous doses of 20, 100, and 200 mg/kg

Study is valid: Yes

5.5.4. Other Genetic Toxicity Studies

5.5.4.1. Bacterial Reverse Mutation Assay (Ames Test) of Lyophilized Extract of CUV1647 Drug Product (Subcutaneous Implants) (b) (4) 746.B)

5.5.4.2. Mammalian Erythrocyte In Vivo Micronucleus Test of Lyophilized Extract of Afamelanotide in the Mouse (b) (4) 746.A)

The genotoxic potential of afamelanotide and impurities extracted from the drug product (implants) was tested. The lyophilized extract was negative in the Ames test when tested in strains TA98, TA100, TA102, TA1535, and TA1537 at up to 5000 µg/plate in the presence and absence of S9 and negative in the in vivo mouse bone marrow micronucleus assay when mice were treated subcutaneously at doses up to 2000 mg/kg.

5.5.5. Carcinogenicity

Afamelanotide is a structural analogue of the endogenous hormone α-melanocyte stimulating hormone (α-MSH). Its primary pharmacological activity results in increased synthesis, release, and transfer of melanin through stimulation of the melanocortin-1 (MC-1) receptor. The increase in melanin synthesis following afamelanotide treatment is expected to confer photoprotection against DNA damaging effects of sun exposure by its ability to quench reactive oxygen radicals.

Afamelanotide has been evaluated in appropriate nonclinical toxicity studies. Afamelanotide was negative in the standard battery of genotoxicity testing. No reproductive and developmental toxicity was noted in albino and pigmented rats treated with afamelanotide subcutaneously. There were no treatment-related effects in a 10-month subcutaneous implant

toxicity study in dogs and a 6-month subcutaneous implant toxicity study in pigmented rats; the NOAEL for rats was 32 mg or approximately 64 mg/kg and the NOAEL for dogs was 16 mg or 1.6 mg/kg. The NOAEL in rats (64 mg/kg or 384 mg/m^2) represents approximately 39 times the human therapeutic dose (9.9 mg/m^2) based on one afamelanotide implant (16 mg) given to a 60 kg patient. Afamelanotide inhibited the growth of cultured melanoma cells and showed no stimulating effects on primary melanoma or lung metastasis in mice bearing malignant melanoma. Currently, there is no accurate animal model to address the potential of afamelanotide to induce melanomas.

Following subcutaneous administration of the afamelanotide implant in patients, most of the drug is released within the first 48 hours with over 90% released by Day 5 and levels mostly below the limit of detection by Day 7. In adult EPP patients, afamelanotide implant is administered subcutaneously once every 2 months and a maximum of five implants per year are to be administered to each patient. Under the proposed administration regimen and taking pharmacokinetic characteristics into account, total exposure to the drug was expected to be between 25 and 35 days per year, assuming a maximum exposure of 5 and 7 days, respectively, after each dose.

On March 10, 2017, the Applicant was granted a waiver request for conduct of carcinogenicity studies with afamelanotide implant under IND 103131. No carcinogenicity studies are required for this NDA submission for the proposed indication and treatment regimen.

5.5.6. Reproductive and Developmental Toxicology

5.5.6.1. Subcutaneous Fertility and Early Impanation Study in the Rat (1564/011)

Fertility and Early Embryonic Development

Four groups of 28 male SD rats were treated by subcutaneous injections at doses of 0 (vehicle, 0.9% saline), 0.2, 2, or 20 mg/kg/day afamelanotide from 33 days before mating to Day 15 after mating. Four groups of 28 female SD rats were treated by subcutaneous injections at doses of 0 (vehicle, 0.9% saline), 0.2, 2, or 20 mg/kg/day afamelanotide from 19 days before mating to Day 7 of pregnancy. Animals were sacrificed on Day 15 of pregnancy.

Key study findings:

- There were no treatment-related parental toxicity or effects on fertility and reproductive performance.

5.5.6.2. Subcutaneous Embryofetal Development Study in the Rat (1564/007)

Embryo-Fetal Development

Four groups of 24 mated SD female rats subcutaneously received 0 (vehicle, 0.9% saline), 0.2, 2, or 20 mg/kg/day afamelanotide from gestation days (GD) 6 to 17 and were sacrificed on GD 20.

Key study findings:

- There were no treatment-related effects on mortality, clinical signs, body weights, food consumption, number of corpora lutea, number of implants, fetus sex, embryonic/fetal deaths, implantation loss, fetal weight, and fetal external or skeletal findings, except incidents of generalized fur loss in dams at 20 mg/kg/day
- The NOAEL for reproductive toxicity was 20 mg/kg/day.

5.5.6.3. Afamelanotide: Embryofetal Developmental Subcutaneous Injection Toxicity Study in Lister Hooded Rats (10/070-105P)

A preliminary embryo-fetal development toxicology study was conducted in rabbits with afamelanotide. It appeared that rabbits were remarkably intolerant to afamelanotide. As an alternative model, an embryo-fetal developmental toxicity study was conducted in a pigmented strain of rat, the Lister Hooded rat.

Key study findings:

- There were no treatment-related effects on maternal mortality, clinical signs, body weights, food consumption, number of corpora lutea, implantation, uterus weight, and macroscopic findings
- There were no treatment-related effects on number of viable fetuses, fetal death, sex ratio, fetal weight, and fetal external, visceral, or skeletal findings
- The NOAEL was 20 mg/kg/day.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes, OECD

Table 13. Study 10/070-105P Methods

Dose and frequency of dosing:	0 (vehicle), 0.2, 2, and 20 mg/kg/day, once daily
Route of administration:	Subcutaneous
Formulation/vehicle:	0.9% saline
Species/strain:	Lister hooded rats
Number/sex/group:	24 to 25 presumedly pregnant females/group
Satellite groups:	6 mated females in the vehicle control and high-dose groups
Study design:	Female rats were treated from GD 6 to GD 17 and sacrificed on GD 20.
Deviation from study protocol affecting interpretation of results:	No

GD = gestation day

Table 14. Observations and Results

Parameters	Major Findings
Mortality	No deaths
Clinical signs	No treatment-related effects
Body weights	No treatment-related effects
Necropsy findings Cesarean section data	No treatment-related effects on number of corpora lutea, implantation, uterus weight, and macroscopic findings
Necropsy findings Offspring	No treatment-related effects on number of viable fetuses, fetal death, sex ratio, fetal weight, and external, visceral, or skeletal findings

5.5.6.4. Subcutaneous Pre- and Post-Natal Development Study in the Rat (1564/010)

Prenatal and Postnatal Development

Four groups of 28 mated SD female rats (F_0) subcutaneously received 0 (vehicle, 0.9% saline), 0.2, 2, or 20 mg/kg/day afamelanotide from GD 6 through lactation day 21. Females and offspring were maintained throughout gestation and lactation until weaning. At weaning, twenty-four male and twenty-four female offspring from each group were selected to produce the F_1 generation. The F_1 males and females were maintained up to 10 weeks of age during which time they were assessed for physical, behavioral and sexual development. At 10 weeks of age F_1 males and females were paired within their respective dose groups for up to 3 weeks. After positive evidence of mating was observed, the F_1 females were maintained until Day 20 *post coitum* when they were sacrificed (approximately 13 weeks of age) and their uterine contents examined. F_1 males were sacrificed and examined macroscopically after confirmation of successful mating (approximately 14 weeks of age).

Key study findings:

- There were no treatment-related effects on maternal (F_0) body weights, food consumption, gestation length, parturition, macroscopic findings, litter size, sex ratio, and offspring survival. At 20 mg/kg/day, the majority of F_0 females showed fur loss or scabbing around the injection sites indicating some local reaction to treatment.
- There were no treatment-related effects on fetal (F_1) clinical signs, physical, behavioral and sexual development, estrous cycle of females, mating performance, number of corpora lutea, implantation, and macroscopic findings, except lower bodyweight gain (up to 17%) seen only prior to weaning in the F_1 offspring derived from females receiving 20 mg/kg/day.
- There were no treatment-related effects on fetal (F_2) weight, sex ratio, and external appearance.
- The NOAEL for reproductive and developmental toxicity was 20 mg/kg/day.

5.5.7. Other Toxicology Studies

5.5.7.1. Excipients

[redacted] (b) (4): Poly (DL-Lactide-co-glycolide) [redacted] (b) (4). Degradation

(b) (4) occurs by hydrolysis. The use of biodegradable polymers comprising of lactide and glycolide in medicine is well established. Polylactide is hydrolyzed in the body to lactic acid; polyglycolide is degraded by hydrolysis to glycolic acid. Poly (DL-Lactide-co-glycolide) (b) (4) ill be degraded to lactic acid and glycolic acid in the body. (b) (4) This drug product has been tested in the chronic studies in rats and dogs, which can further support the safety of the (b) (4) excipients. This drug product will be used in patients once every 2 months and a maximum of (b) (4) implants will be subcutaneously injected into a patient's body per year. From a Pharmacology/Toxicology perspective, there is no safety concern for the two excipients in the afamelanotide implant for this NDA.

6. Clinical Pharmacology

6.1. Executive Summary

Afamelanotide is a new molecular entity (NME) and a small peptide (molecular weight of 1647 Da.) comprised of 11 L-amino acids, one D-phenyl-alanine and one glycine moieties. The Applicant developed a controlled release resorbable implant formulation containing 16 mg of afamelanotide for (b) (4) adult patients with erythropoietic protoporphyria (EPP). The proposed dosing regimen is to administer subcutaneously once every 2 months when required for photoprotection; the overall duration of treatment will be at the health care provider's discretion.

The Applicant evaluated the pharmacokinetic (PK) of afamelanotide in healthy volunteers in 8 Phase 1 studies. Among these studies, the PK of the to-be-marketed formulations was characterized in two studies: CUV028 and CUV038. Study CUV028 was a relative bioavailability study comparing implants manufactured using the previous and final (i.e., to-be-marketed product) manufacturing processes. Study CUV038 employed more frequent PK sampling timepoints and a more sensitive bioanalytical method to quantify afamelanotide systemic concentrations. The results of Study CUV038 would be included in product labeling.

The pharmacodynamics (PD) of afamelanotide was evaluated by measuring melanin density (MD), which reflects changes in melanogenesis. The MD measurements after administration of afamelanotide in solution and implants were assessed in nine studies in healthy volunteers and two studies in patients with EPP (CUV010 and CUV017).

The key review findings with specific recommendations and comments are summarized below in Table 15.

Table 15. Summary of Clinical Pharmacology Review

Review Issues	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The selection of the 16-mg dose is supported by dose response evaluated in three Phase 1 studies (CUV006, CUV007, CUV009).
Pharmacokinetics (PK)	The PK of afamelanotide following administration of a single 16-mg dose of the to-be-marketed formulation was evaluated in healthy volunteers in studies CUV028 and CUV038.
Pharmacodynamics (PD)	Afamelanotide increases production of eumelanin which was evaluated by measuring changes in MD. The PD effects of afamelanotide were evaluated in 5 studies (CUV006, CUV009, CUV028, CUV038 and CUV017).
General dosing instruction	The proposed dosing regimen of one 16 mg implant to be administered subcutaneously every 2 months when required for photoprotection is acceptable and supported by dose-response.
Bridge between the to-be-marketed and clinical trial formulations	The to-be-marketed formulation was used in the three trials that are considered pivotal for efficacy and safety (CUV030, CUV039 and CUV029), and thus no bridge is needed.
Immunogenicity	The immunogenicity potential appears to be low. The immunogenicity potential of afamelanotide was evaluated in 17 patients (CUV010 and CUV017) and 9 patients during the Compassionate Use Program in Europe (this product is approved in the EU).
QTc prolongation potential	The Applicant requested a wavier for TQT study. The request has been determined unacceptable by CDER DCRP QT Interdisciplinary Review Team (See QT-IRT Review by Dr. Nan Zheng in DARRTS dated Feb 15, 2019). TQT assessment will be requested as a Post Marketing Requirement (PMR).

MD = melanin density, EU = European Union, TQT = thorough QT/QTc, CDER = Center for Drug Evaluation and Research, DCRP = Division of Cardiovascular and Renal Products, IRT = interdisciplinary review team

6.1.1. Recommendations

From a clinical pharmacology standpoint, this NDA is acceptable.

6.1.2. Postmarketing Requirement

Conduct TQT assessment to adequately characterize the effect of afamelanotide on cardiac repolarization.

Reviewer's Comment: The Applicant's request to not conduct a QT study is not acceptable because the available nonclinical and clinical data are not adequate for the characterization of afamelanotide's effect on the QT interval. The detailed recommendations for TQT assessment were provided by Dr. Nan Zheng in the QT IRT consult memorandum (dated February 15, 2019 in DARRTS).

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Table 16. Summary of Pharmacology and Clinical Pharmacokinetics of Scenesse

Mechanism of action	The proposed mechanism of action suggests that afamelanotide binds to MC1R and activates the synthesis of eumelanin, which provides photoprotection through absorbing and scattering visible and UV light and decreasing free radicals and reactive oxygen species.
Pharmacokinetics (PK)	The Applicant did not conduct a formal ADME study to fully characterize the PK of afamelanotide. The plasma concentrations of afamelanotide following a single-dose SQ (implant) administration of 16 mg were evaluated in healthy subjects in two Phase 1 studies (CUV028 and CUV038). For most subjects, the last measurable concentration was at 4 days post-dose. The PK parameters from these two studies following a single-dose of 16 mg implant are summarized in the table below.

PK Parameters	CUV028 (Mean ± SD, n=12)	CUV038 (Mean ± SD, n=12)
C_{max} (ng/mL)	5.60±4.28	3.65±1.27
T_{max} (hr)	31.0±19.3	36.0±7.5
$AUC_{0\text{-last}}$ (hr*ng/mL)	191.2±85.9	136.6±43.1
$AUC_{0\text{-inf}}$ (hr*ng/mL)	272.4±87.8	138.9±42.6

Pharmacodynamics (PD)	Administration of afamelanotide implant resulted in an increased MD, suggesting an increased production of eumelanin. In CUV038, following a single dose administration of 16 mg implant in healthy subjects, MD increased by an average of 0.35 MD units across 6 anatomical sites from baseline to Day 7 and then sustained up to Day 28. While MD started to decrease slightly after Day 28, a statistically higher MD level compared to baseline was observed until Day 60. When MD was measured in patients with EPP in Study CUV017, the changes in average melanin density followed a cyclic pattern consistent with the alternate dosing schedule of the implants with placebo, demonstrating the efficacy of afamelanotide in increasing melanin density.
Drug-drug interaction	Evaluation of drug-drug interaction was not performed in this NDA. The lack of drug-drug interaction evaluation with Scenesse was addressed in the proposed labelling.
Immunogenicity	The immunogenicity potential of Scenesse was evaluated in a total of 26 patients from studies CUV010 and CUV017 and the EU Compassionate Use Program. Except in 3 patients who had pre-existing immunoreactivity, no immunoreactivity was found in the rest of the patients. The immunoreactivity data in 3 patients is considered as inconclusive.
Bioanalytical method	Adequately validated HPLC/MS/MS method was used to determine afamelanotide in human plasma.

MC1R = melanocortin-1 receptor, ADME = Absorption, Distribution, Metabolism and Excretion, AUC = area under the curve, MD = melanin density; SD = standard deviation; PK = pharmacokinetic; UV = ultraviolet

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The Applicant's proposed dosing regimen is one implant (16 mg) administered subcutaneously every 2 months during periods when photoprotection is required. The overall duration of treatment is at the health care provider's discretion. This dose and dosing regimen are supported by Phase 2 dose-response studies, PK and PD results from studies CUV006, CUV007 and CUV009 as well as by the efficacy results from studies CUV039, CUV030 and CUV029.

Therapeutic Individualization

Therapeutic individualization was not evaluated in this NDA.

6.2.3. Outstanding Issues

Afamelanotide's effect on the QT interval has not been adequately characterized. A PMR will be issued to address this issue.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

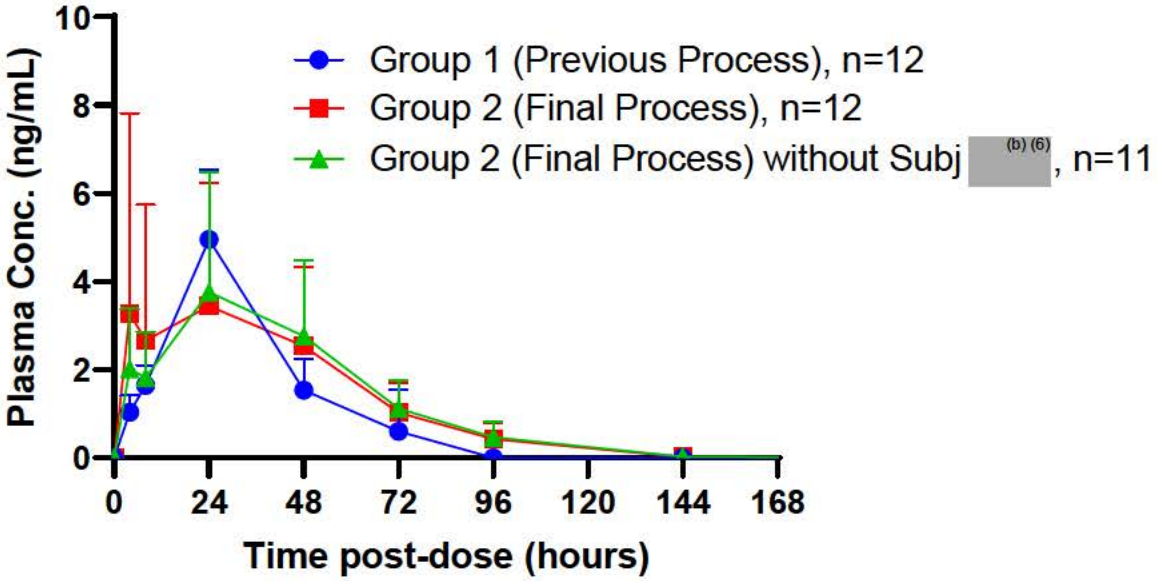
PK Assessments

The PK of afamelanotide in solution and implants were assessed in healthy volunteers in 8 Phase I studies. Study CUV038 employed more frequent PK sampling time points and a more sensitive bioanalytical method compared to Study CUV028.

<u>Study CUV028</u>

This was a single dose, parallel-group, open-label PK and PD study in healthy adult male and female subjects. It served as a clinical bridging study comparing PK and PD measurements following administration of implants manufactured using the old (previous) manufacturing process compared to the final (i.e., to-be-marketed product) manufacturing processes. A total of 24 subjects were assigned to receive either an afamelanotide 16 mg implant from the old manufacturing process (Group 1) or an afamelanotide 16 mg implant from the final manufacturing process (Group 2). Blood samples were collected at pre-dose and then at 4 h and 8 hours post-dose on Day 1 and on Days 2, 3, 4, 5, 7, 15 and 60. The PK profiles from Groups 1 and 2 are shown in Figure 2 and the PK parameters are summarized in Table 17. The relative bioavailability comparisons of PK parameters from the two groups are summarized in Table 18. One subject from Group 2 (Subject (b) (6) showed an initial spike in afamelanotide concentration shortly following administration of the implant, which was not observed in other subjects (Figure 34). Data in Figure 2, Table 17, and Table 18 are presented by including and excluding data from Subject (b) (6)

Figure 2. Mean (± SD) Plasma Concentrations of Afamelanotide From Study CUV028



Source: Reviewer's plot; mean ± SD

Table 17. Summary of Pharmacokinetic Parameters for Afamelanotide Following a Single Dose of 16 mg Afamelanotide Implant in Healthy Subjects From Study CUV028

Parameter	Afamelanotide		
	GROUP 1 (Previous Manufacturing Process) Lot #470 n=12	GROUP 2 (Optimized Final Manufacturing Process) Lot #504 n=12	*p* =
C_{max} (mean; ng/mL)	4.95 ± 1.58	5.60 ± 4.28 [4.56 ± 2.40]*	0.39 [0.15]*
T_{max} (median; h)	24 (Day 2)	24 (Day 2) [24 (Day 2)]*	0.63 [0.64]*
$AUC_{(0\text{-last})}$ (mean; h*ng/mL)	162.5 ± 32.1	191.2 ± 85.9 [200.2 ± 84.0]*	0.29 [0.16]*
$AUC_{(0\text{-}\infty)}$ (mean; h*ng/mL)	N/A	272.4 ± 87.8 [272.4 ± 87.8]	N/A

*Results in brackets exclude subject (b) (6)

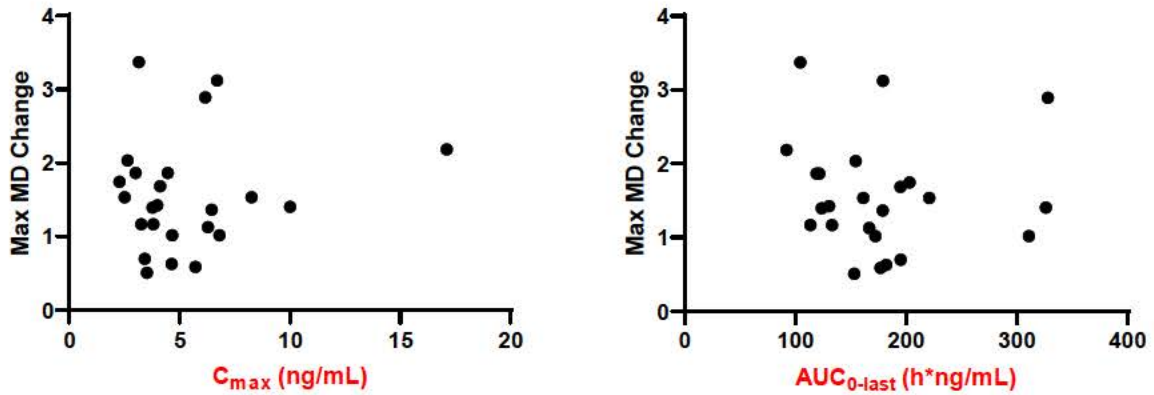
An initial burst of afamelanotide was observed in subject (b) (6)
AUC = area under the curve
Source: Adapted from Table 2.7.2-3 in Module 2.7.2 Summary of Clinical Pharmacology Studies.

Table 18. Summary of Relative Bioavailability Results Comparing Previous and Final Manufacturing Processes From Study CUV028

Log-Transformed Parameters (Geometric Mean)	Group 1 (Previous Manufacturing Process) n=12	Group 2 (Final Manufacturing Process) n=12	%Ratio (Group 2/Group 1)	90% Confidence Interval
C_{max} (ng/mL)	4.75	4.60 [4.08]*	96.8 [85.9]*	68.9 – 136.1 [64.6 – 114.2]*
$AUC_{0\text{-last}}$ (h*ng/mL)	159.5	174.8 [185.3]*	109.6 [116.1]*	86.2 – 139.3 [92.4 – 146.0]*

* Results in brackets exclude subject (b) (6); An initial burst of afamelanotide was observed in subject (b) (6).
AUC = area under the curve
Source: Adapted from Tables 3 and 4 in CSR for Study CUV028.

Figure 3. Examination of PD (Melanin Density Change) - Exposure (C_{max} or AUC) Relationship From Study CUV028



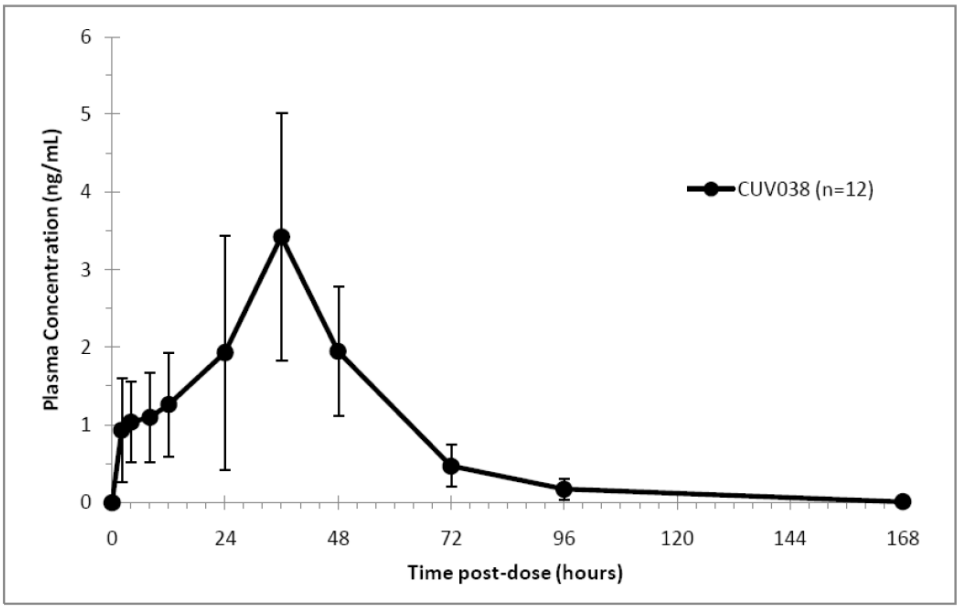
Max MD Change (maximum melanin density change) was determined from 49 measurements per subject (7 anatomical sites x 7 timepoints =49).
AUC = area under the curve; PD = pharmacodynamics
Source: Reviewer's plot

<u>Reviewer's Comments</u>: In Group 2, an initial burst release of afamelanotide was observed in one subject (Subject (b) (6), Figure 34 under Section 20.2.2), resulting in a slightly higher mean C_{max} in this group compared to that of Group 1 (Table 17). However, the different PK profile of Subject (b) (6) does not appear to have a significant effect on PD of afamelanotide (Figure 35 under Section 20.2.2). In addition, the mean change in melanin density per anatomical site from Group 1 and Group 2 were generally comparable suggesting that the possible differences in PK due to the change in manufacturing process is unlikely to impact the PD (Figure 6) and therefore efficacy. The aforementioned statements are also supported by the lack of clear correlation between the maximal melanin density change and C_{max} or $AUC_{0\text{-last}}$ (Figure 3). Given the low number of subjects evaluated in the study and the relatively high inter-subject variability, it appears that the potential differences that might exist between the products manufactured by the two processes is unlikely to result in a clinically meaningful difference. Furthermore, the final to-be-marketed formulation manufactured using the new manufacturing process was used in the pivotal Phase 3 efficacy and safety trials.

Study CUV038

This was a single dose, open-label PK, safety, tolerability and efficacy study in healthy male volunteers. A total of 12 subjects received a single 16-mg dose of afamelanotide implant. Blood samples were collected at pre-dose and then at 2, 4, 8, 12, 24, 36, 48, 72, 96, 168, 240, and 336 hours post-dose. The PK profile is presented in Figure 4 and the PK parameters are summarized in Table 19. For most subjects, the last measurable concentration (LOQ =0.025 ng/mL) was at 96 hours post-dose.

Figure 4. Mean (± SD) Plasma Concentrations of Afamelanotide From Study CUV038



Source: Adapted from Figure 2.7.2-1 in Module 2.7.2 Summary of Clinical Pharmacology Studies.

Table 19. Summary of Mean Plasma PK Parameters for Afamelanotide Following a Single Dose of 16 mg Afamelanotide Implant in Healthy Subjects From Study CUV038

Parameter	Pharmacokinetic Population (n=12)					
	Mean	SD	Median	Minimum	Maximum	Geometric Mean
C_{max} (ng/mL)	3.65	1.27	3.38	2.12	6.03	3.47
T_{max} (hr)	36.0	7.5	36.0	24.1	49.6	NA
$AUC_{0\text{-last}}$ (hr*ng/mL)	136.6	43.1	134.8	83.9	238.7	131.0
$AUC_{0\text{-inf}}$ (hr*ng/mL)	138.9	42.6	138.1	87.8	239.5	133.5
$AUC_{0\text{-96h}}$ (hr*ng/mL)	133.1	38.7	130.4	84.9	225.4	128.5

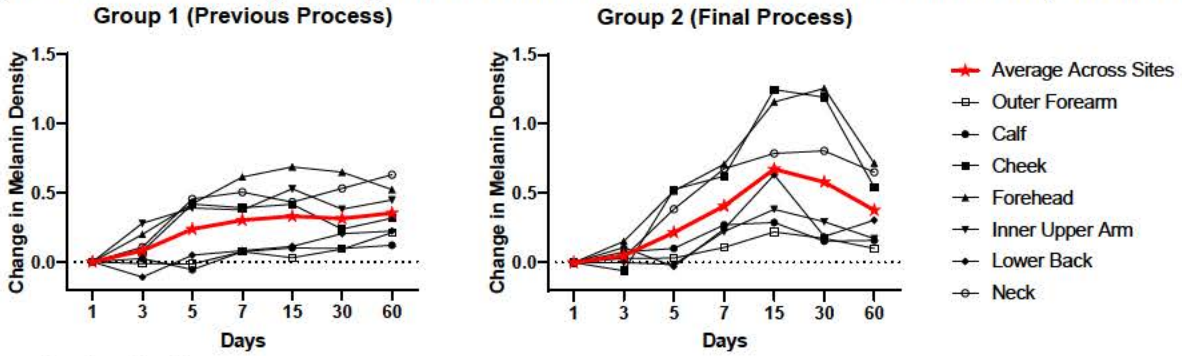
SD= Standard Deviation
AUC = area under the curve
Source: Adapted from Table 2.7.2-5 in Module 2.7.2 Summary of Clinical Pharmacology Studies.

PD Assessments

The PD effects of afamelanotide were assessed by MD measurements, which reflect changes in melanogenesis. The MD measurements after administration of afamelanotide in solution and implants were assessed in nine studies in healthy volunteers and two studies in patients with

EPP. Of these 11 studies, five studies (CUV006, CUV009, CUV028, CUV038 and CUV017) used the final implant formulation in the proposed strength of 16 mg. The changes in MD following a single dose of 16 mg afamelanotide implant from CUV028 and CUV038 are shown in Figure 5 and Figure 7, respectively. The comparisons of previous and final manufacturing processes in terms of the change in melanin density from baseline per anatomical site from CUV028 are shown in Figure 6. An overall increase in MD across different anatomical sites was observed following administration of afamelanotide. An increase in MD was observed to Day 7 with the effect being sustained to approximately Day 28. Although an increase in MD started to decrease after Day 28, the change was still positive compared to baseline until approximately 60 days post-dose.

Figure 5. Melanin Density Change From Baseline Across Anatomical Sites From Study CUV028



Source: Reviewer's plot

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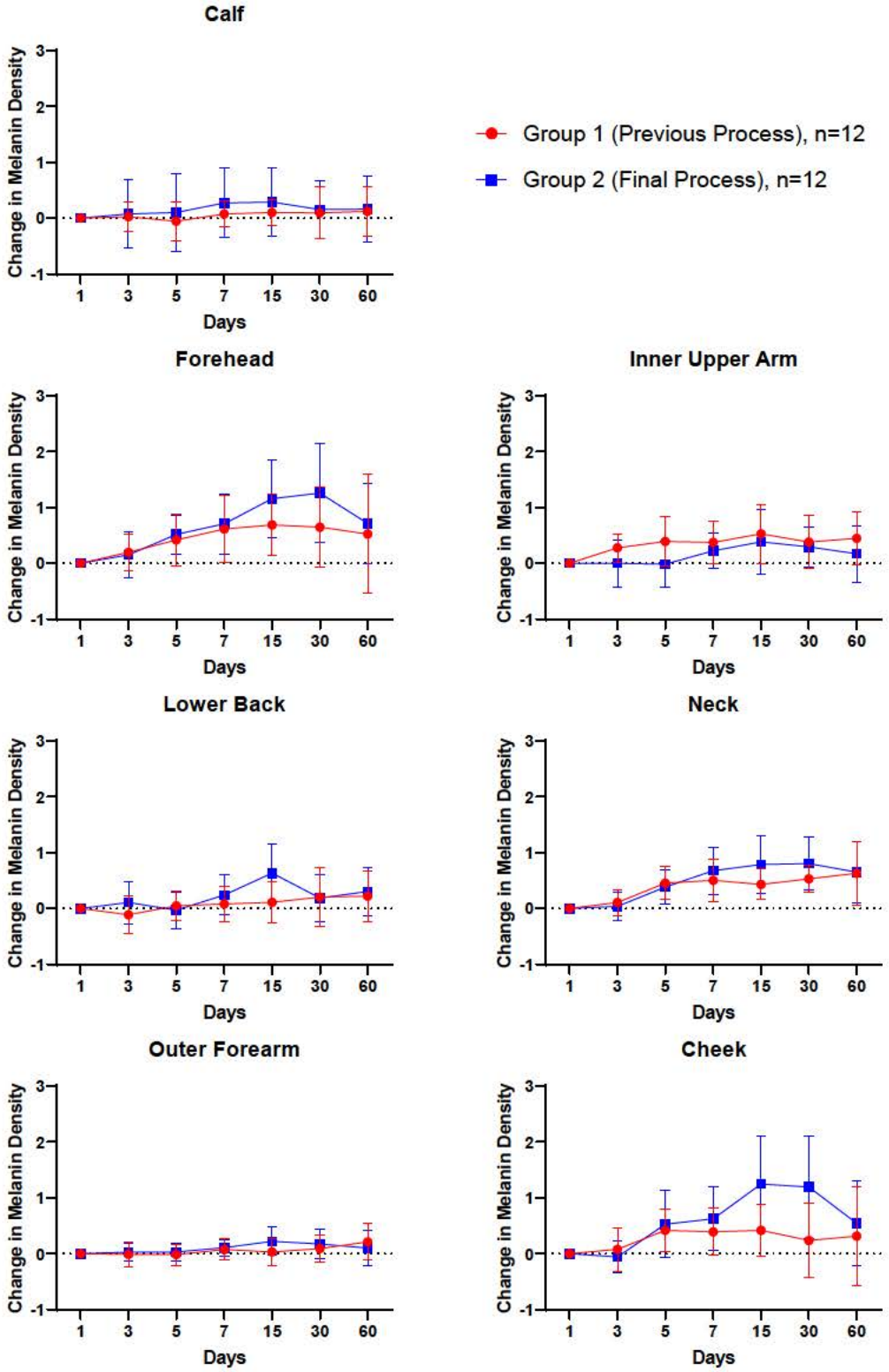
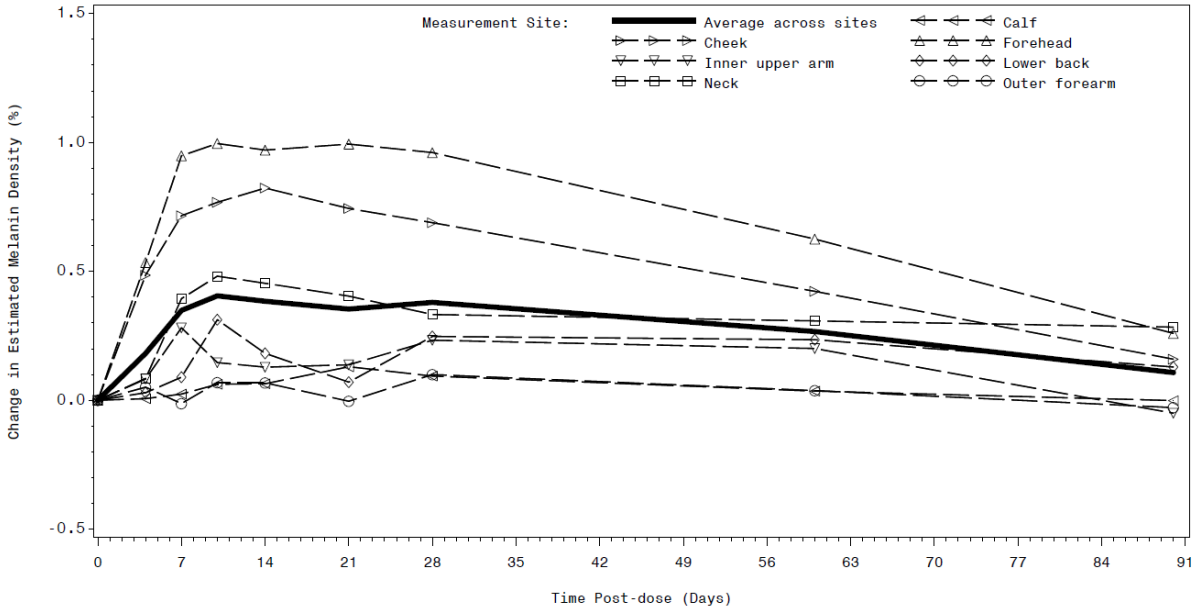
Figure 6. Comparison of Change in Melanin Density From Baseline Per Anatomical Site in Group 1 vs. Group 2 From Study CUV028



Source: Reviewer's plot

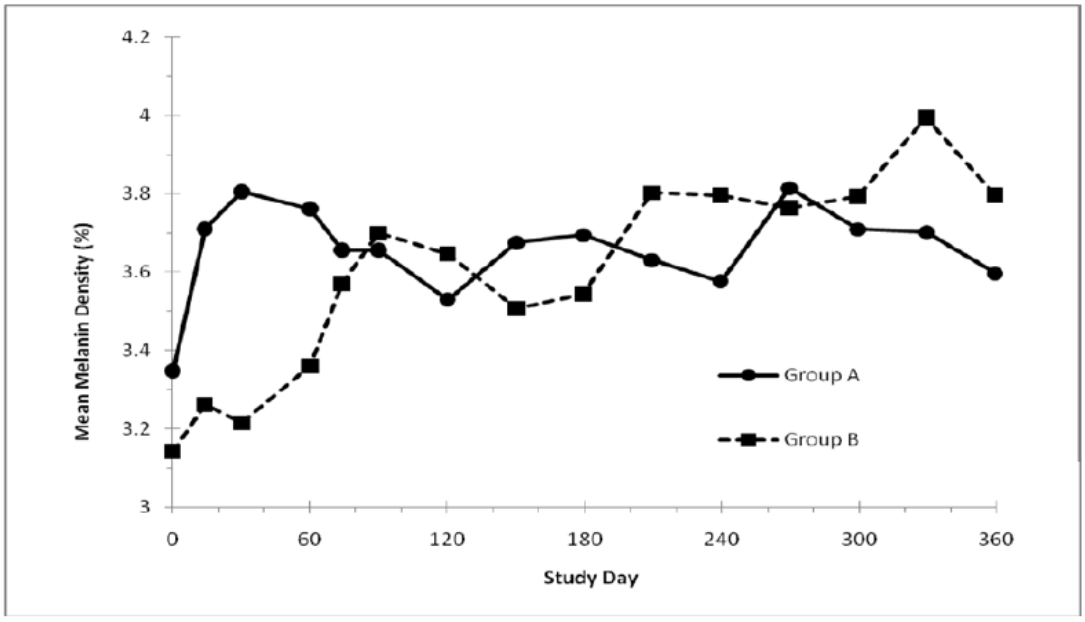
Figure 7. Mean Melanin Density Change From Baseline Across Anatomical Sites From Study CUV038



Source: Adapted from Figure 14.3.3.4 in CSR for Study CUV038.

In addition, the PD effect of afamelanotide compared to placebo was demonstrated in study CUV017 in which subjects received implants of 16 mg afamelanotide or placebo in alternative crossover fashion. The changes in mean MD followed a cyclic pattern consistent with the administration of afamelanotide and placebo as shown in Figure 8 below.

Figure 8. Mean Melanin Density Change Over Time From Study CUV017



Group A: Active/Placebo/ Active/Placebo/ Active/Placebo on Days 0/60/120/180/240/300
Group B: Placebo/ Active/Placebo/ Active/Placebo/Active on Days 0/60/120/180/240/300

Source: Adapted from Figure 11.E in CSR for Study CUV017.

Reviewer's Comments: The sustained effect of increased MD up to approximately 60 days post dosing in both Figure 7 and Figure 8 supports the proposed dosing frequency of administering once every 2 months. In addition, it appears that the change in melanin density is generally more pronounced in anatomical sites that are exposed to light (i.e., forehead, cheek and neck) compared to those that are not (i.e., lower back and calf) as evidenced in Figure 7 (CUV038) and Figure 5 (CUV028).

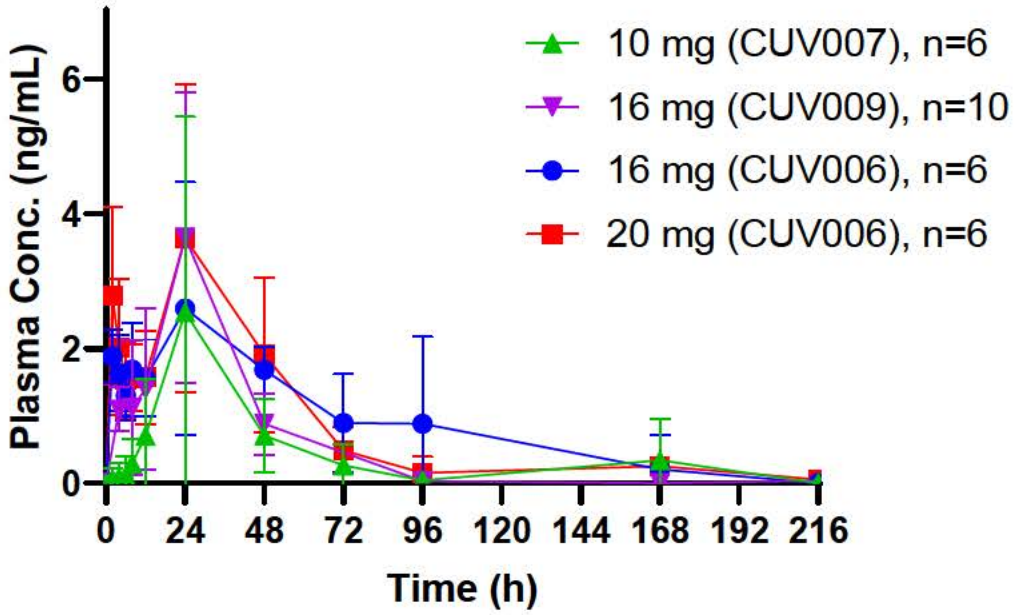
Dose Selection

The Applicant's rationale on dose selection was based on three Phase 1 studies (CUV006, CUV007 and CUV009) comparing the PK and PD effects following an administration of implants in three different strengths (10, 16 and 20 mg). The Applicant concluded that the PK profiles of 16 mg and 20 mg strengths are comparable (Figure 9). The Applicant also concluded that the PD effects measured by change in melanin density of 16 mg and 20 mg strengths are comparable, but higher than the 10 mg strength (Figure 10). Ultimately, the 16 mg strength was selected.

The key study designs of these three studies are:

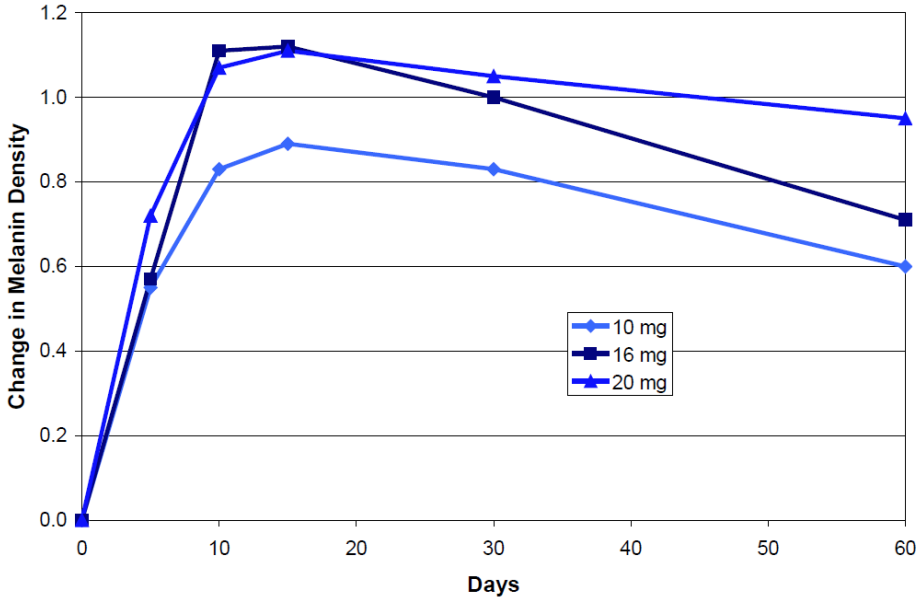
- CUV006: A single dose of 16 or 20 mg SC in 12 healthy volunteers
- CUV007: A single dose of 10 mg SC in 6 healthy volunteers
- CUV009: Two doses of 16 mg SC administered 28 days apart in 10 healthy volunteers

Figure 9. The PK Profiles of Afamelanotide Following Administration of 10 mg, 16 mg, and 20 mg Implants From Studies CUV006, CUV007 and CUV009



Source: Reviewer's plot, mean ± SD

Figure 10. Change in Melanin Density Over Time from Baseline on Sun Exposed Areas Following Administration of 10 mg, 16 mg, and 20 mg of Afamelanotide Implants



Source: Adapted from Figure 2.7.2-7 in Module 2.7.2 Summary of Clinical Pharmacology Studies.

Reviewer's Comments: The Applicant did not specify which anatomical sites were identified as "sun exposed areas" and used as data in Figure 10. In the study reports for CUV007 and CUV009, cheek and forehead are identified as the "exposed sites" and it is likely that data from the same sites were used from CUV006. Since the MD data for the 10-mg dose comes from possibly more sun exposed areas of forehead and cheek, which have shown greater effect (Figure 7), the lack of exact anatomical site information for MD data for the 16 mg and 20-mg dose would not matter. The MD with the 10-mg dose is indeed lower than the 16 mg and 20-mg doses.

Immunogenicity Assessments

The Applicant assessed immunogenicity potential in 17 patients in two studies (CUV010 and CUV017) and nine patients during the EU Compassionate Use Program. The mean and median exposure time of these patients were 3.2 years (range: 8 months to >6 years). There were three patients (out of 26) who had pre-existing immunoreactivity; their immunoreactivity did not change during the treatment with afamelanotide. No immunoreactivity was found in the rest of patients.

Reviewer's Comment: The immunogenicity potential of afamelanotide appears to be low.

6.3.2. Clinical Pharmacology Questions

Does the Clinical Pharmacology Program Provide Supportive Evidence of Effectiveness?

The Clinical Pharmacology program in this NDA is supported by the dose selection data from three Phase 1 studies which evaluated dose-response by characterizing PK and PD of afamelanotide from three different strengths in healthy subjects. The efficacy of Scenesse in

patients with EPP was evaluated in Phase 2/3 studies CUV039, CUV030 and CUV029. See Section 8 for the review of efficacy.

Is the Proposed Dosing Regimen Appropriate for the General Patient Population for Which the Indication is Being Sought?

The proposed dose and dosing regimen are appropriately supported by dose-response study, PK/PD assessment and Phase 2/3 efficacy and safety data in adult patients with EPP.

Is an Alternative Dosing Regimen or Management Strategy Required for Subpopulations Based on Intrinsic Patient Factors?

No. The effect of intrinsic and extrinsic factors was not evaluated in this NDA. EPP is a rare disease and the Applicant did not obtain data to permit population PK assessments to carry out such analysis. Lack of this assessment is going to be reflected in the product labeling.

Are There Clinically Relevant Food-Drug or Drug-Drug Interactions, and What is the Appropriate Management Strategy?

Food-drug interaction are not assessed for implant formulations as they are not administered orally.

The Applicant has not conducted any dedicated drug-drug interaction studies. The proposed labelling language (b) (4) . The labeling also addresses that no specific interaction studies have been performed with Scenesse.

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The development program for afamelanotide implant included five trials:

- Phase 3 trials

  Randomized, vehicle-controlled trials to evaluate the efficacy and safety of an afamelanotide implant administered subcutaneously every 2 months in adults with EPP.

  – CUV039
  – CUV030
  – CUV029

- Phase 2 trials

  Afamelanotide implant administered subcutaneously in adults with EPP.

  – CUV017: multicenter, crossover, randomized, vehicle-controlled study

- CUV010: open-label, proof-of-concept study

The table below provides a summary of all trials pertinent to the evaluation of the efficacy and safety of afamelanotide implant to increase the duration of pain-free sun exposure in adults with EPP.

Table 20. Listing of Clinical Trials Relevant to NDA 210797

Trial Identity NCT #	Trial Design	Regimen/ Schedule/Route	Study Efficacy Endpoints	Treatment Duration/ Follow-Up	No. of Patients Enrolled	Study Population	Countries and Number of Sites
Controlled Studies to Support Efficacy and Safety							
CUV039 NCT# 01605136	Phase 3, multicenter (MC), vehicle-controlled (VC) trial	Afamelanotide (afa) 16 mg implant subcutaneously (SC) every 2 months (Q2M) (Day 0, 60, and 120)	Primary • Duration of direct sunlight exposure between 10:00 and 18:00 hours on days when no pain was experienced	3 implants 6 months with safety follow-up 1 year	93 Afa: 48 Veh: 45	Adults 18yo and older with EPP	United States - 7
CUV030 NCT# 01097044	Phase 3, MC, VC trial	Afa 16 mg implant SC Q2M (Day 0, 60, and 120)	Adapted evaluation • Number of hours of direct sunlight exposure between 10:00 and 15:00 hours on days when no pain was experienced (pain score of 0).	3 implants 6 months	77 Afa: 39 Veh: 38	Adults 18yo and older with EPP	United States – 7
CUV029 NCT# 00979745	Phase 3, MC, VC trial	Afa 16 mg implant SC Q2M (Day 0, 60, 120, 180, and 240)	Primary (modified) • Time spent in direct sunlight between 10:00 and 15:00 hours	5 implants 9 months	74 Afa: 38 Veh: 36	Adults 18 to 70yo with EPP	EU – 8 Finland -1 France – 1 Germany – 1 Ireland - 1 Netherlands - 2 UK - 2

Trial Identity NCT #	Trial Design	Regimen/ Schedule/Route	Study Efficacy Endpoints	Treatment Duration/ Follow-Up	No. of Patients Enrolled	Study Population	Countries and Number of Sites
Studies to Support Safety							
CUV010	Phase 2, proof-of-concept study	Afa 20 mg implant SC Q2M	Primary • The amount and type of rescue medication used on days of spontaneous phototoxic reactions. • Change in melanin density (MD) from baseline to Days 30, 60, 90 and 120 across 6 anatomic sites (forehead, left cheek, right inside upper arm, left medial forearm, right side of abdomen left side of sacral region/buttock)	2 implants 4 months	5 Afa: 5	Adults 18 to 70yo FST I-IV with EPP	Switzerland – 1
CUV017 NCT# 04053270	Phase 2, MC, multiple crossover, VC study	Alternating afa 16 mg implant SC Q2M with vehicle implant SC Q2M, subjects randomized at baseline to Group A or B:	Primary • The mean severity score for phototoxic reactions that occurred whilst patients were on active compared with vehicle implants.	12 months 6 implants alternating active and vehicle	100 Afa: 100	Adults 18 to 70yo with EPP	Australia – 1 <u>EU – 7</u> France – 1 Germany – 1 Italy - 1 Netherlands – 1 Sweden - 1 Switzerland - 1 UK - 1

7.2. Review Strategy

The Applicant conducted five clinical studies in subjects with erythropoietic protoporphyria (EPP). The first clinical study in the EPP development program was a small single-arm open-label Phase 2 proof-of-concept study (Study 010). The study enrolled five subjects, and all subjects were treated with an afamelanotide 20 mg implant (compared with the 16 mg implant used in subsequent studies). Subjects in the study received two implants and efficacy was assessed under controlled photoprovocation. This study was conducted in Europe from September 2006 to February 2007. Because this study did not include a control arm and used a higher dose than the proposed to-be-marketed product, this study will not be evaluated for efficacy.

The second study (Study 017) was a cross-over study where 100 subjects alternated between afamelanotide 16 mg implants (A) or placebo implants (P) for six treatment cycles (either A-P-A-P-A-P or P-A-P-A-P-A). This study was conducted in Europe from May 2007 to December 2009. The study was designed to assess efficacy by comparing the number and severity of phototoxic reactions between periods where subjects were treated with active and placebo implants. The Applicant made post hoc changes to the analysis population (using data only from subjects who had a minimum total pain score during the study) and to the analyses. Because the results reported by the Applicant were based on post hoc changes to the analyses and the study design and endpoints are different from the other studies in the development program, the efficacy results for this study will not be discussed in this review.

Studies 029 and 030 were randomized, parallel group, placebo-controlled studies and both were initiated before the analysis results from Study 017 were available. Study 029 was conducted in Europe and Study 030 was conducted in the US. Subjects in Study 029 received five implants and were followed for 270 days. Subjects in Study 030 received 3 implants and were followed for 180 days. Study 029 was conducted from January 2010 to May 2011. Study 030 was conducted from April 2010 to January 2011. The studies were designed to assess efficacy based on the number and severity of phototoxic reactions during the study. Topline results for the shorter study (Study 030) were analyzed in June 2011, and the results of the prespecified primary endpoints based on the overall severity of phototoxicity reactions were not statistically significant. Thus, in consultation with outside experts, the Applicant identified an alternate endpoint that could be assessed based on the collected data that measured the duration of time that subjects were able to spend outdoors in direct sunlight without experiencing pain. Study 029 remained blinded while the results of Study 030 were re-analyzed with the new endpoints. Based on the findings from Study 030, the statistical analysis plan for Study 029 was updated prior to unblinding Study 029 to match the analysis plan that was developed for Study 030. Studies 029 and 030 will be reviewed as supportive studies.

The final Phase 3 study (Study 039) was a randomized, parallel group, placebo-controlled study conducted in the US. Subjects in Study 039 received 3 implants and were followed for 180 days. The study was conducted from May 2012 to July 2013. The primary endpoint was prespecified

as the number of hours that subjects were able to spend outdoors in direct sunlight on days with no pain. Study 039 will be reviewed as a pivotal study.

8. Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study CUV039

Trial Design

Study CUV039 is a randomized, double-blind, placebo-controlled study of afamelanotide implants, 16 mg in subjects with EPP. The primary objective of the study is to assess whether afamelanotide can enable EPP subjects to expose themselves to direct sunlight without incurring pain.

Study 039 was designed to enroll between 75 and 100 subjects age 18 years and older with characteristic symptoms of EPP phototoxicity and a biochemically-confirmed diagnosis of EPP. The study was conducted in the US. Subjects were randomized 1:1 within-center using blocks of size 4. Because of the limited number of subjects with EPP, subjects who had been randomized to placebo in Study 030 (the failed earlier US Study) were eligible for enrollment in Study 039. Subjects in Study 039 received three implants on Days 0, 60, and 120 and were followed for 180 days. Subjects were evaluated at screening, baseline (Day 0) and Days 60, 120, and 180. A follow-up safety visit was to be held on Day 360. All subjects initiated treatment in May through July of 2012 so that the study treatment period would include summer months. A subset of subjects enrolled at one center were to undergo controlled photoprovocation. These subjects underwent photoprovocation on the hand and back on Days 0, 30, 60, 90, 120, 150, and 180.

Study Endpoints

Efficacy information was collected from subject diaries regarding the level of phototoxic pain and the amount of time spent outdoors in direct sun or in shade. In the earlier studies (017, 029 and 030), the protocols were designed to assess primary endpoints based on the number and total severity of phototoxic reactions during the study. However, because the earlier studies were unable to detect a treatment effect related to the total severity of phototoxic reactions, the Applicant sought out additional expert opinion and designed Study 039 to assess efficacy in terms of the number of hours of sun exposure on days with no pain.

Subjects recorded data on sun exposure and phototoxic pain daily for 180 days. Phototoxic pain for each day was recorded by answering the question “Have you experienced any reactions to light today” (Yes/No) and indicating the pain level on a Likert scale from 0 to 10 (from ‘No Pain’ to ‘Worst Imaginable’). Subjects also recorded the amount of time spent outdoors in either direct sunlight or shade from 10:00 to 18:00 hours. A copy of the daily diary for Study 039 is presented below:

Figure 11. Daily Diary for Study 039

1. EPP Monitoring

1.1 Have you experienced any reactions to light today? Yes ☐ No ☐

1.2 If 'yes', please indicate on the scale below how bad your pain was from this reaction:

0	1	2	3	4	5	6	7	8	9	10
No Pain	Mild			Moderate			Severe			Worst Imaginable

2. Time Spent Outdoors

2.1 Did you spend any time outdoors today? Yes ☐ No ☐

2.2 If 'yes', please enter the time period that you were in ***direct sunlight***. *(Each box represents 15 minutes)*

10:00 11:00 12:00 13:00 14:00 15:00 16:00 17:00 18:00

2.3 If 'yes', please enter the time period that you were in the ***shade***. *(Each box represents 15 minutes)*

10:00 11:00 12:00 13:00 14:00 15:00 16:00 17:00 18:00

Source: page 41 of Protocol CUV039 v. 4.

The primary efficacy endpoint was the total number of hours spent in direct sunlight between 10:00 and 18:00 hours on days when no pain was experienced (Likert score of 0). The secondary efficacy endpoints were:

- Total number of hours spent in direct sunlight between 10:00 and 18:00 hours on days when no pain or mild pain was experienced (Likert scores of 0 to 3) (*allows mild pain*).
- Total number of hours spent in direct sunlight between 10:00 and 15:00 hours on days when no pain was experienced (Likert score of 0) (*shorter time window*)
- Total number of hours spent in direct sunlight between 10:00 and 18:00 hours (*allows any level of pain*)
- Change from baseline to each time point in the quality of life (QoL) assessment scores (Dermatology Life Quality Index (DLQI) and EPP-QoL).
- Change from baseline to each time point in the minimum symptom dose following photoprovocation on the lower back and dorsal surface of the hand
- The maximum and total pain severity scores for phototoxic episodes (defined as consecutive days with Likert score ≥4)
- The number of phototoxic episodes per subject

The EPP-QoL instrument is presented in Appendix 20.3.

Statistical Analysis Plan

All primary and secondary endpoints were to be analyzed with a Kruskal-Wallis non-parametric test. All tests were to be conducted at the 0.05 significance level. The protocol did not propose

any adjustments for multiplicity among the set of secondary endpoints. Although not included in the protocol or the statistical analysis plan (SAP), the Applicant included Hodges-Lehmann estimates for the treatment effect for the primary and secondary endpoints in the study report.

The ITT population was defined as all treated subjects who provided at least one post-dose efficacy assessment. Analyses were to be performed on available data and there was no plan to impute any missing efficacy data, except to align contradictory diary data as follows:

- If subjects marked the diary indicating that they had no reaction to light that day, but did not mark a pain severity score, the pain score was to be imputed as 0.
- If subjects did not check the box indicating that they spent time outdoors that day, but shaded one or more time slot boxes, the times would still be used in the analysis.

Protocol 039 was submitted to the FDA on March 16, 2012. FDA provided the following advice on the statistical analysis plan related to multiplicity adjustments and the handling of missing data (Advice Letter dated July 2, 2012):

- You listed a number of secondary endpoints. Propose a method to control multiplicity over the set of secondary endpoints. Secondary endpoints should be clinically relevant and limited in number.
- Define the ITT population as all randomized subjects who are dispensed treatment rather than excluding subjects who do not provide at least one post-dose efficacy assessment.
- Include in your protocol a proposal for handling missing data, as an observed case analysis is not sufficient. In addition to a primary method of handling missing data, propose two or three alternate imputation methods that use alternate assumptions as sensitivity analyses to ensure that the conclusions of the study are not driven by the methods of handling missing data.

The Applicant did not incorporate these recommendations into the protocol. The statistical analysis plan was finalized on August 28, 2013 and the analyses are consistent with the analyses specified in the protocol, however, the Applicant did not incorporate FDA's advice regarding multiplicity control for secondary endpoints, the ITT population, or the handling of missing data.

Protocol Amendments

The original version of the protocol was finalized on March 16, 2012. The protocol was amended three times and the final version of the protocol was dated June 17, 2013. Subject participation was from May 2012 to July 2013. The key substantive modifications were the extension of final follow-up from 3 to 6 months post-treatment, the addition of ECG monitoring, and the addition of one secondary endpoint (total number of hours spent in direct sunlight between 10:00 and 15:00 hours on days when no pain was experienced).

8.1.2. Study Results

Compliance With Good Clinical Practices

The Applicant stated that studies were designed, monitored, and conducted in accordance with GCP requirements and ethical principles. Study protocols, the subject information and informed consent forms, subject recruitment procedures were reviewed by the responsible Institutional Review Board (IRB). The Applicant obtained an approval from the IRB prior to study initiation.

Financial Disclosure

Refer to Appendix 19.2.

Patient Disposition

Study 039 randomized 94 subjects with 48 randomized to afamelanotide and 46 randomized to placebo. One subject randomized to placebo was discovered to have a benign choroidal nevus during an ophthalmologic examination at screening and was withdrawn from the study prior to receiving the first dose. Because the subject was not dispensed medication, the subject was not included in any efficacy or safety analyses. An additional six subjects (3 on each treatment arm) discontinued the study. One placebo subject was discontinued after receiving two doses based on the physician's decision after an adverse event of malignant melanoma in situ. One afamelanotide subject was discontinued after receiving two doses based on the subject's decision after an adverse event of compound nevus with mild dysplasia. The remaining four subjects were lost to follow-up or discontinued due to non-compliance with visit schedule. See Table 21.

Table 21. Disposition of Subjects in Study 039

Subject Disposition	Afamelanotide	Placebo
Subjects randomized	48	46
Discontinued	3 (6%)	4 (9%)
Sponsor decision		1 (2%)[a]
Physician decision	1 (2%)[b]	1 (2%)[c]
Subject decision	2 (4%)	
Other (lost to follow-up)		2 (4%)

[a] Subject randomized, but not administered medication due to pre-existing condition
[b] Subject non-compliant with visit schedule
[c] Adverse event
Source: pg 98 of CUV039 study report and reviewer analysis.

Most subjects (95%) received all three doses. As stated above, one placebo subject was withdrawn from the study prior to receiving the first dose. Two afamelanotide and 3 placebo subjects received only 1 or 2 doses. See Table 22.

Table 22. Extent of Exposure in Study 039

Number of Doses	Afamelanotide N=48	Placebo N=46
3	46	42
2	1	1
1	1	2
0		1

Source: pg 344 of CUV039 study report and reviewer analysis.

Four subjects (two afamelanotide and two placebo) did not return any diary cards and thus provided no information on phototoxic pain or sun exposure information. These four subjects are excluded from the Applicant's intent-to-treat population and are not accounted for in analyses based on diary information. Two subjects (one afamelanotide and one placebo) did not return all diaries because they discontinued the study early and five subjects (two afamelanotide and three placebo) received all three doses but did not return all diaries.

Demographic Characteristics

Enrollment in Study 039 was generally balanced across demographic subgroups. The study enrolled similar numbers of male and female subjects. The majority of subjects were less than 65 years of age and Caucasian. See Table 23.

Table 23. Baseline Demographics in Study 039 (Safety Population)

Baseline Demographics	Afamelanotide N=48	Placebo N=45
Sex		
Male	28 (58%)	21 (47%)
Female	20 (42%)	24 (53%)
Age		
Mean years	40.4	39.1
Min, max (years)	20, 65	18, 74
Age group		
≥18–<65 years	47 (98%)	42 (93%)
≥65 years	1 (2%)	3 (7%)
Race		
Caucasian	47 (98%)	43 (96%)
Hispanic	1 (2%)	
Asian		1 (2%)
American Indian or Alaska Native		1 (2%)
Fitzpatrick skin type		
(I) Never tans, always burns	13 (27%)	10 (22%)
(II) Tans less than average (with difficulty), mostly burns	20 (42%)	15 (33%)
(III) Tans about average, sometimes mild burn	12 (25%)	16 (36%)
(IV) Rarely burns, tans more than average (with ease)	3 (6%)	4 (9%)

Source: pg 99-100 of CUV039 study report

Other Baseline Characteristics

At baseline, subjects reported the "severity of their current condition" as mild, moderate, severe, or worst imaginable. No definitions for these categories were provided. Enrollment was generally balanced across baseline severity categories and type of usual first phototoxic

reaction. Subjects also were queried two ways regarding their tolerance to light. As part of the EPP medical history, investigators were to record the "Approximate time from UV exposure to onset of first symptoms" and as part of a subject-recorded screening questionnaire subjects were asked to "Please estimate how long you are now able to spend in direct sunlight."

Subjects on the afamelanotide arm reported longer time periods before the onset of phototoxic symptoms than subjects on the placebo arm. See Table 24. However, it is not clear how subjects interpreted the two queries, as while many subjects gave concordant responses to the two questions, other subjects did not. When responses were discordant, most subjects reported shorter times to first symptom than time able to spend in direct sunlight. See Table 25.

Table 24. Baseline Disease Severity in Study 039 (Safety Population)

Baseline Characteristics	Afamelanotide N=48	Placebo N=45
Baseline severity		
Mild	11 (23%)	9 (20%)
Moderate	17 (35%)	18 (40%)
Severe	19 (40%)	15 (33%)
Worst imaginable	1 (2%)	3 (7%)
Usual first EPP phototoxic reaction after sun exposure		
Burning	26 (54%)	26 (58%)
Itching	8 (17%)	6 (13%)
Pain	4 (8%)	3 (7%)
Erythema	0 (0%)	0 (0%)
Other[a]	10 (21%)	10 (22%)
Approximate time from UV exposure to first symptom		
Mean minutes (SD)	44.4 (112.2)	23.9 (38.1)
Median	15	10
Min, max	0, 600	0, 240
Estimated time subject is able to spend in direct sunlight		
Mean minutes (SD)	35.7 (72.3)	37.3 (45.1)
Median	15	20
Min, max	0, 480	0, 240

[a] Tingling, tingling with heat sensation/ burning / numbness /paresthesia, or stinging
EPP = erythropoietic protoporphyria; SD = standard deviation; UV = ultraviolet
Source: pg 59 of CUV039 study report and reviewer analysis

Table 25. Cross-tabulations of Tolerated Light Responses at Baseline

Time (Minutes) Able to Spend in Direct Sunlight	Time (Minutes) From UV Exposure to First Symptom				
	0-9	10-19	20-44	≥45	Total
Afamelanotide					
0-9	12	1	0	0	13
10-19	4	7	2	0	13
20-44	3	5	3	0	11
≥45	0	0	3	7	10
Total	19	13	8	7	47
Placebo					
0-9	8	1	0	0	9
10-19	1	10	0	0	11
20-44	3	2	6	0	11
≥45	2	0	3	9	14
Total	14	13	9	9	45

Note: Groupings selected based on quartiles for "Time able to spend in Direct Sunlight".
UV = ultraviolet
Source: Reviewer analysis.

Efficacy Results – Primary Endpoint

Subjects recorded data on sun exposure and phototoxic pain daily in a diary for 180 days. Phototoxic pain for each day was recorded on a Likert scale from 0 to 10 and the amount of time spent outdoors in either direct sunlight or shade was recorded from 10:00 to 18:00 hours in 15-minute increments. A copy of the subject diary is presented above in Section 8.1.1.

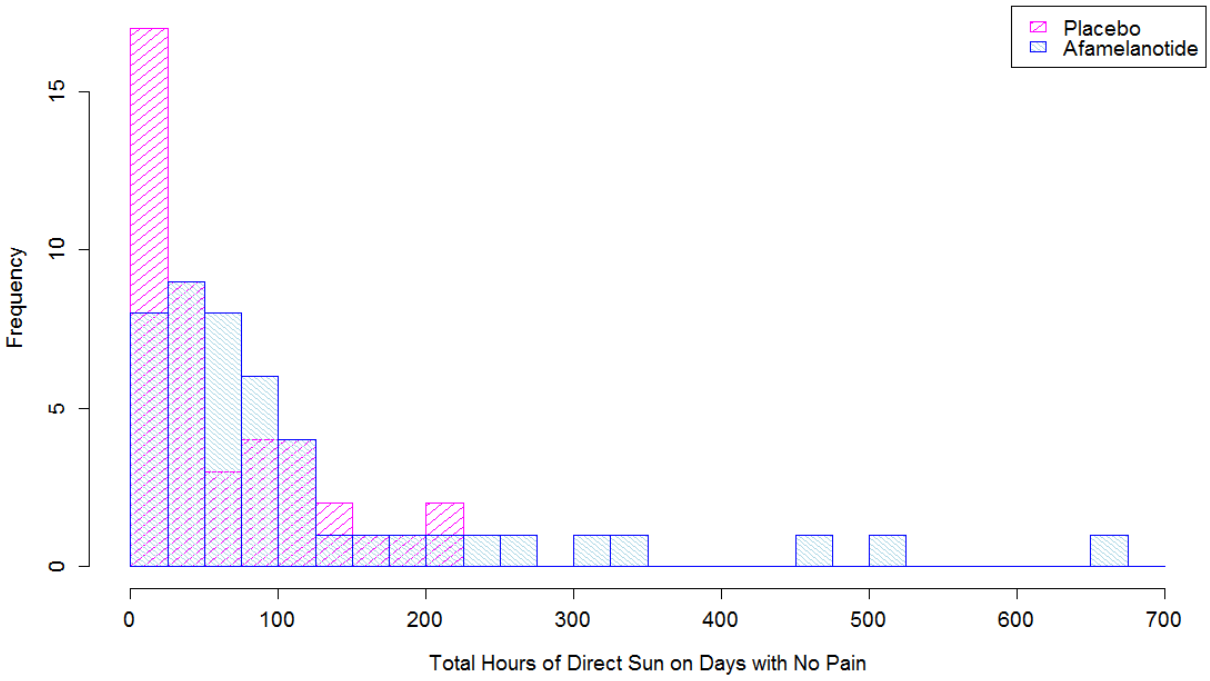
The primary efficacy endpoint was the total number of hours spent in direct sunlight between 10:00 and 18:00 hours on days when no pain was experienced (Likert score of 0). The subject diaries covered 180 days. The primary endpoint was analyzed with a Kruskal-Wallis non-parametric test. Although not included in the protocol or the SAP, the Applicant included the Hodges-Lehmann estimate for the primary endpoint in the study report. The Applicant conducted the primary efficacy analysis in the ITT-Diary Card population which included all subjects who provided at least one post-dose efficacy assessment. This population excluded four subjects (2 afamelanotide and 2 placebo subjects) who did not return any diary cards. The efficacy results are presented in Table 26 and a histogram of the data is presented in Figure 12.

Table 26. Primary Efficacy Endpoint: Total Hours of Direct Sun Exposure Between 10:00 and 18:00 on Days With No Pain in Study 039 (ITT-Diary Card Population)

Statistics	Afamelanotide N=46	Placebo N=43	Estimate[a] 95% CI	p-value[b]
Mean (SD)	115.6 (140.6)	60.5 (60.6)	24.0	0.044
Median	69.4	40.8	(0.3, 50.3)	

[a] Hodges-Lehmann estimate
[b] Kruskal-Wallis test
CI = confidence interval
Source: pg 62 of CUV039 study report and reviewer analysis

Figure 12. Histogram for the Total Hours of Direct Sun Exposure Between 10:00 and 18:00 on Days With No Pain in Study 039 (ITT-Diary Card Population)



Source: Reviewer analysis

The primary endpoint was analyzed with a Kruskal-Wallis test, which is equivalent to the Wilcoxon test in the case with two treatment arms and where the asymptotic test is conducted without continuity corrections. The treatment effect was estimated with the Hodges-Lehmann estimator. If the distributions for the two treatment groups have the same shape, then the test can be interpreted as a test for the difference in medians. However, if the distributions have different shapes, then the test can be interpreted as assessing whether the distributions are different, and the estimator can be interpreted as median of the differences of all pairs of observations from the two treatment groups. From the summary statistics and histograms, we see that the distributions for the two treatment groups are right skewed with the afamelanotide group having a longer right tail and larger standard deviation. Thus, the results of the test indicate that there is evidence that the distributions differ, however interpreting the results simply as a difference in medians may not be appropriate.

Missing Data Handling

The Applicant analyzed observed case data and did not attempt to impute any data for diary days that were not completed or returned by the subjects. Subjects were to return completed diaries to the investigator on Days 60, 120 and 180. As noted above, the Applicant's primary analysis population excluded four subjects who did not return any subject diaries. Seven additional subjects only returned one or two of the 60-day diaries. See Table 27. Note that some of the subjects that did not return one or more diaries received all three doses, and that sometimes the missing diaries corresponded to earlier periods in the study, rather than only at

the end of the study. See Table 28. In addition, some diaries returned by the subjects had days for which no data was recorded. While most subjects had only a few days with missing diary data, a few subjects had higher numbers of days with missing data. One apparent cause for missing diary data was when subjects had more than 60 days between visits. In such cases, some subjects did not record diary data after the 60th day until they attended their next visit and received a new diary.

Table 27. Missing Diary Data in Study 039

Number of Diaries Returned	Afamelanotide (N=48)	Placebo (N=45)
0 diaries returned	2 (4%)	2 (4%)
Subject ID		(b) (6)
1 diary returned	--	1 (2%)
Subject ID		5012
2 diaries returned	3 (6%)	3 (7%)
Subject ID		(b) (6)
3 diaries returned	43 (90%)	39 (87%)
With 0 missing days	21 (44%)	16 (36%)
With 1-3 missing days	16 (33%)	16 (36%)
With 4-10 missing days	4 (8%)	5 (11%)
With 11-21 missing days	2 (4%)	2 (4%)

[a] Subjects who discontinued and did not receive all three doses.
Note: each diary covered approximately 60 days
Source: Reviewer analysis

Table 28. Doses Received and Specific Diaries Returned for Subjects Who Did Not Return All 3 Diaries in Study 039

Treatment	Subject ID	Doses Received	Specific Diaries Returned
Afamelanotide	(b) (6)	1	None
		1,2,3	None
		1,2,3	1,2
		1,2	1,2
		1,2,3	1,2
Placebo		1	None
		1	None
		1,2,3	2
		1,2,3	1,2
		1,2,3	2,3
		1,2	1,2

Source: Reviewer analysis

Because the Applicant did not include any analyses that account for subjects who had missing data, this reviewer devised two sensitivity analyses to handle subjects who did not return all 3 pain and sun exposure diaries. These analyses do not impute any values for individual days of missing data within a diary, instead they impute values only for cases with entire missing diaries, as the data loss due to missing individual day responses was minimal. The two sensitivity analyses are as follows:

- Including all randomized subjects “as reported”.
  - For subjects who returned at least one diary, use the observed data.
  - For subjects who did not return any diaries, impute 0 hours of pain-free sun exposure.

- Imputing an "internally consistent" value for subjects who are missing 1 or 2 diaries. This imputation will assume that a subject who discontinues treatment will accrue no additional pain-free sun exposure following treatment discontinuation. Specifically:
  - For subjects who returned 1 or 2 diaries but received all 3 doses, impute the amount of pain-free sun exposure for the missing time periods consistent with what was reported in the returned diaries (i.e., use 3 times the observed value for those who returned 1 out of 3 diaries and 1.5 times the observed value for those who returned 2 out of 3 diaries).
  - For subjects who returned 1 or 2 diaries because they discontinued the study and did not receive all three doses (and the missing diaries correspond to time period(s) following treatment discontinuation) use the data from the returned diaries as reported without imputing any additional pain-free sun exposure following discontinuation.
  - For subjects who did not return any diaries, impute 0 hours of pain-free sun.
  - For subjects who returned all 3 diaries, use the observed data.

For this second sensitivity analysis, the imputation leads to the following changes for subjects who returned only 1 or 2 diaries. See Table 29.

Table 29. Imputed Values for the Reviewer-Specified "Internally Consistent" Imputation*

Treatment Group	Subject ID	Observed	Imputed
Afamelanotide	(b) (6)	22.25 (2 diaries)	33.375
		13.25 (2 diaries)	19.875
Placebo		48.25 (2 diaries)	72.375
		0.25 (2 diaries)	0.375
		40.25 (1 diary)	120.75

* Subjects who received all 3 doses, but did not return all 3 diaries
Note: Imputed value is 1.5 times observed if subjects returned 2 diaries and 3 times observed if subjects returned 1 diary.
Source: Reviewer analysis.

Because the Applicant's analysis for the primary endpoint (observed values in the ITT-Diary Card Population) had a p-value of p=0.044 that was so close to the nominal 0.05 cutoff, sensitivity analyses that reduce the magnitude of the treatment effect or increase variability even slightly will lead to results with p-values >0.05. The two sensitivity analyses described above yield results that are generally similar to the Applicant's analysis (see Table 26), though both sensitivity analyses lead to slight reductions in the estimated treatment effect and corresponding p-values that are greater than 0.05 (p=0.055 and p=0.091, respectively). See Table 30.

Table 30. Sensitivity Analyses (Missing Data Handling) for the Primary Efficacy Endpoint in Study 039 (Randomized and Dispensed Population)

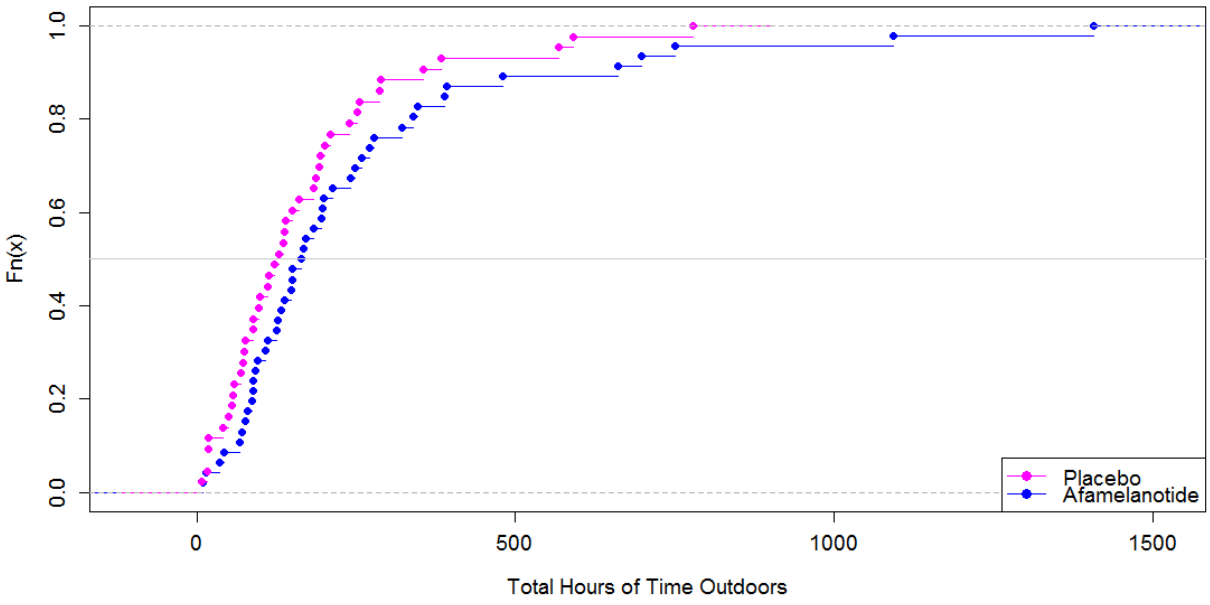
Population		Afamelanotide N=48	Placebo N=45	Estimate[a] 95% CI	p-value[b]
All randomized, "as reported"	Mean (SD) Median	110.7 (139.6) 64.1	57.9 (60.5) 40.5	23.5 (0.0, 48.0)	0.055
All randomized, "internally consistent" for subjects missing 1 or 2 diaries	Mean (SD) Median	111.1 (139.3) 64.1	60.2 (61.2) 40.8	22.8 (-1.8, 47.0)	0.091

[a] Hodges-Lehmann estimate
[b] Kruskal-Wallis test
SD = standard deviation
Source: Reviewer analysis

Analyses of Components of the Primary Endpoint

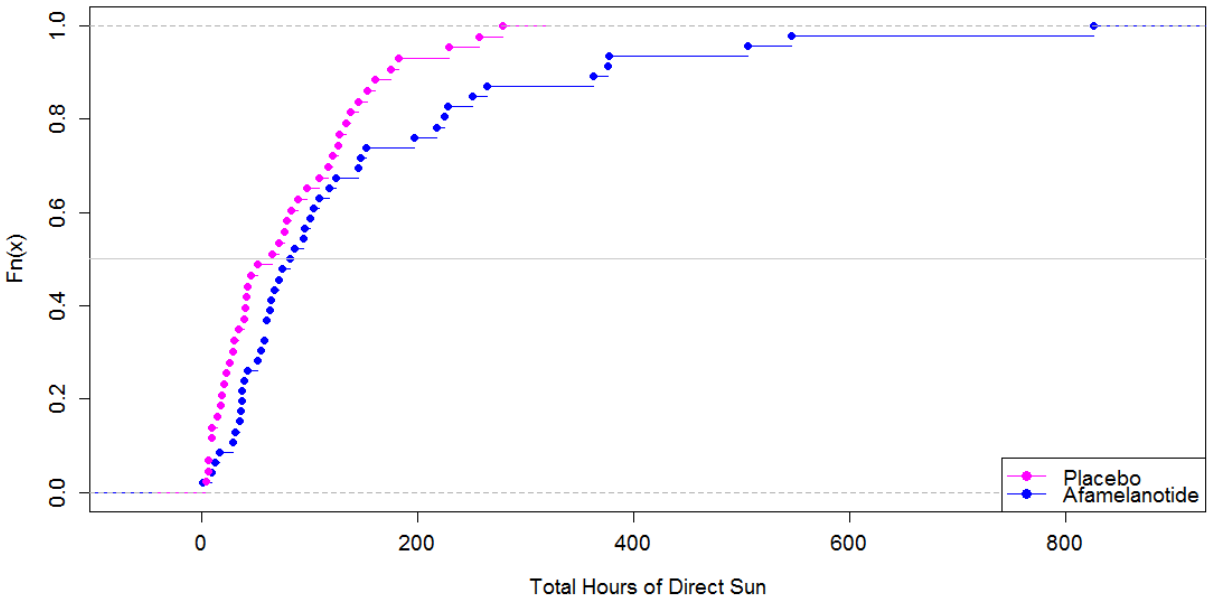
The primary endpoint is complex, requiring both behavioral aspects (spending time outdoors, and in direct sun rather than shade) and physiological response (having no pain on days where time was spent outdoors in direct sunlight). The nesting definitions of total hours spent outdoors, total hours spent outdoors in direct sunlight, and total hours spent outdoors in direct sunlight on days with no pain were explored graphically to evaluate the varying impacts of the different components. Figure 13 through Figure 15 present the empirical cumulative distribution functions for the total hours spent outdoors, total hours spent outdoors in direct sunlight, and total hours spent outdoors in direct sunlight on days with no pain (the primary endpoint). In each case, the afamelanotide group is shifted to the right of the placebo group, representing longer durations on afamelanotide, and the difference is the greatest for the graph for the primary endpoint, which includes all of the components.

Figure 13. Empirical Cumulative Distribution Function for the Total Hours Spent Outdoors in Study 039



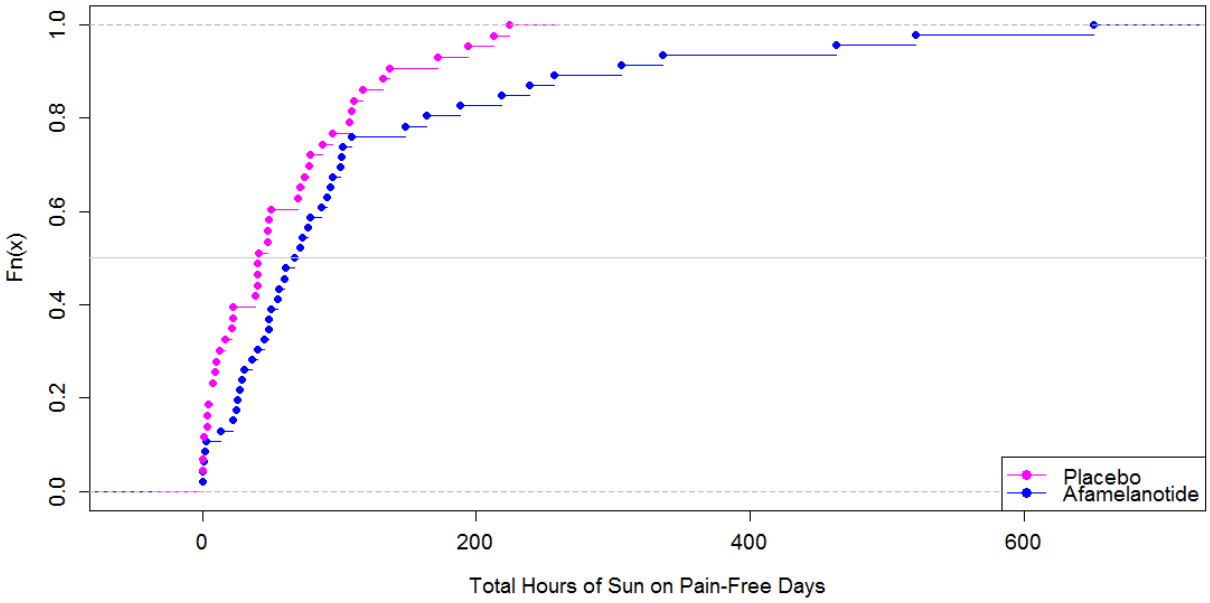
Source: Reviewer analysis

Figure 14. Empirical Cumulative Distribution Function for the Total Hours Spent Outdoors in Direct Sunlight in Study 039



Source: Reviewer analysis

Figure 15. Empirical Cumulative Distribution Function for the Total Hours Spent Outdoors in Direct Sunlight on Days With No Pain in Study 039

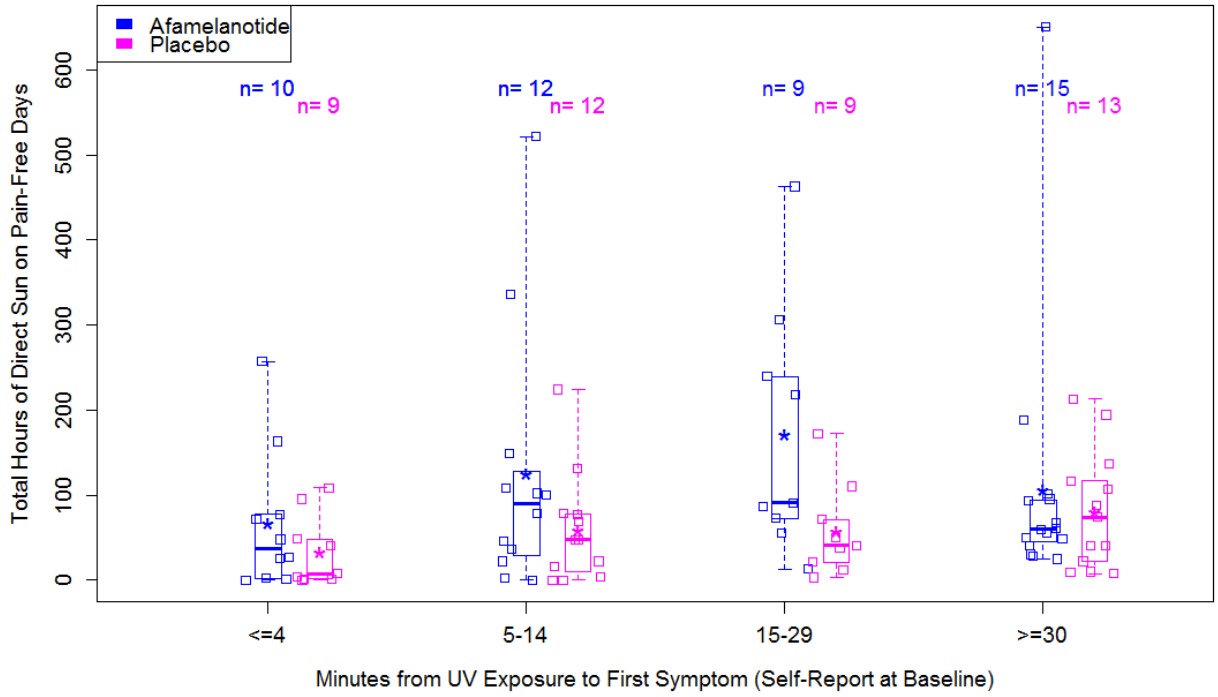


Source: Reviewer analysis

Efficacy by Baseline Severity

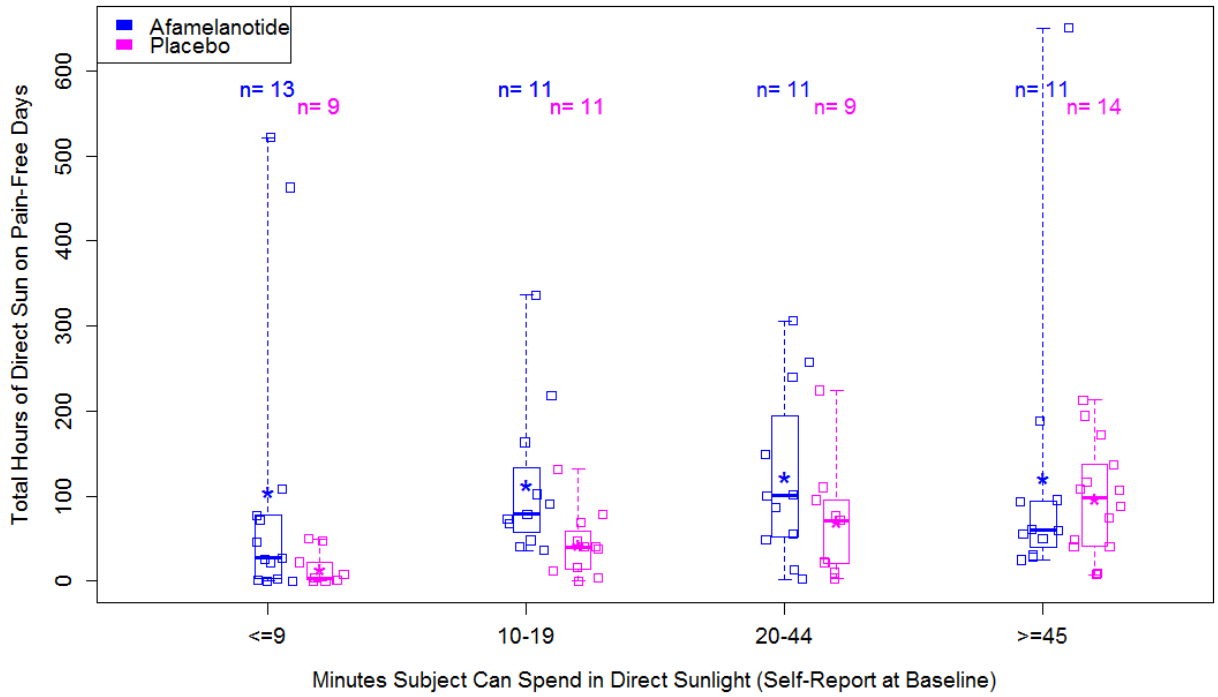
To further explore the impact of subject variability on the primary outcome, this reviewer graphed the primary outcome versus the subject-reported tolerance to light responses at baseline. Subjects were queried two ways regarding their tolerance to light, reporting both the "approximate time from UV exposure to onset of first symptoms" and estimating "how long you are now able to spend in direct sunlight." Responses for each of these questions were divided into quartiles. Figure 16 and Figure 17 present boxplots of the primary outcome by the baseline exposure report. For both ways of assessing baseline tolerance to light, except for subjects in the largest quartile of baseline tolerance, subjects on the afamelanotide arm tended to have higher values for total sun exposure than those on the placebo. For subjects with the greatest tolerance of light at baseline, the results were similar for afamelanotide and placebo subjects for the primary outcome.

Figure 16. Total Hours of Direct Sun on Days With No Pain by Minutes From UV Exposure to First Symptom, as Reported at Baseline in Study 039



Asterisk represents the mean.
Source: Reviewer analysis

Figure 17. Total Hours of Direct Sun on Days with No Pain by Minutes Subject Can Spend in Direct Sunlight, as Reported at Baseline in Study 039

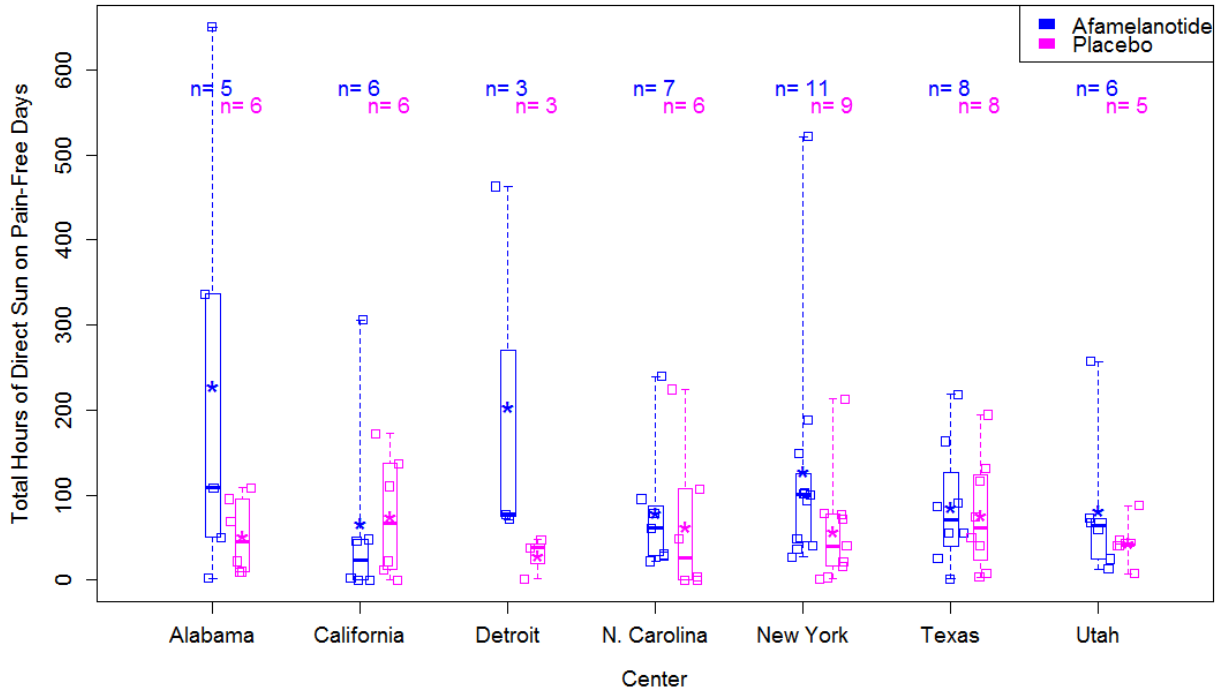


Asterisk represents the mean.
Source: Reviewer analysis.

Efficacy by Center

The total hours of direct sun on days with no pain is presented by center in Figure 18. The variability in responses was similar across centers. Generally the results were consistent across sites with the means and medians for subjects on the afamelanotide arm were higher than the means and medians for the placebo arm, except for the California site.

Figure 18. Total Hours of Direct Sun on Days With No Pain by Center in Study 039



Asterisk represents the mean.
Source: Reviewer analysis.

Efficacy by Gender, Race, and Age

The majority of subjects were Caucasian (97%) and less than 65 years of age (96%) so subgroup analysis by race and geriatric subgroups is not meaningful. Both male and female subjects had more time in the sun with no pain among subjects receiving afamelanotide relative to those on vehicle, though the observed treatment effect was higher in males than females. Study 039 was conducted in the United States. See Table 31.

Table 31. Total Hours of Direct Sun on Days With No Pain by Subgroup in Study 039 (ITT-Diary Card Population)

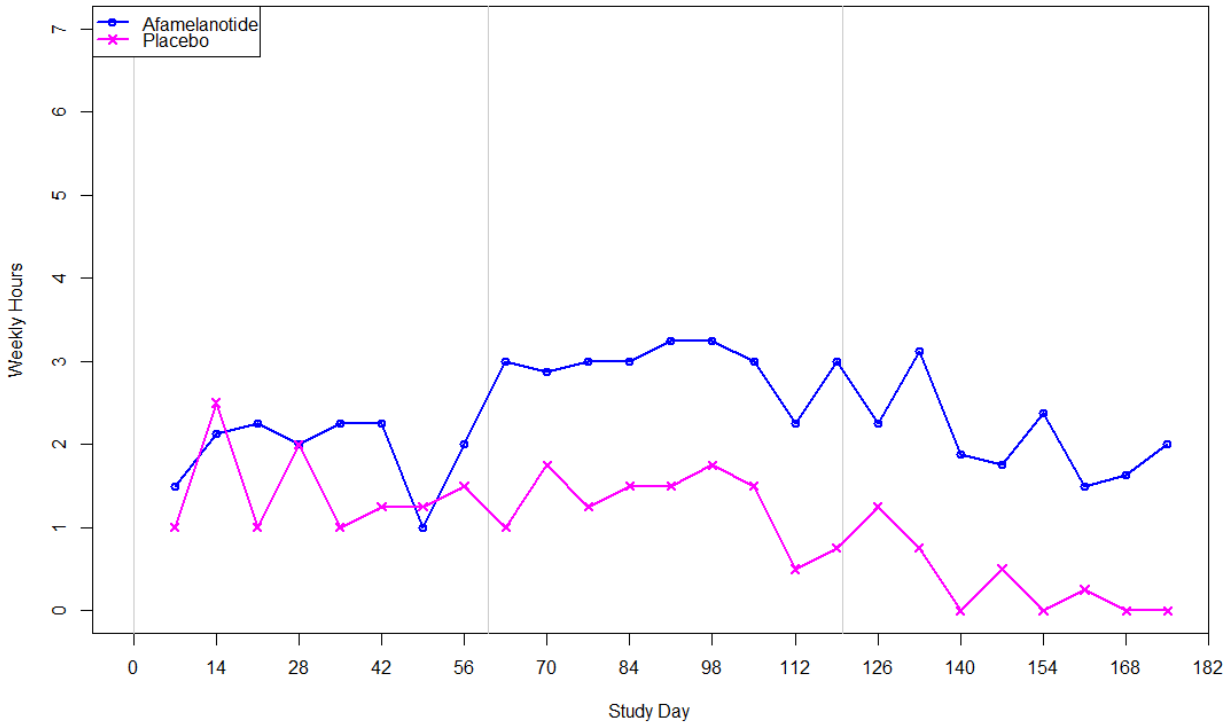
Population		Afamelanotide N=46	Placebo N=43	Estimate[a] 95% CI
Sex				
Male	N	28	20	
	Mean (SD)	133.4 (166.4)	60.7 (61.1)	30.0
	Median	77.9	40.5	(8.5, 69.5)
Female	N	18	23	
	Mean (SD)	87.8 (83.9)	60.4 (61.4)	14.8
	Median	52.3	47.8	(-16.0, 52.3)
Race				
Caucasian	N	45	41	
	Mean (SD)	116.9 (141.9)	61.5 (61.9)	24.3
	Median	71.5	47.5	(0.3, 51.5)
Hispanic	N	1		
	Value	55.3		
Asian	N		1	
	Value		40.0	
Amer. Ind./ AK Nat.	N		1	
	Value		40.25	
Age				
≥18 to <65 years	N	45	40	
	Mean (SD)	110.7 (138.2)	61.7 (61.7)	22.0
	Median	67.3	44.1	(2.0, 47.0)
≥65 years	N	1	3	
	Mean (SD)	336.5	44.9 (47.4)	
	Median		38.3	

[a] Hodges-Lehmann estimate
SD = standard deviation; CI = confidence interval; Amer. Ind./AK Nat. = American Indian/Alaskan Native
Source: reviewer analysis

Efficacy Over Time

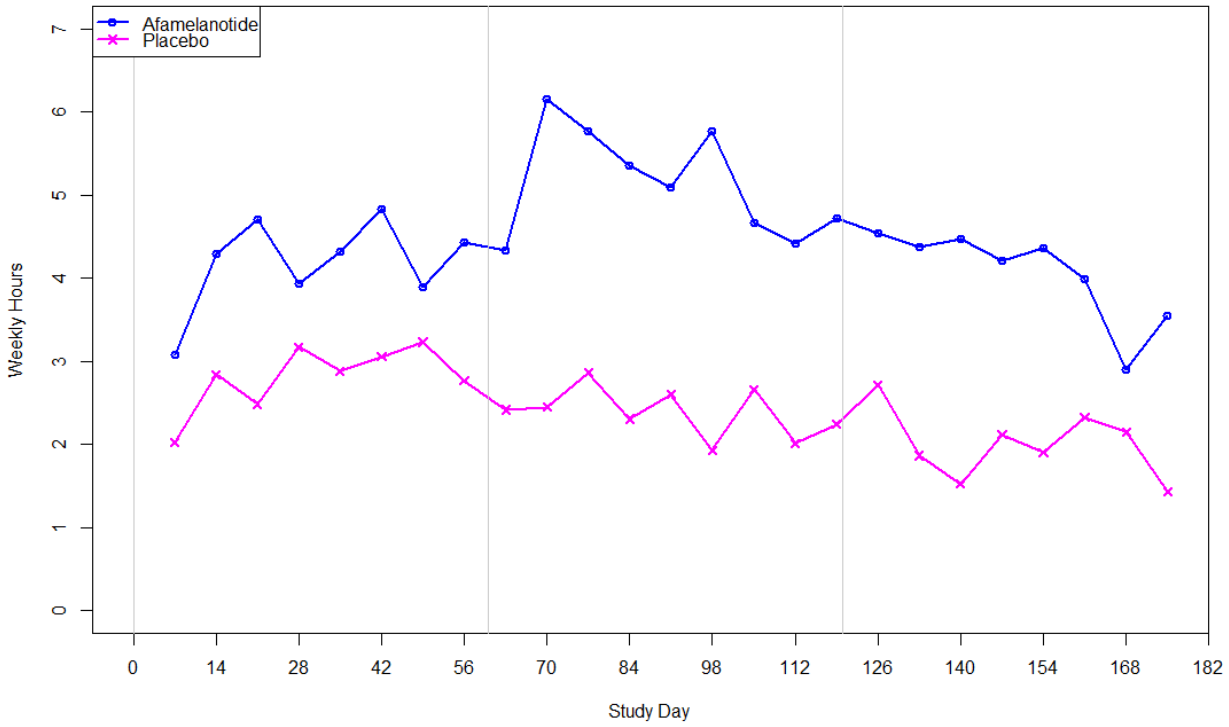
It is of interest to learn about the pattern of pain-free direct sun exposure over the course of the trial. Checking efficacy over time can provide information of the start of the treatment effect, the pattern of the treatment effect over successive treatments, and the duration of effect following treatment. Because the amount of time spent in direct sunlight can vary greatly from day to day due to weather and scheduled activities (work days versus days off, etc.), considering the total hours of time spent in direct sunlight without pain over the course of a week may reduce some of the noise inherent in the data. To ensure that subjects who discontinued the study or did not fully complete study diaries were included throughout the study period, subjects with missing diary entries were imputed as having 0 hours of pain-free sun reported for that study day. Thus, the weekly value corresponds to the total number of hours of pain-free sun reported by the subject over a 7-day period (study days 1 to 7, 8 to 14, etc.). Figure 19 and Figure 20 present the median and mean, respectively, duration of time that subjects spent in direct sunlight on pain-free days in any given study week. For most 7-day periods, the median and mean for the afamelanotide group was larger than the median or mean for the placebo group. The treatment effect is smaller following the first dose, and larger following the second and third dose, though the total number of hours appears to decline over the study period. However, the values exhibit a lot of variability.

Figure 19. Total Hours of Pain-Free Direct Sun Exposure Per Week Over the Treatment Period in Study 039 (Median)



Vertical bars represent the nominal dosing days.
Source: Reviewer analysis.

Figure 20. Total Hours of Pain-Free Direct Sun Exposure Per Week Over the Treatment Period in Study 039 (Mean)



Vertical bars represent the nominal dosing days.
Source: Reviewer analysis.

Efficacy Results – Secondary Endpoints

The secondary efficacy endpoints were:

- Total number of hours spent in direct sunlight between 10:00 and 18:00 hours on days when no pain or mild pain was experienced (Likert scores of 0 to 3).
- Total number of hours spent in direct sunlight between 10:00 and 15:00 hours on days when no pain was experienced (Likert score of 0)
- Total number of hours spent in direct sunlight between 10:00 and 18:00 hours
- Change from baseline to each time point in the quality of life (QoL) assessment scores (Dermatology Life Quality Index (DLQI) and EPP-QoL).
- Change from baseline to each time point in the minimum symptom dose following photoprovocation on the lower back and dorsal surface of the hand.
- The maximum and total pain severity scores for phototoxic episodes (defined as consecutive days with Likert score ≥4).
- The number of phototoxic episodes per subject.

The Applicant did not propose any statistical methods for controlling multiplicity among the set of secondary endpoints.

Time in Direct Sunlight Endpoints

The first three secondary endpoints are variations on the primary endpoint that change either the time window considered (10:00 to 15:00 rather than 10:00 to 18:00) or the daily pain level permitted (Likert scores of 0 to 3 or any score (0 to 10), rather than only scores of 0). The results for these secondary endpoints are similar to the results of the primary endpoint in terms of the magnitude of the treatment effect estimates (relative to the size of the daily window for assessment), however, all of the nominal p-values for these endpoints are >0.05. Each of these variations on hours in direct sunlight are less sensitive than the primary endpoint, which is defined as the hours spent in direct sunlight from 10:00 to 18:00 on pain-free days. See Table 32.

Table 32. Secondary Endpoints based on Sun Exposure and Pain Level in Study 039 (ITT-Diary Card Population)

Secondary Endpoint		Afamelanotide N=46	Placebo N=43	Estimate[a] 95% CI	p-value[b]
Hours of direct sunlight exposure (10:00 to 15:00) on days with no pain	Mean (SD) Median	71.2 (89.2) 39.6	41.6 (45.3) 31.8	13.1 (-1.3, 28.0)	0.092
Hours of direct sunlight exposure (10:00 to 18:00) on days with no or mild pain	Mean (SD) Median	141.1 (165.1) 80.0	74.6 (67.5) 51.0	26.8 (-0.3, 57.5)	0.053
Hours of direct sunlight exposure (10:00 to 18:00)	Mean (SD) Median	145.0 (164.1) 83.5	81.8 (71.1) 65.3	26.1 (-2.3, 57.3)	0.066

[a] Hodges-Lehmann estimate
[b] Kruskal-Wallis test
SD = standard deviation; CI = confidence interval; ITT = intent-to-treat
Source: Reviewer analysis

Phototoxic Episode Endpoints

Phototoxic episodes were defined in the protocol as consecutive days with Likert pain score ≥4. The secondary endpoints based on the number and severity of phototoxic episodes were:

- The maximum and total pain severity scores for phototoxic episodes (defined as consecutive days with Likert score ≥4)
- The number of phototoxic episodes per subject

Note that the number of phototoxic episodes may be difficult to interpret, as for an extreme example, a subject who reported a pain score of 10 every day in the study and a subject who reported a pain score of 4 on only 1 day during the study would both be recorded as having one phototoxic episode, even though these subjects experienced very different levels of phototoxic pain during the study. Conversely, a subject who reported a pain score of 4 every day in the study (180 days) would be recorded as having one phototoxic episode and a subject who alternated between scores of 4 and 3 every day of the study would be recorded as having 90 phototoxic episodes (one for each day the score of 4 was recorded), even though the subject who recorded pain scores of 4 every day had the greater total severity. Possibly because of this issue, the Applicant also provided an analysis counting the number of days during the study

that a subject had a pain score ≥4, even though such an analysis was not prespecified in the protocol.

The protocol and statistical analysis plan were not clear on how to handle the days on which subjects recorded pain scores ≤3 in the analyses of phototoxic pain. In the study report, the Applicant presented results in two ways, both of which may be subject to bias. In the first presentation, the Applicant only included results from subjects who experienced at least 1 phototoxic episode, dropping subjects from the analysis who did not experience an episode. Because this analysis selects subjects based on a post-randomization event expected to be affected by treatment (reporting at least one pain score ≥4), it is not based on a valid randomized population. These analyses will not be presented in this review because they are not based on a valid randomized population.

The second analysis used all subjects in the ITT-Diary Card population, however, it treated any phototoxic pain scores ≤3 as if they were equivalent to a pain score of 0. Consequently, the summary statistics (such as the mean) for the Applicant's analysis of the maximum severity score and total severity score do not represent the as-observed dataset, but are biased, relative to results that are based on the full observed values that do not use "0 imputation". The mean and median are biased downward, because observed values of 1 to 3 are replaced with 0s, compared with analyses that used all pain score data as observed. This reviewer also conducted analyses that used the data "as-observed" rather than treating all observed scores 1 to 3 as if they were 0s. The effect of converting all pain scores with observed values of 1 to 3 to 0 is particularly pronounced in the total severity score analysis, because many subjects had pain scores of 1 to 3 throughout the study. For each analysis (both the Applicant's analyses and the supportive reviewer analyses), the means and medians on the afamelanotide arm were similar or smaller than the means and medians on the placebo arm. However, the p-values were all in the range from 0.4 to 0.7 and thus the study was unable to detect an effect for any of these endpoints. See Table 33.

Table 33. Secondary Endpoints Based on Phototoxic Episodes in Study 039 (ITT-Diary Card Population)

Secondary Endpoint		Afamelanotide N=46	Placebo N=43	p-value[a]
Maximum severity score[b] (converting scores 1-3 to 0)	Mean (SD) Median Range	3.5 (3.1) 4.0 0, 8	3.9 (3.3) 5.0 0, 9	0.544
Maximum severity score[c] (using all data as observed)	Mean (SD) Median Range	4.3 (2.2) 4.0 0, 8	4.5 (2.6) 5.0 0, 9	0.710
Total severity score[b] (converting scores 1-3 to 0)	Mean (SD) Median Range	16.3 (33.2) 4.0 0, 196	34.1 (86.7) 6.0 0, 507	0.442
Total severity score[c] (using all data as observed)	Mean (SD) Median Range	44.4 (57.6) 24.0 0, 291	69.0 (124.1) 31.0 0, 634	0.448
Number of episodes[b]	Mean (SD) Median Range	2.0 (3.3) 1.0 0, 15	3.3 (6.8) 1.0 0, 35	0.602
Number of days with pain Score ≥4[b]	Mean (SD) Median Range	3.2 (6.0) 1.0 0, 34	6.6 (16.8) 1.0 0, 98	0.503

[a] Kruskal-Wallis test
[b] Applicant analysis
[c] Reviewer analysis
SD = standard deviation
Source: pg 333 of CUV039 study report and reviewer analysis

A graphical representation of each subject's phototoxic episodes is presented in Figure 21. In this figure, each row represents the recorded pain score for a subject by study day. Each red bar represents a phototoxic episode (one or more days with pain score ≥4). The gold bars represent days with "mild" pain (pain scores from 1 to 3). White space represents either a pain score of 0 or missing data. From this graph we can see that a relatively small number of subjects experienced most of the phototoxic reactions, and many subjects did not report any phototoxic episodes.

Figure 21. Phototoxic Episodes for Each Subject in Study 039 (ITT-Diary Card Population)

Note: Each row represents one subject. Each red bar represents a phototoxic episode (one or more days with pain score ≥4).
Source: Reviewer analysis.

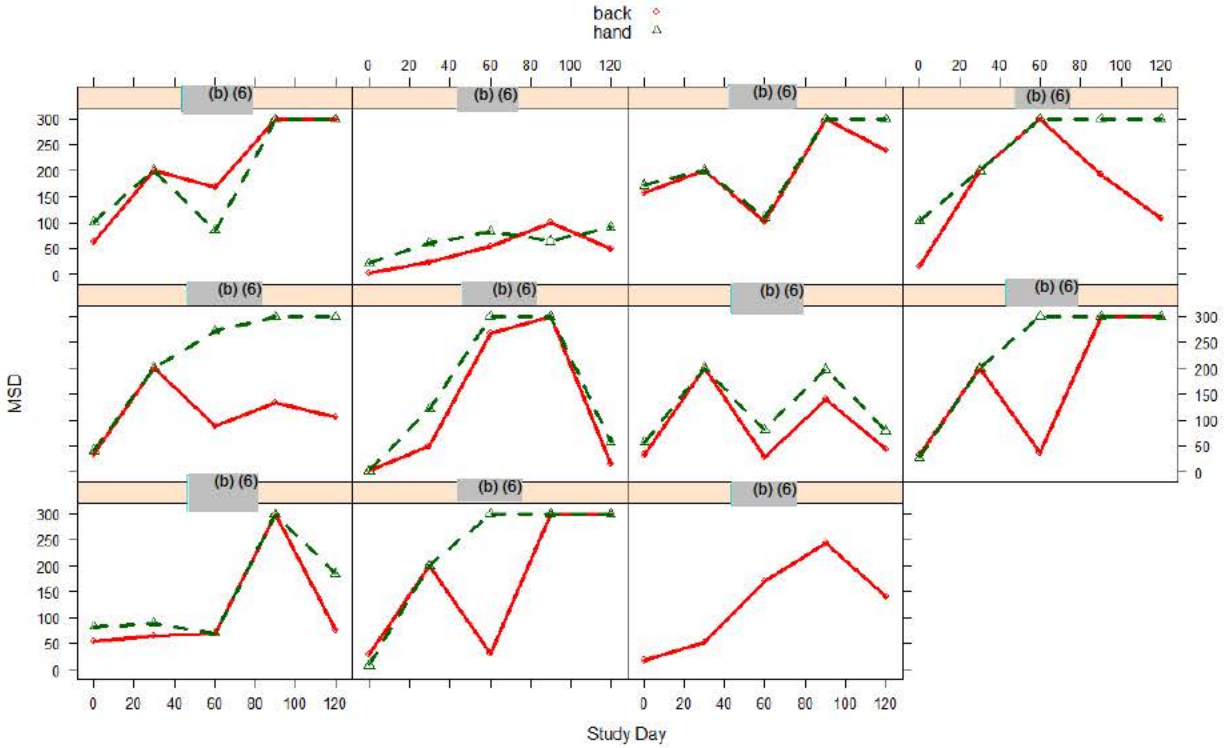
Photoprovocation

A photoprovocation sub-study was conducted at Site 1 (New York) in 21 subjects (11 afamelanotide and 10 placebo). For the photoprovocation, areas approximately 33 mm in diameter on the dorsal surface of the hand and on the back were irradiated with filtered light on Days 0, 30, 60, 90, and 120. The subjects were to be irradiated either until the subject experienced the first phototoxic symptoms or until a maximum dose of 300 J/cm^2 was received. The minimum dose of radiation to induce the first symptom (minimum symptom dose or MSD) was recorded for the hand and the back for each visit. While the maximum dose was supposed to be 300 J/cm^2 at each visit, the investigator mistakenly exposed all subjects at Day 0 and all but one subject at Day 30 to a maximum dose of only 200 J/cm^2 because the investigator misread the protocol. (In Study 030, which had a similar photoprovocation sub-study and in which the investigator at Site 1 participated, the maximum irradiation dose was 200 J/cm^2.) At the Day 60 and subsequent photoprovocation visits, the maximum irradiation dose was 300 J/cm^2. One subject (randomized to afamelanotide) only had photoprovocation assessments conducted on the back because the subject had neuropathy which precluded the ability to feel symptoms on the dorsal surface of the hand.

Because the photoprovocation sub-study was conducted in only a small number of subjects, it is possible to look at the responses for individual subjects. Figure 22 presents the results on the back and the hand for subjects on the afamelanotide arm and Figure 23 presents the results on the back and the hand for subjects on the placebo arm. Subjects' responses on the hand and

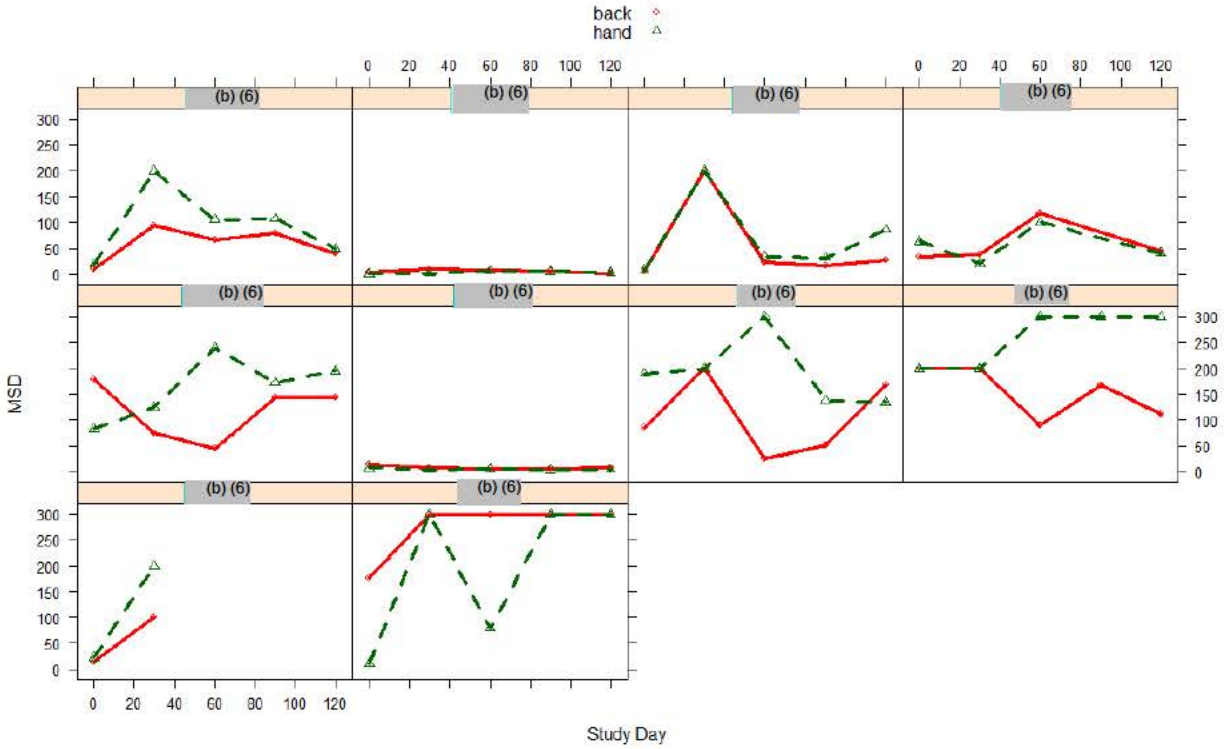
back were generally similar, however, when they differed, the tolerated dose on the hand was usually higher.

Figure 22. Minimum Symptom Dose for Subjects on the Afamelanotide Arm in Study 039 (Photoprovocation Analysis Set)



Source: Reviewer analysis.

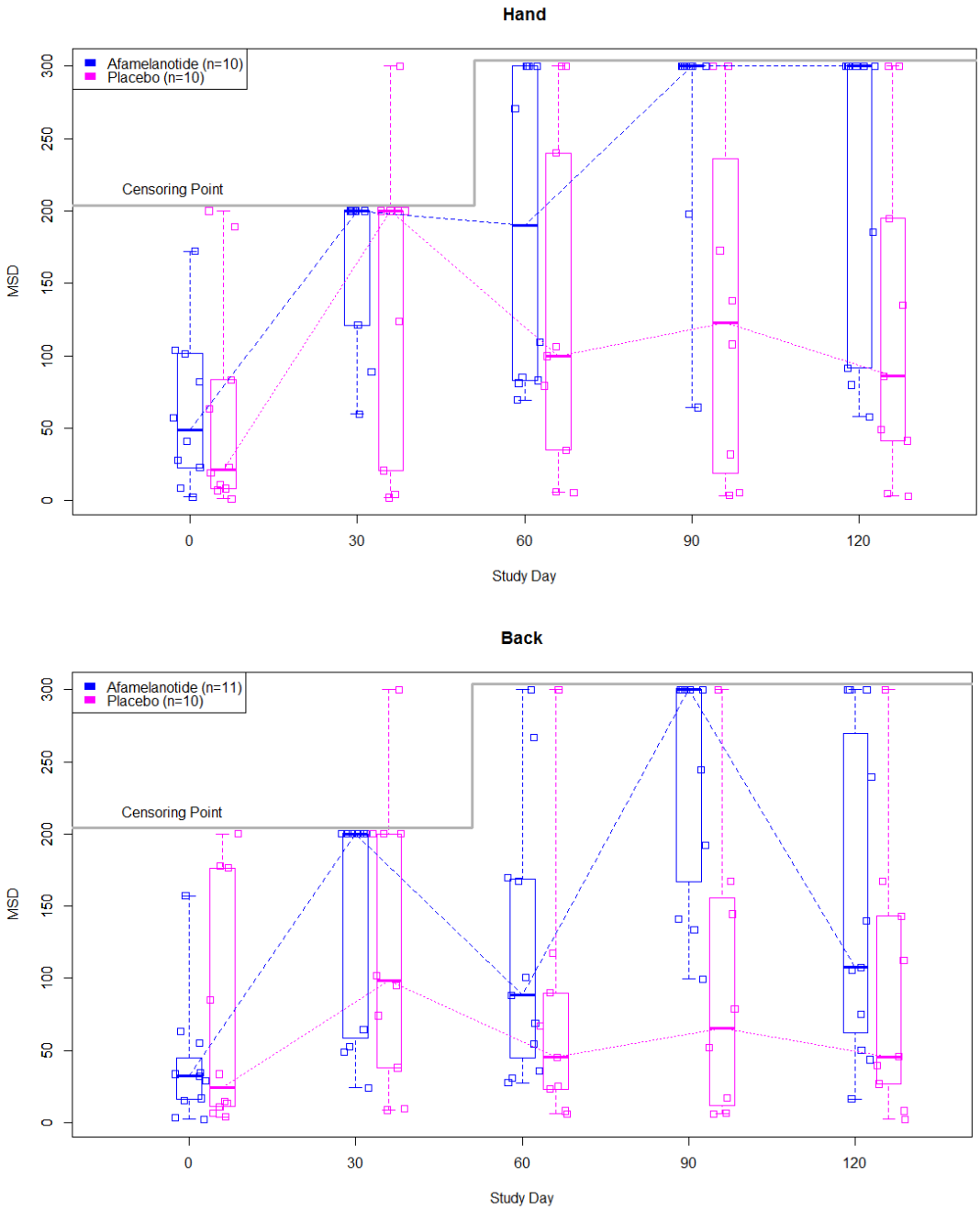
Figure 23. Minimum Symptom Dose for Subjects on the Placebo Arm in Study 039 (Photoprovocation Analysis Set)



Source: Reviewer analysis.

When summarizing the MSD by visit across subjects, the minimum symptom dose appears to generally follow a cyclic pattern with higher doses tolerated 30 days post-dose (Days 30 and 90) on both the afamelanotide and placebo arms than on days where a new dose was scheduled (Days 0, 60, and 120). See Figure 24. The median MSD was similar or higher on the afamelanotide arm than the placebo arm at each post-baseline timepoint on both the hand and back assessments.

Figure 24. Minimum Symptom Dose Following Photoprovocation in Study 039 (Photoprovocation Analysis Set)



Dashed lines connect the medians at each visit.
Source: Reviewer analysis

The censoring of subjects at either 200 or 300 J/cm^2 makes the analysis of the photoprovocation results challenging. The protocol proposed analyzing the change from baseline to each timepoint. While analyzing the change from baseline minimizes the number of tied values relative to analyzing the original scale values (because many of the ties on the original scale are due to reaching the censoring limit), it is difficult to interpret change from

baseline values where one or both observations are subject to censoring. As with the analyses for the other endpoints in this study, the Applicant proposed analyzing the endpoint with the Kruskal-Wallis test. However, in the study report for this endpoint, the Applicant presented p-values for a continuity-corrected asymptotic Wilcoxon test analysis (referred to as Wilcoxon test p-values), rather than the non-continuity-corrected asymptotic p-values that the Applicant provided of the other endpoints in this study (referred to as Kruskal-Wallis test p-values). This reviewer confirmed the Applicant's summary statistics and nominal p-values for all of the Applicant's photoprovocation endpoint analyses, except for the "change to Day 30" analysis on the hand. For this endpoint, the reviewer was able to verify the summary statistics, but not the Applicant's p-value. See Table 34. The results from the analyses for the change from baseline are similar to the results for the analyses on the original scale, where the largest treatment effects were observed at Day 90. The Applicant proposes including information on the change from baseline to Days 90 and 120 on the minimum symptom dose for both the hand and back in labeling (the analyses with nominal p-values <0.05 in this study). However, the protocol did not include any proposals for handling multiplicity due to multiple secondary endpoints, and the protocol included a large number of secondary endpoints. Thus, the fact that individual p-values are <0.05 is not adequate for determining the statistical significance of individual secondary endpoints, and the endpoints should not be described as meeting a statistical significance criterion.

Table 34. Change From Baseline in Minimum Symptom Dose Following Photoprovocation in Study 039 (Photoprovocation Analysis Set)

		Dorsal Hand		Back	
Change From Baseline		**Afamelanotide N=10**	**Placebo N=10**	**Afamelanotide N=11**	**Placebo N=10**
Baseline value	Median	48.9	21.0	32.0	24.1
	Range	2.3, 172	1.1, 200	2.1, 157	3.7, 200
Change to day 30	Median	108.7	25.6	137.1	44.8
	Range	6.4, 191	-42.7, 289	9.1, 185	-103.8, 294
	p-value	0.571[a]		0.098	
Change to day 60	Median	128.3	68.3	50.7	4.3
	Range	-62.8, 298	-1.5, 157	-56.4, 285	-132.7, 124
	p-value	0.653		0.197	
Change to day 90	Median	208.3	56.2	227.5	-2.4
	Range	41.6, 298	-51.3, 289	96.0, 298	-33.3, 124
	p-value	0.011		<0.001	
Change to day 120	Median	162.1	30.0	82.5	12.1
	Range	22.9, 291	-54.3, 289	10.0, 271	-87.4, 124
	p-value	0.045		0.028	

[a] Reviewer analysis: 0.571, Applicant-reported analysis: 0.348
Source: pg 281 and 289 of CUV039 study report and reviewer analysis

Quality of Life Endpoints

The final two secondary endpoints specified in the protocol are the change from baseline to each time point in the Dermatology Life Quality Index (DLQI) and EPP-QoL. A copy of the EPP-QoL is presented in Appendix 20.3. The EPP-QoL includes 15 questions, each with 4 response options. Each question recalled the subject's experience over the past 2 months. The questions are scored such that a lower number represents a better quality of life. Thus, a question about

a subject's well-being with response choices of 'much better', 'better', 'same', and 'worse' would be scored as -2, -1, 0, and 1, while a question about how often the subject felt at risk for developing EPP symptoms with responses of 'very often', 'often', 'a little', or 'not at all' would be scored as 3, 2, 1, and 0. All potential scores for individual questions were between -3 and +3, and the sum of the 15 scores could range from -10 (best possible) to +35 (worst imaginable). In the study report the Applicant claims that the EPP-QoL has undergone psychometric validation, however, the Applicant has not submitted information to assess whether the tool is fit for purpose. Thus, the changes observed for the quality of life endpoints may not be clinically meaningful.

For subjects on the afamelanotide arm, the mean total score on the EPP-QoL decreased by 19 to 21 units from baseline at the Day 60, 120, and 180 visits and about 4 units at the follow-up visit on Day 360. For subjects on the placebo arm, the mean total score decreased by 10 to 15 units from baseline at the Day 60, 120, and 180 visits and about 8 units at the follow-up visit. See Table 35 and Table 36. The nominal p-values for the change from baseline to Days 60, 120, and 180 were <0.05. The Applicant did not propose any adjustments for multiplicity due to multiple secondary endpoints. The Applicant proposes presenting the ratios of the mean changes from baseline (afamelanotide/placebo) for Days 60, 120, and 180 in labeling, which differs from the pre-specified analysis method of the Kruskal-Wallis test (a non-parametric test). However, the Applicant has not provided sufficient information to justify that the EPP-QoL tool is fit for purpose or adequately designed the trial to support claims regarding secondary endpoints.

Table 35. EPP-QoL Scores at Each Visit in Study 039 (ITT-QoL Population)

Visit		Afamelanotide N=47	Placebo N=43
Baseline	N	47	43
	Mean (SD)	21.7 (8.3)	22.0 (8.2)
	Median	23.0	24.0
Day 60	N	47	43
	Mean (SD)	3.0 (10.2)	12.0 (12.5)
	Median	1.0	9.0
Day 120	N	46	42
	Mean (SD)	0.4 (9.6)	9.4 (12.5)
	Median	-2.0	8.0
Day 180	N	46	43
	Mean (SD)	0.5 (10.4)	6.9 (10.6)
	Median	-2.5	5.0
Follow-up (Day 360)	N	44	40
	Mean (SD)	17.0 (11.2)	14.2 (11.9)
	Median	19.5	14.0

SD = standard deviation; EPP = erythropoietic protoporphyria; ITT = intent-to-treat; QoL = quality of life
Source: pg 198 of CUV039 study report and reviewer analysis

Table 36. Change From Baseline in EPP-QoL at Each Visit in Study 039 (ITT-QoL Population)

Change From Baseline		Afamelanotide N=47	Placebo N=43	Ratio of Means	Estimate[a] 95% CI	p-value[b]
Change to Day 60	N	47	43		-9	<0.001
	Mean (SD)	-18.7 (11.0)	-10.1 (10.5)	1.9	(-15, -4)	
	Median	-19.0	-11.0			
Change to Day 120	N	46	42		-8	0.001
	Mean (SD)	-21.1 (11.3)	-13.0 (10.8)	1.6	(-14, -2)	
	Median	-21.5	-11.5			
Change to Day 180	N	46	43		-6	0.020
	Mean (SD)	-21.1 (12.2)	-15.1 (10.9)	1.4	(-11, -1)	
	Median	-22.0	-14.0			
Change to follow-up (Day 360)	N	44	40		4	0.053
	Mean (SD)	-4.4 (11.7)	-7.9 (10.1)	0.6	(0, 9)	
	Median	-0.5	-5.5			

[a] Hodges-Lehmann estimate
[b] Kruskal-Wallis test
EPP = erythropoietic protoporphyria; ITT = intent-to-treat; QoL = quality of life; SD = standard deviation
Source: pg 230-231 of CUV039 study report and reviewer analysis

The Applicant also evaluated the change from baseline to each timepoint for the Dermatology Life Quality Index (DLQI). No differences were observed between the afamelanotide and placebo arms for the DLQI. See Table 37.

Table 37. Change From Baseline in DLQI at Each Visit in Study 039 (ITT-QoL Population)

Change From Baseline		Afamelanotide N=47	Placebo N=43	Estimate[a] 95% CI	p-value[b]
Change to Day 60	N	47	43	-1	0.214
	Mean (SD)	-6.0 (5.9)	-4.0 (5.5)	(-4, 1)	
	Median	-6.0	-5.0		
Change to Day 120	N	46	42	-1	0.589
	Mean (SD)	-7.8 (6.0)	-6.5 (6.2)	(-3, 2)	
	Median	-7.0	-6.5		
Change to Day 180	N	46	43	0	0.799
	Mean (SD)	-8.1 (6.2)	-7.3 (5.6)	(-3, 2)	
	Median	-7.5	-8.0		

[a] Hodges-Lehmann estimate
[b] Kruskal-Wallis test
Source: pg 194-195 of CUV039 study report

Data Quality and Integrity

The data in Study 039 was collected on paper case report forms and subject diaries and was transcribed by the Applicant into the electronic database. A number of transcription errors have been identified by either the Applicant or investigators from EMA (European Medicines Agency) and FDA. The most critical transcription error involved recording one subject who had been randomized and treated with afamelanotide to be recorded as receiving placebo (Subject (b) (6)) and one subject who had been randomized and treated with placebo to be recorded as receiving afamelanotide (Subject (b) (6)). This error was identified by the Applicant only after the regulatory application was submitted to the EMA and the Applicant was preparing for Good Clinical Practice (GCP) inspections. The Applicant needed to completely revise the clinical study

report following the identification of this transcription error. The timeline for this correction was as follows:

- February 3, 2012 - Initial application submission to EMA. The initial submission did not include the study report for Study 039.
- December 3, 2013 - Original version of the study report for Study 039 finalized.
- December 2013 or January 2014 – The Applicant submitted the study report and data for Study 039 to CHMP (Committee for Medicinal Products for Human Use).
- February 2014 – Two sites from Study 039 were inspected based on CHMP request.
- March 11, 2014 – Applicant informed CHMP regarding their findings about the treatment allocation transcription error.
- July 20, 2014 – Applicant finalized a revised version of the study report with new analyses using the corrected treatment allocation.

This transcription error had a significant impact on the interpretation of the primary endpoint. In the initial study report, the p-value for the primary endpoint as analyzed by the Applicant using the incorrect treatment allocation was 0.107 (not significant), while in the revised study report, the p-value for the primary endpoint was 0.044 (significant). Because FDA was aware of this issue with the treatment assignments for two subjects being changed and leading to a change from a p-value>0.05 to <0.05 in the Applicant's analysis prior to the NDA submission, FDA requested that the Applicant include a full discussion of how the transcription error was identified in their NDA submission. The Applicant responded that while preparing for the EMA inspection, they undertook a further detailed review of the clinical data and noted that one subject ([redacted] (b) (6) who was recorded in the database as receiving placebo) had a reported adverse event of "increased number of moles" which is an expected adverse event for afamelanotide, but less likely to occur in a subject receiving placebo. The Applicant submitted copies of the randomization list and pharmacist dispensing records that indicate that the treatments for subjects [redacted] (b) (6) were incorrectly recorded in the database. The Applicant noted that the person responsible for transcribing the treatment allocations for the electronic database did not reference back to the pre-specified treatment allocation list. The Applicant also noted that the problem could have been avoided by providing the original randomization codes to the CRO providing data management rather than having them transcribe the allocations from the pharmacy dispensing records.

An additional database error was identified by the FDA regarding the dataset including descriptions of the analysis populations. This dataset (ANALPOP) incorrectly included subject [redacted] (b) (6) in the ITT population, even though this subject was a screening failure and not randomized. This dataset also failed to include Subject [redacted] (b) (6), who completed the study and was in the ITT population. The Applicant attributed this error to a programming error in which datasets were not properly merged causing records to be shifted and the last subject in the database [redacted] (b) (6)) to be dropped from the dataset. Fortunately, this dataset was only used to create a data listing regarding analysis populations in the study report, and the programming error had no impact on the efficacy or safety analyses.

Between the EMA and FDA, five of the seven sites in Study 039 were inspected. EMA inspected the sites in New York and Texas. FDA inspected the sites in North Carolina, Alabama, and Utah. EMA noted one "major finding" with the overall study, (b) (4) therwise, EMA concluded that for the two inspected sites, the study was performed in compliance with ICH GCP. FDA inspectors identified 12 data values (efficacy observations or laboratory values) where the value recorded in the CRF or electronic database did not correspond to the value in the source data. Only one of these discrepancies related to the primary endpoint of total hours of direct sun on days with no pain. For this transcription error, the number of hours spent in the sun and the number of hours spent in the shade were reversed for one subject on one day. Subject (b) (6) was recorded as having 0.75 hours of direct sun exposure with no pain on (b) (6), when the subject really had 0 hours of direct sun exposure and 0.75 hours of shade exposure. However, because subject (b) (6) was treated with placebo and the error caused this subject's total pain-free sun exposure for the study to increase from 3.25 to 4, correcting this subject's total hours of pain-free direct sun exposure would have no meaningful impact on the analysis.

8.2. Study CUV029

8.2.1. Study Design

Overview and Objective

Study CUV029 is a randomized, double-blind, placebo-controlled study of afamelanotide implants, 16 mg in subjects with EPP. Study 029 (conducted in Europe) was conducted concurrently with Study 030 (conducted in the US) and both studies had the same objective. Both Studies 029 and 030 were conducted before Study 039. The protocols specified that the primary objective of the trials was to determine whether afamelanotide can reduce the severity of phototoxic reactions in patients with EPP. Study 030 was completed first, and the results of the prespecified primary endpoints based on phototoxicity reactions were not statistically significant. Thus, in consultation with outside experts, the Applicant identified a post hoc, alternate endpoint that measured the amount of time that subjects were able to spend outdoors in direct sunlight without experiencing pain based on the data from Study 030. Study 029 remained blinded while the results of Study 030 were analyzed with the new endpoint. Based on the findings from Study 030, the statistical analysis plan for Study 029 was updated prior to unblinding Study 029 to match the analysis plan that was developed after the fact for Study 030. The revised primary objective of Study 029 was to assess whether afamelanotide can enable EPP subjects to expose themselves to direct sunlight during the most intense periods of sunlight without incurring pain.

Trial Design

Study 029 enrolled 76 subjects age 18 to 70 years with a biochemically-confirmed diagnosis of EPP and symptoms of sufficient severity to request treatment. The study was conducted in Europe (UK, the Netherlands, Finland, France, Germany, and Ireland). Subjects were randomized 1:1 to afamelanotide 16 mg or placebo within center. Subjects received five implants on Days 0, 60, 120, 180, and 240 and were followed for 270 days. Subjects were evaluated at screening, baseline (Day 0) and Days 60, 120, 180, 240, and 270. All subjects initiated treatment in January through August of 2010. A subset of subjects enrolled at two centers were to undergo controlled photoprovocation. These subjects underwent photoprovocation on the hand and back on Days 0, 30, 60, 90, 120, 180, 240, and 270.

Study Endpoints

Efficacy information was collected from subject diaries regarding the level of phototoxic pain, the amount of time spent outdoors in the sun, and whether most of the day was spent in direct sunlight, shade, or a combination of both. The protocol was designed to assess primary endpoints based on the number and total severity of phototoxic reactions during the study. However, after the Applicant analyzed data from Study 030, which was completed first, and sought out additional expert opinion, the primary objective and endpoints in Study 029 were modified to assess efficacy in terms of the number of hours spent outdoors where most of the day was spent in direct sunlight on days with no pain. Study 029 remained blinded while the analysis plan was revised.

Subjects recorded data on sun exposure and phototoxic pain daily for 270 days. Phototoxic pain for each day was recorded by answering the question “Have you experienced any reactions to light today” (Yes/No) and indicating the pain level on a Likert scale from 0 to 10 (from ‘No Pain’ to ‘Worst Imaginable’). Subjects also recorded the amount of time spent outdoors in the sun from 05:00 to 24:00 hours and whether ‘most’ of the day was spent in direct sunlight, shade, or a combination of both. Note that the diary used in Study 029 (and Study 030) differs from the way time in the sun was collected in the diary used in Study 039. In particular:

- The diary in Study 029 asked subjects to record time from 05:00 to 24:00, while the diary in Study 039 asked subjects to record time from just 10:00 to 18:00.
- The diary in Study 029 had one set of boxes to shade for time spent outdoors along with a question regarding whether most of the day was spent in direct sunlight, shade, or a combination of both, while the diary in Study 039 had one set of boxes to mark for time spent in direct sunlight and a separate set of boxes to mark for time spent in shade.

In addition, the diaries for Studies 029 and 030 had a printing error so that there was no space to record time spent outdoors between 14:00 and 15:00. This printing error was identified in May 2010, approximately 4 months after the study began enrollment. The Applicant notified investigators and subjects to ask them to include hand-drawn boxes to serve as replacements for the 4 missing time boxes.

A copy of the daily diary for Study 029 (including the misprint) is presented below (Figure 25):

Figure 25. Daily Diary for Study 029

DATE:_____(DD/MMM/YYYY)

1. EPP Monitoring

Have you experienced any reactions to light today? Yes ☐ No ☐

If 'yes', please indicate on the scale below how bad your pain was from this reaction:

0	1	2	3	4	5	6	7	8	9	10
No Pain	Mild			Moderate			Severe			Worst Imaginable

2. Time Spent Outdoors

2.1 Did you spend any time outdoors that day? Yes ☐ No ☐

2.2 Please enter the time period that you were outdoors that day by shading the time period you were out in the sun today. ***(Each box represents 15 minutes)***

05:00 06:00 07:00 08:00 09:00 10:00 11:00 12:00 13:00 14:00

15:00 16:00 17:00 18:00 19:00 20:00 21:00 22:00 23:00 24:00

2.3 Was most of your day spent in: ***(Tick the one box only)***

Direct sunlight ☐
Shade ☐
Combination of both ☐

Note that due to a printing error, the diary did not include boxes to record time spent outdoors between 14:00 and 15:00.
EPP = erythropoietic protoporphyria
Source: "Attachment 1 to Response to FDA Question #2: CUV029 Patient Diary v3".

After the SAP was revised based on the results observed in already-completed Study 030, the primary efficacy endpoint was the total number of hours spent outdoors in direct sunlight between 10:00 and 15:00 hours on days when no pain was experienced (Likert score of 0). Time outdoors was considered to be spent in direct sunlight on a particular day if the subject reported that most of the day was spent in direct sunlight (but not if the subject reported that time was spent in a combination of both sunlight and shade).

The secondary efficacy endpoints were:

- Total number of hours spent outdoors in direct sunlight between 10:00 and 20:00 on days when no pain was experienced (Likert score of 0)
- Total number of hours spent outdoors in direct sunlight on days when no or mild pain was experienced (Likert score of 0 to 3) for 10:00 to 15:00 hours and 10:00 to 20:00 hours
- Phototoxicity-related pain per unit sun exposure (in direct sunlight) for 10:00 to 15:00 hours and 10:00 to 20:00 hours

- Total number of hours spent outdoors in direct sunlight for 10:00 and 15:00 hours and 10:00 to 20:00 hours
- Dermatology Life Quality Index (DLQI)
- Supplementary EPP-specific quality of life questionnaire on Days 0, 60, 120, 180, 240, and 270.
- Minimum symptom dose following photoprovocation on the lower back and dorsal surface of the hand on Days 0, 30, 60, 90, 120, 180, 240, and 270
- Minimum erythema dose which produces unambiguous erythema following photoprovocation on the lower back on Days 0, 30, 60, 90, 120, 180, 240, and 270
- The distribution of daily phototoxic pain severity scores using categories of 0, 1 to 3, 4 to 6, and 7 to 10.
- Number of phototoxic reactions (a phototoxic reaction is defined as consecutive days with Likert score ≥4)

In the original protocol, the primary endpoint was the 'median maximum severity score and the median total severity score for all reported phototoxic reactions.' Note that this definition implies two ways of summarizing the daily severity scores for each subject: by way of the maximum score and the total (sum) score. The secondary endpoints were the proportion of subjects experiencing a phototoxic reaction with a score ≥4 and the proportion of subjects experiencing a phototoxic reaction with a score ≥7. Without specifying details, the protocol also listed the DLQI, EPP questionnaire, minimum symptom dose, minimum erythema dose, and duration of sunlight exposure as secondary endpoints.

Statistical Analysis Plan

All primary and secondary endpoints were to be analyzed with a Kruskal-Wallis non-parametric test. All tests were to be conducted at the 0.05 significance level. The protocol did not propose any adjustments for multiplicity among the set of secondary endpoints.

The randomized population was defined as all subjects who were assigned a randomized treatment. The SAP stated that no imputations for missing data were conducted, except that subjects who responded "No" to the question "Have you experienced any reactions to light today?" and did not provide a pain severity score will have their pain severity imputed as 0. Note, however, that the imputation actually conducted by the Applicant was to impute a pain score of 0 for any subject who did not provide a pain score, whether or not the subject responded "No" to the reaction question.

Protocol Amendments

The original version of the protocol was finalized in December 2009. The final amended version of the protocol was dated October 5, 2010. Subject participation was from January 2010 to May 2011. Because the study was conducted in Europe, the protocol was not submitted to the IND. However, the protocol for the contemporaneous study conducted in the US (Study 030) with

the same primary objective and endpoints was submitted to the IND in February 2010. Study 030 was denoted in the submission as a Phase 2 protocol. FDA issued an Advice Letter dated July 9, 2010 which made the following comments regarding the endpoints and analyses in Protocol 030, and which would have also been relevant to Protocol 029.

- The definition of the primary endpoint of total severity and maximum severity of phototoxic reactions was not clear, and that it appeared the analysis unit was the phototoxic reaction, rather than the subject, and that such an analysis would not address within-subject correlations.
- The analysis did not take into account length of subject follow-up which would impact the number and duration of phototoxic reactions that could be observed.
- It was not clear how the missing data would be handled.

The Applicant did not engage the Agency further in the design of Study 029 or 030 prior to initiation, including any further clarification of the phototoxicity endpoints.

8.2.2. Study Results

Compliance With Good Clinical Practices

The Applicant stated that studies were designed, monitored, and conducted in accordance with GCP requirements and ethical principles. Study protocols, the subject information and informed consent forms, subject recruitment procedures were reviewed by the responsible Institutional Review Board (IRB). The Applicant obtained an approval from the IRB prior to study initiation.

Financial Disclosure

Refer to Appendix 19.2.

Patient Disposition

Study 029 randomized 76 subjects, of which 74 subjects received treatment medication, 38 who received afamelanotide and 36 who received placebo. Six subjects discontinued the study (4 afamelanotide and 2 placebo). One subject (randomized to afamelanotide) had a suspected pregnancy at the time for the second dose. The investigator broke the blind, but the subject remained blinded. The subject was found not to be pregnant and continued the study with another investigator who was blinded to treatment assignment. Subsequently, the subject was discontinued after receiving 4 doses of study treatment for protocol violation. Another subject was discontinued after receiving one dose when it was found that the subject had participated in another clinical trial within 30 days of the screening visit (Applicant decision). The remaining subjects discontinued due to the physician's decision (adverse event of migraine) or subject decision. See Table 38.

Table 38. Disposition of Subjects in Study 029

	Afamelanotide	Placebo
Subjects randomized	38	36
Discontinued	4 (11%)	2 (6%)
Sponsor decision		1 (3%)[a]
Physician decision	1 (3%)[b]	
Subject decision	2 (5%)	1 (3%)
Serious violation of protocol	1 (3%)[c]	

[a] Subject previously enrolled in another study
[b] Adverse event
[c] Blind broken due to suspected pregnancy, subject transferred to another site, and then discontinued
Source: pg 69 of CUV029 study report, and reviewer analysis.

Most subjects (93%) received all five doses (including one placebo subject who discontinued the study due to subject decision after receiving the last implant but before the final visit). Four afamelanotide subjects received 2 to 4 doses and 1 placebo subject received 1 dose. See Table 39.

Table 39. Extent of Exposure in Study 029

Number of Doses	Afamelanotide N=38	Placebo N=36
5	34	35
4	2	
3	1	
2	1	
1		1

Source: reviewer analysis.

All subjects returned at least one diary card and reported sunlight exposure and pain for at least 64 days.

Demographic Characteristics

Enrollment in Study 029 was generally balanced across demographic subgroups. The study enrolled similar numbers of male and female subjects. The majority of subjects were less than 65 years of age and Caucasian. See Table 40.

Table 40. Baseline Demographics in Study 029 (Safety Population)

	Afamelanotide N=38	Placebo N=36
Sex		
Male	17 (45%)	20 (56%)
Female	21 (55%)	16 (44%)
Age		
Mean years	38.3	38.6
Min, max (years)	19, 70	18, 62
Age group		
≥18–<65 years	36 (95%)	36 (100%)
≥65 years	2 (5%)	
Race		
Caucasian	38 (100%)	35 (97%)
Mixed		1 (3%)

Source: pg 74 of CUV029 study report and reviewer analysis.

Other Baseline Characteristics

At baseline, subjects reported the "severity of their current condition" as mild, moderate, severe, or worst imaginable. No definitions for these categories were provided. Enrollment was generally balanced across baseline severity categories and type of usual first phototoxic reaction, except that more subjects on the afamelanotide arm reported "mild" disease severity. Subjects also recorded the "Approximate time from UV exposure to onset of first symptoms". Subjects on the afamelanotide arm reported longer time periods before the onset of phototoxic symptoms than subjects on the placebo arm. See Table 41.

Table 41. Baseline Disease Severity in Study 029 (Safety Population)

Baseline Characteristics	Afamelanotide N=38	Placebo N=36
Baseline severity		
Mild	9 (24%)	3 (8%)
Moderate	17 (45%)	21 (58%)
Severe	11 (29%)	11 (31%)
Worst Imaginable	1 (3%)	1 (3%)
Usual first EPP phototoxic reaction after sun exposure		
Burning	18 (47%)	20 (56%)
Itching	4 (11%)	3 (8%)
Pain	7 (18%)	3 (8%)
Other[a]	9 (24%)	10 (28%)
Approximate time from UV exposure to first symptom		
Mean minutes (SD)	52.6 (75.3)	40.1 (53.8)
Median	25	20
Min, max	0, 360	0, 240

[a] Prickling/Stinging/Tingling/Swelling/Sharp Pin-l ke Pain/Numb Feeling
EPP = erythropoietic protoporphyria; SD = standard deviation; UV = ultraviolet
Source: reviewer analysis

Efficacy Results – Primary Endpoint

Subjects recorded data on sun exposure and phototoxic pain daily in a diary for 270 days. Phototoxic pain for each day was recorded by answering the question "Have you experienced any reactions to light today" (Yes/No) and indicating the pain level on a Likert scale from 0 to 10 (from 'No Pain' to 'Worst Imaginable'). Subjects also recorded the amount of time spent outdoors in the sun from 05:00 to 24:00 hours and whether 'most' of the day was spent in direct sunlight, shade, or a combination of both. The diary for Study 029 had a printing error so that there was no space to record time spent outdoors between 14:00 and 15:00. A copy of the subject diary is presented above in Section 8.2.1.

Although the protocol defined the primary endpoint as the 'median maximum severity score and the median total severity score for all reported phototoxic reactions,' prior to unblinding the study and based on the results of Study 030, the primary efficacy endpoint was redefined in the SAP as the total number of hours spent outdoors in direct sunlight between 10:00 and 15:00 hours on days when no pain was experienced (Likert score of 0). Time outdoors was considered to be spent in direct sunlight on a particular day if the subject reported that most of the day was spent in direct sunlight. The subject diaries covered 270 days. The primary

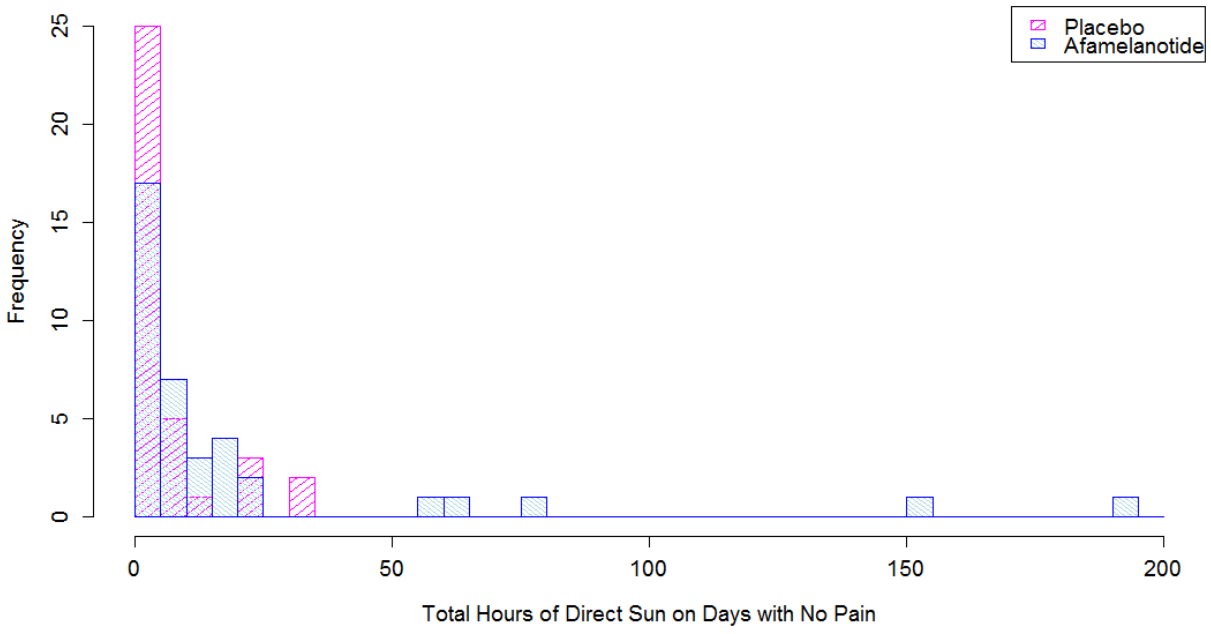
endpoint was analyzed with a Kruskal-Wallis test, which is equivalent to the Wilcoxon test in the case with two treatment arms and where the asymptotic test is conducted without continuity corrections. The Applicant conducted the primary efficacy analysis in the ITT population which included all subjects who were randomized and received at least one dose of study treatment. To provide analyses similar to what were conducted for Study 039, this reviewer also calculated the Hodges-Lehmann estimator. The efficacy results are presented in Table 42 and a histogram of the data is presented in Figure 26. From the summary statistics and histograms, we see that the distributions for the two treatment groups are right skewed with the afamelanotide group having a longer right tail and larger standard deviation. The results of the test are statistically significant. Thus, the results of the test indicate that there is evidence that the distributions differ.

Table 42. Primary Efficacy Endpoint: Total Hours Outdoors between 10:00 and 15:00 on Days With No Pain and Where Most of the Day was Spent in Direct Sun in Study 029 (ITT Population)

	Afamelanotide N=38	Placebo N=36	Estimate[a] 95% CI	p-value[b]
Mean (SD)	20.4 (40.5)	5.6 (9.3)	2.75	0.005
Median	6.0	0.75	(0.75, 6.5)	

[a] Hodges-Lehmann estimate
[b] Kruskal-Wallis test
ITT = intent-to-treat; SD = standard deviation
Source: pg 50 of CUV029 study report and reviewer analysis

Figure 26. Histogram for the Total Hours Outdoors Between 10:00 and 15:00 on Days With No Pain and Where Most of the Day was Spent in Direct Sun in Study 029 (ITT Population)



Source: Reviewer analysis

Missing Data Handling

The Applicant analyzed observed case data and did not attempt to impute any data for diary days that were not completed or returned by the subjects. Subjects were to return completed diaries to the investigator on Days 60, 120, 180, 240, and 270. All subjects returned at least 64 days of diary data. Note that one subject who did not return all diaries received all five doses. See Table 43.

Table 43. Missing Diary Data in Study 029

	Afamelanotide N=38	Placebo N=36
1 diary returned	1 (3%)	1 (3%)
Subject ID (Diary #)	(b) (6) [a] (1)	(b) (6) [a] (1)
3 diaries returned	2 (5%)	
Subject ID (Diary #)	(b) (6) [a] (1-3), (b) (6) (1,2,5)	
4 diaries returned	2 (5%)	
Subject ID (Diary #)	(b) (6) [a] (1-4), (b) (6) (1-4)	
All diaries returned	33 (87%)	35 (97%)

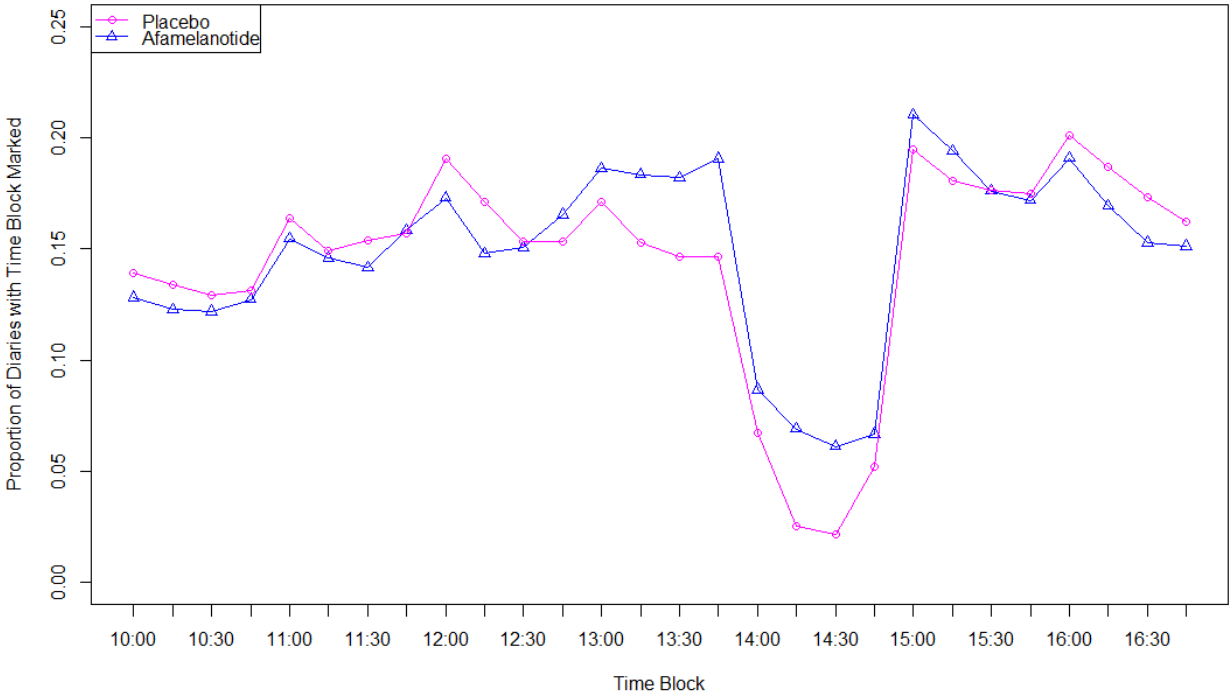
[a] Subjects who discontinued and did not receive all five doses.
Note: The first 4 diaries covered approximately 60 days each and the last diary covered approximately 30 days.
Source: Reviewer analysis

All treated subjects returned at least one diary and the Applicant analyzed the observed results "as reported" by subjects without any imputation for missing information. The Applicant did not include any sensitivity analyses regarding the handling of missing data. However, only one subject (Subject (b) (6) who received afamelanotide) did not return all diaries for the period where the subject received treatment. In addition, more subjects on the afamelanotide arm (4) discontinued treatment than subjects on the placebo arm (1). Thus, the impact of missing data on the results is minimal, and the only sensitivity analysis that would lead to a more conservative estimate of the treatment effect than the "as reported" analysis would be an analysis that imputed a greater amount of pain-free sun exposure for the placebo subject who discontinued the study.

Impact of Misprinted Diaries

Subject diaries were misprinted and did not include boxes for subjects to mark time spent outdoors between 14:00 and 15:00 hours, part of the time period intended to be included in the primary endpoint. Subjects were instructed to freehand responses for this time period, but it is likely that subjects did not consistently record time spent outdoors between 14:00 and 15:00. To assess the impact of the misprinted diary on the amount of information collected between 14:00 and 15:00, Figure 27 presents the proportion of daily diaries returned by the subjects for which the subject marked various blocks representing 15-minute periods of time spent outdoors between 10:00 and 17:00. Note that this figure presents the time spent outdoors but does not take into account whether the time was spent in direct sun, or whether the subject reported pain. The figure demonstrates that information on the time spent outdoors for the time period between 14:00 to 15:00 was significantly underreported compared to 13:00 to 14:00 and 15:00 to 16:00.

Figure 27. Proportion of Daily Subject Diaries With Time Blocked Marked as Representing a 15-Minute Period Spent Outdoors between 10:00 and 17:00 in Study 29



Source: reviewer analysis

Because data from 14:00 to 15:00 was not consistently collected, this reviewer conducted an analysis only considering the data collected from 10:00 to 14:00. Because subjects recorded data from 14:00 to 15:00 at a lower rate, the results from the analysis from 10:00 to 14:00 are very similar to the results from 10:00 to 15:00. Thus, although the primary endpoint ostensibly collected information from 10:00 to 15:00 each day, in practice, it primarily represents time spent outdoors from 10:00 to 14:00.

Table 44. Primary Efficacy Endpoint: Total Hours Outdoors between 10:00 and 14:00 on Days With No Pain and where Most of the Day was Spent in Direct Sun in Study 029 (ITT Population)

	Afamelanotide N=38	Placebo N=36	Estimate[a] 95% CI	p-value[b]
Mean (SD)	18.1 (37.6)	5.2 (9.0)	2.75	0.006
Median	5.125	0.75	(0.75, 5.5)	

[a] Hodges-Lehmann estimate
[b] Kruskal-Wallis test
CI = confidence interval; SD = standard deviation; ITT = intent-to-treat
Source: reviewer analysis

Efficacy Over Time

Inspection of the dataset that contained the subject diary information on pain and sun exposure revealed that diary observations given consecutive sequence numbers did not always follow chronological order. Some observations do not appear to be listed in chronological order. In addition, dates were recorded in a variety of formats in this dataset (e.g., September 26, 2010; December 5, 2010; May 8, 2010), making it impossible to re-sort the observations by

date without extensive data reentry. Thus, it was not feasible to conduct any analyses over time for the primary endpoint as the submitted data was not suitable for this task.

Combination Sun/Shade Versus Direct Sun Exposure

The subject diary used in Study 029 asked subjects to record the amount of time spent outdoors each day and to record an overall assessment as to whether "most" of the day was spent in direct sunlight, shade, or a combination of both. Thus, time spent in direct sunlight on days for which subjects spent part of the time in shade and part of the time in direct sunlight is not captured by the primary endpoint. The Applicant conducted a supportive analysis looking at the total hours spent outdoors between 10:00 and 15:00 on days with no pain and where most of the day was spent in direct sunlight or a combination of direct sunlight and shade. For this analysis, the difference between afamelanotide and placebo was minimal, and the result was non-significant. See Table 45.

Table 45.Total Hours Outdoors Between 10:00 and 15:00 on Days With No Pain and Where Most of the Day was Spent in Direct Sun or a Combination of Direct Sun and Shade in Study 029 (ITT Population)

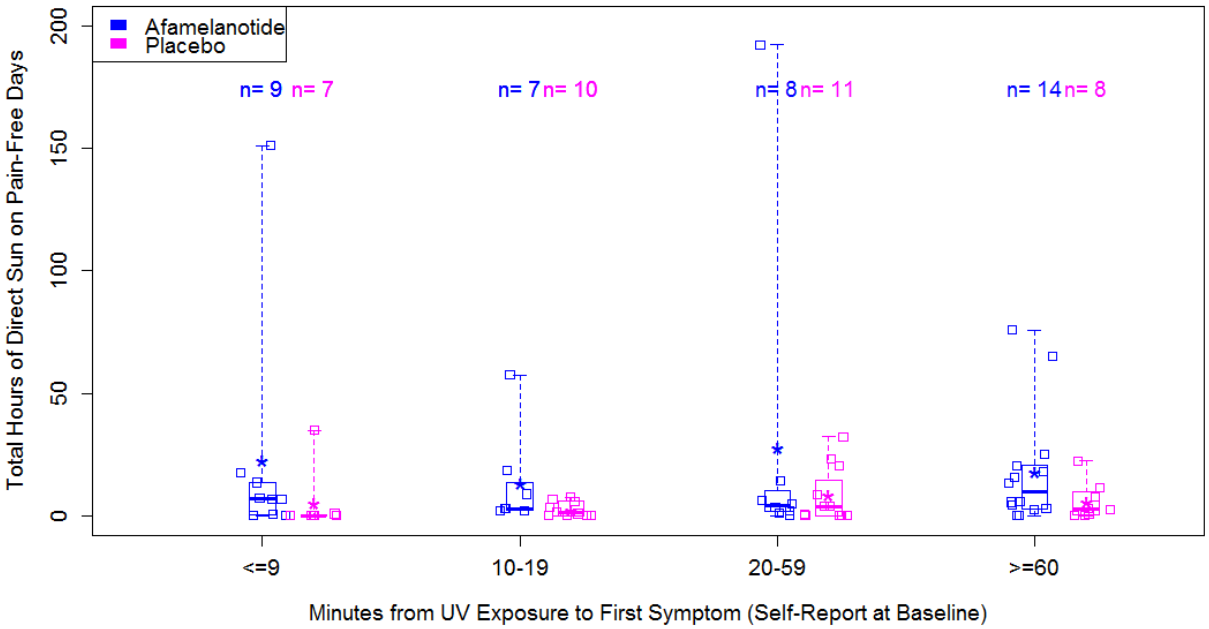
	Afamelanotide N=38	Placebo N=36	Estimate[a] 95% CI	p-value[b]
Mean (SD)	102.1 (151.0)	91.5 (122.6)	0.25	0.97
Median	51.625	53.375	(-21.5, 27.0)	

[a] Hodges-Lehmann estimate
[b] Kruskal-Wallis test
CI = confidence interval; SD = standard deviation; ITT = intent-to-treat
Source: pg 92 of CUV029 study report and reviewer analysis

Efficacy by Baseline Severity

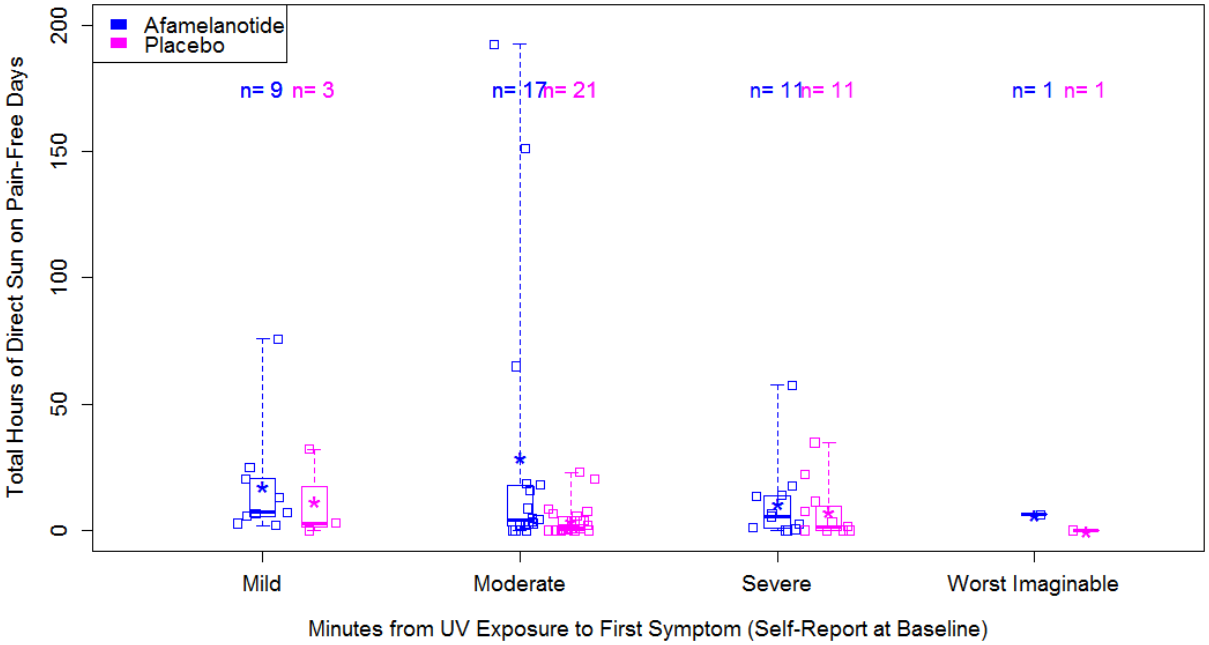
To further explore the impact of subject variability on the primary outcome, this reviewer graphed the primary outcome versus the subject-reported tolerance to light responses at baseline. As noted under the description of baseline characteristics, subjects on the afamelanotide arm self-reported somewhat milder disease at baseline in terms of severity and "approximate time from UV exposure to onset of first symptoms". Responses for time to symptom onset were divided into quartiles. Figure 28 presents boxplots of the primary outcome by the baseline exposure report quartile and Figure 29 presents boxplots of the primary outcome by baseline self-reported EPP severity category. Subjects on the afamelanotide arm tended to have higher values for total sun exposure than those on the placebo within each subgroup, and the results were not driven by results from any particular subgroup.

Figure 28. Total Hours of Direct Sun on Days With No Pain by Minutes From UV Exposure to First Symptom, as Reported at Baseline in Study 029



Asterisk represents the mean.
UV = ultraviolet
Source: Reviewer analysis.

Figure 29. Total Hours of Direct Sun on Days With No Pain by Baseline-Reported EPP Severity in Study 029

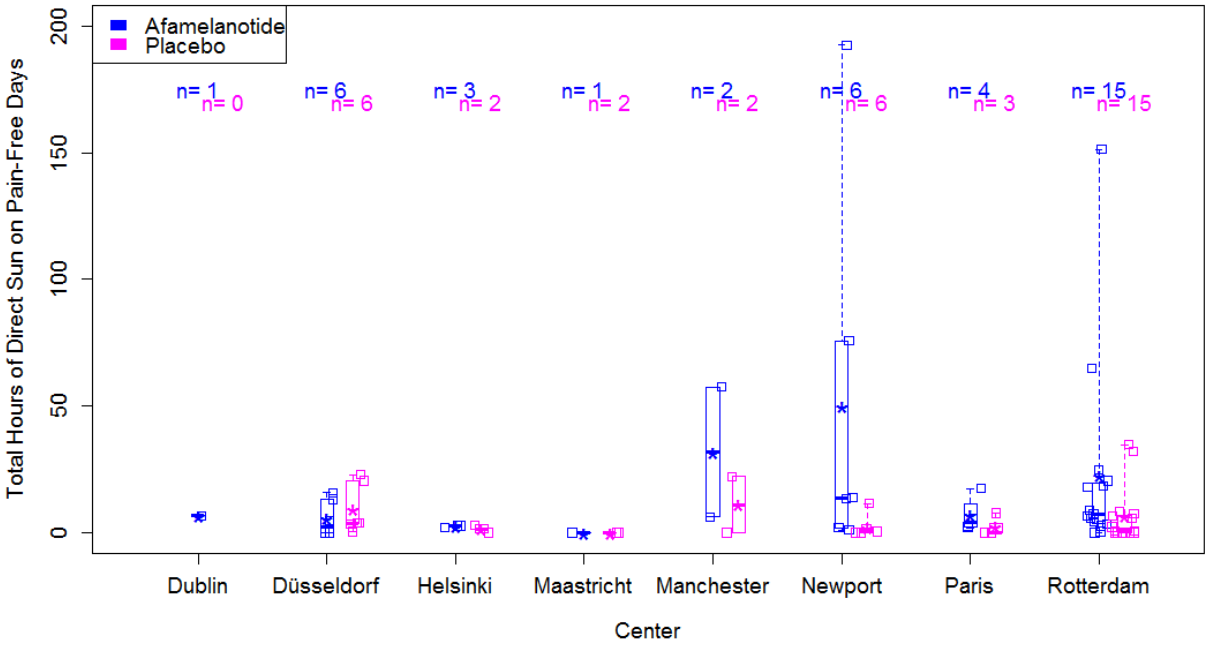


Asterisk represents the mean.
EPP = erythropoietic protoporphyria
Source: Reviewer analysis.

Efficacy by Center

The total hours of direct sun on days with no pain is presented by center in Figure 30. Five of the eight centers had fewer than 10 subjects enrolled. Because many of the centers enrolled few subjects, it is difficult to assess center-to-center variability.

Figure 30. Total Hours of Direct Sun on Days With No Pain by Center in Study 029



Asterisk represents the mean.
Source: Reviewer analysis.

Efficacy by Gender, Race, and Age

The majority of subjects were Caucasian (99%) and less than 65 years of age (97%) so subgroup analysis by race and geriatric subgroups is not meaningful. Female subjects had more time in the sun with no pain among subjects receiving afamelanotide relative to those on vehicle, while there was no observed treatment effect in males. Study 029 was conducted in Europe. See Table 46.

Table 46. Total Hours of Direct Sun on Days With No Pain by Subgroup in Study 029 (ITT Population)

Subgroup		Afamelanotide N=38	Placebo N=36	Estimate[a] 95% CI
Sex				
Male	N	17	20	
	Mean (SD)	21.5 (49.0)	8.8 (11.3)	0
	Median	3.5	3.625	(-3.75, 3.25)
Female	N	21	16	
	Mean (SD)	19.5 (33.3)	1.6 (2.9)	8.75
	Median	13.25	0	(2.75, 15.75)
Race				
Caucasian	N	38	35	
	Mean (SD)	20.4 (40.5)	5.7 (9.4)	2.75
	Median	6.0	0.75	(0.5, 6.5)
Mixed	N		1	
	Value		0.75	
Age				
≥18 to <65 years	N	36	36	
	Mean (SD)	21.0 (41.5)	5.6 (9.3)	2.75
	Median	6.0	0.75	(0.5, 6.5)
≥65 years	N	2		
	Mean (SD)	10 (11.3)		
	Median	10		

[a] Hodges-Lehmann estimate
CI = confidence interval; SD = standard deviation
Source: reviewer analysis

Efficacy Results – Secondary Endpoints

The secondary efficacy endpoints defined in the SAP were:

- Total number of hours spent outdoors in direct sunlight between 10:00 and 20:00 on days when no pain was experienced (Likert score of 0)
- Total number of hours spent outdoors in direct sunlight on days when no or mild pain was experienced (Likert score of 0 to 3) for 10:00 to 15:00 hours and 10:00 to 20:00 hours
- Phototoxicity-related pain per unit sun exposure (in direct sunlight) for 10:00 to 15:00 hours and 10:00 to 20:00 hours
- Total number of hours spent outdoors in direct sunlight for 10:00 and 15:00 hours and 10:00 to 20:00 hours
- Dermatology Life Quality Index (DLQI)
- Supplementary EPP-specific quality of life questionnaire on Days 0, 60, 120, 180, 240, and 270.
- Minimum symptom dose following photoprovocation on the lower back and dorsal surface of the hand on Days 0, 30, 60, 90, 120, 180, 240, and 270
- Minimum erythema dose which produces unambiguous erythema following photoprovocation on the lower back on Days 0, 30, 60, 90, 120, 180, 240, and 270

- The distribution of daily phototoxic pain severity scores using categories of 0, 1 to 3, 4 to 6, and 7 to 10
- Number of phototoxic reactions (a phototoxic reaction is defined as consecutive days with Likert score ≥4)

The Applicant did not propose any statistical methods for controlling multiplicity among the set of secondary endpoints. This review will focus on the secondary endpoints based on the time in direct sunlight, phototoxic pain, and photoprovocation.

Time in Direct Sunlight Endpoints

Some of the secondary endpoints are variations on the primary endpoint that change either the time window considered (10:00 to 20:00 rather than 10:00 to 15:00) or the daily pain level permitted to count hours spent in direct sun (Likert scores of 0 to 3 for no or mild pain, or any pain score (0 to 10) for considering time spent outdoors). The results for the hours of direct exposure between 10:00 and 20:00 with no pain and the results for the hours between 10:00 and 15:00 and 10:00 and 20:00 on days with no or mild pain are consistent with the primary endpoint. However, the endpoints that allow for any level of pain did not demonstrate any difference between afamelanotide or placebo (total amount of time spent outdoors in direct sunlight). See Table 47.

Table 47. Secondary Endpoints Based on Sun Exposure and Pain Level in Study 029 (ITT Population)

Sun Exposure and Pain Level		Afamelanotide N=38	Placebo N=36	p-value[b]
Hours of direct sunlight exposure (10:00 to 20:00) on days with no pain	Mean (SD)	40.2 (77.2)	12.84 (20.8)	0.003
	Median	14.5	1.875	
Hours of direct sunlight exposure (10:00 to 15:00) on days with no or mild pain	Mean (SD)	24.7 (42.5)	8.5 (11.3)	0.032
	Median	7.75	5.375	
Hours of direct sunlight exposure (10:00 to 20:00) on days with no or mild pain	Mean (SD)	49.0 (80.3)	18.4 (24.8)	0.012
	Median	12.5	12.875	
Hours of direct sunlight exposure (10:00 to 15:00)	Mean (SD)	177.2 (175.3)	174.1 (138.8)	0.496
	Median	144	141.75	
Hours of direct sunlight exposure (10:00 to 20:00)	Mean (SD)	356.8 (288.3)	373.4 (234.9)	0.358
	Median	307.25	323.5	

[a] Hodges-Lehmann estimate
[b] Kruskal-Wallis test
SD = standard deviation
Source: pg 92, 93, and 122 of CUV029 study report

Phototoxic Episode Endpoints

The protocol specified “median maximum severity score and median total severity score for all reported phototoxic reactions” as the primary endpoint. Phototoxic episodes were defined in the protocol as consecutive days with Likert pain score ≥4. After the companion Study 030 was analyzed, the SAP for Study 029 was modified to change the definition of the primary endpoint to total pain-free sun exposure and the number of phototoxic episodes was designated as a secondary endpoint. Maximum severity and total severity scores were no longer specified as endpoints, but the Applicant included these results in the study report.

As noted in the discussion about phototoxic episodes for Study 039, the number of phototoxic episodes may be difficult to interpret. For an extreme example, a subject who reported a pain score of 10 every day in the study and a subject who reported a pain score of 4 on only 1 day during the study would both be recorded as having one phototoxic episode, even though these subjects experienced very different levels of phototoxic pain during the study. Conversely, a subject who reported a pain score of 4 every day in the study (270 days) would be recorded as having one phototoxic episode and a subject who alternated between scores of 4 and 3 every day of the study would be recorded as having 135 phototoxic episodes (one for each day the score of 4 was recorded), even though the subject who recorded pain scores of 4 every day had the greater total severity.

While evaluating the Applicant's datasets, the reviewer identified issues that further complicate the analysis for the number of phototoxic episodes. Note that the definition of a phototoxic episode requires the identification of consecutive study days where a pain score greater than or equal to 4 was recorded. Upon inspection of the datasets, the reviewer noticed that diary observations given consecutive sequence numbers did not always follow chronological order. For example, Table 48 displays excerpts of the data for Subject (b) (6) which indicate that the sequence numbers for several observations do not match the chronological dates. Because the definition of a phototoxic episode requires observations to be in chronological order in order to determine the length and number of distinct phototoxic episodes (a phototoxic episode is consecutive days with pain scores greater than or equal to 4), the Applicant's analyses of phototoxic episodes may not be reliable. Although not clear from this example, dates were recorded in a variety of formats in this dataset (e.g., (b) (6) , making it impossible to re-sort the observations by date without extensive data reentry.

Table 48. Subject Diary Dates and Sequence Identifiers (Data Excerpts From PDCRDSUM.XPT for Subject Number (b) (6) and Visit Number 3)

SEQID	DATE
23	(b) (6)
24	
25	
26	
27	
28	
29	
30	
41	
42	
43	
44	
45	
46	
47	
48	

SEQID = Sequence ID

In addition, the reviewer identified a programming error in the Applicant's program that caused the analysis to miss a phototoxic episode from one subject randomized to afamelanotide. This programming error caused the Applicant's analysis to miss phototoxic episodes that began on the first day of a new diary page (from visits 2 to 5). Also, for unknown reasons, the Applicant reports different analysis results in the body of the study report (Table 11.4 on page 52) and the appendix of the study report (Table 14.2.7 on page 114). The programs submitted by the Applicant reproduce the results presented in the appendix of the study report.

However, the maximum severity and total severity endpoints are not dependent on the ordering of the observations. The Applicant's results for the maximum severity score and the total severity score (the original primary endpoints in Study 029) are presented in Table 49. Note that Applicant's analysis method treats any pain score that is not considered a phototoxic reaction (pain scores 1 to 3) as if they were equivalent to 0 when calculating maxima or sum scores. Although the p-values are nominally significant for the maximum and total severity endpoints, an analysis that replaces observed pain scores from 1 to 3 with 0 prior to calculating summary statistics introduces bias and makes the results difficult to interpret. The table also presents results for the maximum and total severity scores using all data as observed.

Table 49. Endpoints Based on Phototoxic Episodes in Study 029 (ITT Population)

		Afamelanotide N=38	Placebo N=36	p-value[a]
Maximum severity score[b] (converting scores 1-3 to 0)	Mean (SD)	3.6 (3.1)	5.3 (3.1)	0.010
	Median	4.0	6.0	
	Range	0, 10	0, 10	
Maximum severity score[c] (using all data as observed)	Mean (SD)	4.5 (2.2)	5.8 (2.2)	0.0164
	Median	4.0	6.0	
	Range	1, 10	1, 10	
Total severity score[b] (converting scores 1-3 to 0)	Mean (SD)	18.0 (27.9)	52.9 (98.2)	0.025
	Median	5.0	17.5	
	Range	0, 113	0, 490	
Total severity score[c] (using all data as observed)	Mean (SD)	48.8 (48.7)	92.2 (121.1)	0.107
	Median	38.5	54.0	
	Range	3, 208	4, 528	

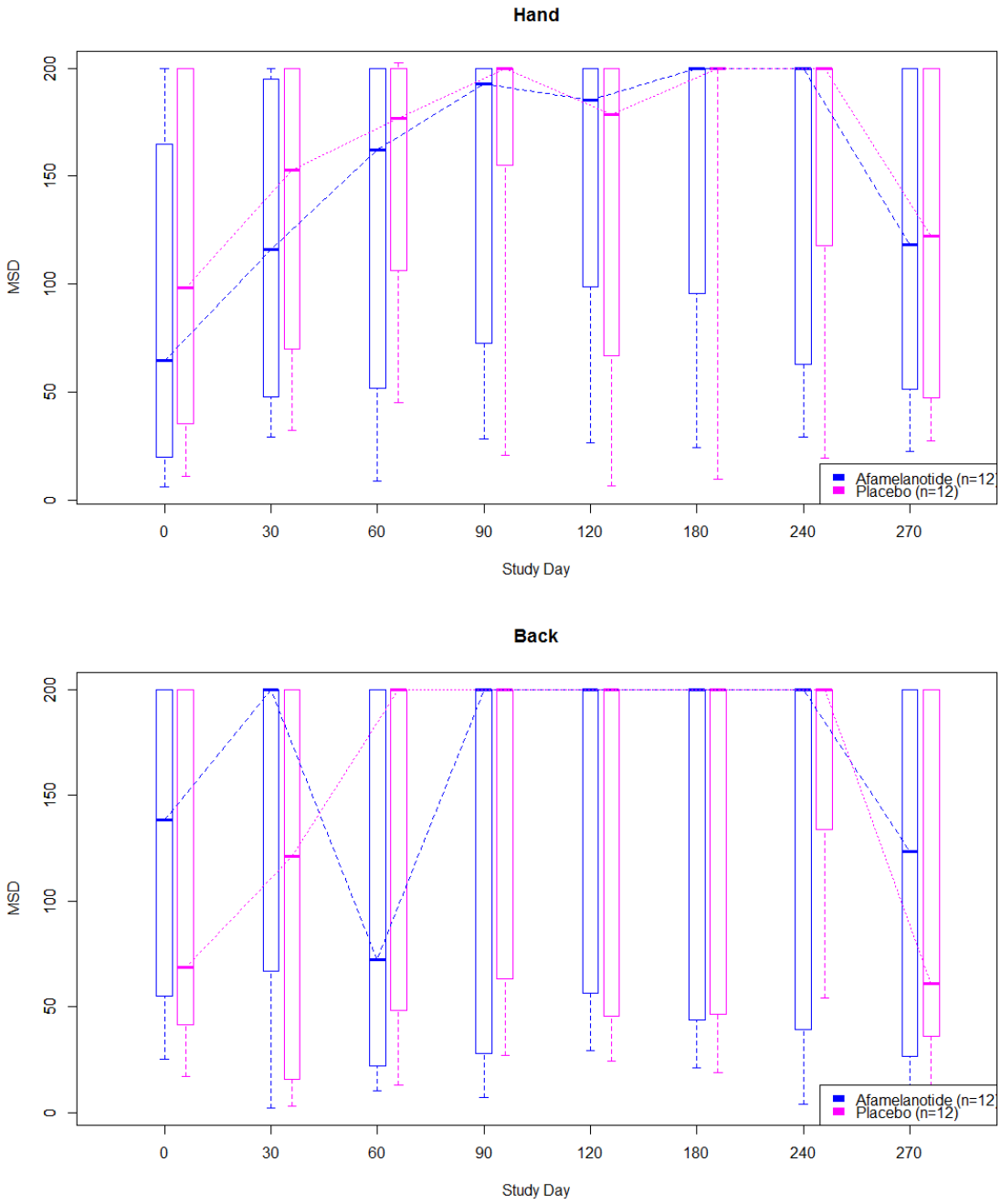
[a] Kruskal-Wallis test
[b] Applicant analysis converting scores 1-3 to 0
[c] Reviewer analysis
ITT = intent-to-treat; SD = standard deviation
Source: pg 333 of CUV039 study report and reviewer analysis

Photoprovocation

A photoprovocation sub-study was conducted at two sites: Site 1 (Newport) and Site 6 in Duesseldorf in 24 subjects (12 afamelanotide and 12 placebo). For the photoprovocation, areas approximately 33 mm in diameter on the dorsal surface of the hand and on the back were irradiated with filtered light on Days 0, 30, 60, 90, 120, 180, 240, and 270. The subjects were to be irradiated either until the subject experienced the first phototoxic symptoms or until a maximum dose of 200 J/cm^2 was received. The minimum dose of radiation to induce the first symptom (minimum symptom dose or MSD) was recorded for the hand and the back for each visit.

When summarizing the MSD by visit across subjects, little difference was observed in the minimum symptom dose between the afamelanotide and placebo arms. At the visits in the middle of the study, the median was at or near the censoring point in both arms. See Figure 31. Study 029 was unable to distinguish between afamelanotide and placebo in terms of the minimum symptom dose.

Figure 31. Minimum Symptom Dose Following Photoprovocation in Study 029 (Photoprovocation Analysis Set)



Dashed lines connect the medians at each visit.
Source: Reviewer analysis

Data Quality and Integrity

Study 029 has many data quality and integrity issues. The key issues include:

- Improper study diary design that did not include space to record time spent outdoors from 14:00 to 15:00.
- Numerous tables in the study report where the table in the main body of the text differs from the appendix. In general, the tables in the appendix are consistent with the submitted datasets.
- Datasets with poor design, including observations that are not in chronological order and lack of standardization of variables (e.g., dates in free text form that differ from observation to observation).
- Poor statistical program design that failed to properly count all phototoxic reactions.
- Poorly defined methods for reconciling inconsistent subject diary information (e.g., how to count a subject who marked having no reactions to light but marked a non-zero pain score).

In their review, EMA classified Study 029 non-GCP (Good Clinical Practice) compliant. The EMA listed the issues with the study diary design, improper statistical planning, and issues with collection and storage of source documents that made it difficult to trace data in the databases as reasons for the non-GCP compliance designation.

Overall Assessment of Efficacy

Because the Applicant originally designed Study 029 to focus on assessing the number and severity of phototoxic reactions, the subject diaries were not designed in a way subjects could clearly record the amount of time spent outdoors in direct sunlight. Subjects were asked to record time spent outdoors and to mark whether the time was “mostly” spent in direct sunlight, shade, or a combination. This along with the diary design issue that failed to leave space to record time from 14:00 to 15:00, makes the pain-free sun exposure endpoint harder to interpret.

The data quality issues make the endpoints difficult to interpret, particularly for the secondary endpoints. However, even with these issues, examination of the data provides support for a treatment effect for the amount of pain-free sun exposure.

Because of these reasons, the results from Study 029 should be considered supportive, however they do provide independent substantiation to the findings of Study 039 regarding the effect of afamelanotide in increasing pain-free sun exposure.

8.3. Study CUV030

8.3.1. Study Design

Overview and Objective

Study CUV030 is a randomized, double-blind, placebo-controlled study of afamelanotide implants, 16 mg in subjects with EPP. Study 030 (conducted in the US) was conducted concurrently with Study 029 (conducted in Europe) and both studies had the same objective. The protocols specified that the primary objective of the trials was to determine whether afamelanotide can reduce the severity of phototoxic reactions in patients with EPP. Study 030 was completed first, and the results of the prespecified primary endpoints based on phototoxicity reactions were not statistically significant. In consultation with outside experts, the Applicant identified an alternate endpoint that measured the amount of time that subjects were able to spend outdoors in direct sunlight without experiencing pain. This endpoint was used to modify the statistical analysis plan for Study 029 which remained blinded at the time of the analysis of Study 030 and to design the protocol for Study 039. However, because Study 030 failed on its prespecified objective, and endpoints based on pain-free sun exposure were defined post hoc, Study 030 cannot be used to support efficacy. However, the results of the prespecified and post hoc endpoints will be summarized briefly for completeness and to assess consistency with Study 029.

Trial Design

Study 030 enrolled 77 subjects age 18 to 70 years with a biochemically-confirmed diagnosis of EPP and symptoms of sufficient severity to request treatment. The study was conducted in the US. Subjects were randomized 1:1 within center. Subjects received three implants on Days 0, 60, and 120 and were followed for 180 days. Subjects were evaluated at screening, baseline (Day 0) and Days 60, 120, and 180. A subset of subjects enrolled at one center were to undergo controlled photoprovocation. These subjects underwent photoprovocation on the hand and back on Days 0, 30, 60, 90, 120, and 180.

Study Endpoints

Efficacy information was collected from subject diaries regarding the level of phototoxic pain, the amount of time spent outdoors in the sun, and whether most of the day was spent in direct sunlight, shade, or a combination of both. The primary endpoint was the “median maximum severity score and the median total severity score” for all reported phototoxic reactions. The secondary endpoints were the number of phototoxic reactions, quality of life endpoints, and the minimum symptom dose based on photoprovocation in a subset of subjects.

Subjects recorded data on sun exposure and phototoxic pain daily for 180 days. The subject diary was identical to the diary used in Study 029, including the missing blocks to record time spent outdoors between 14:00 and 15:00.

8.3.2. Study Results

Compliance With Good Clinical Practices

The Applicant stated that studies were designed, monitored, and conducted in accordance with GCP requirements and ethical principles. Study protocols, the subject information and informed consent forms, subject recruitment procedures were reviewed by the responsible Institutional Review Board (IRB). The Applicant obtained an approval from the IRB prior to study initiation.

Financial Disclosure

Refer to Appendix 19.2.

Patient Disposition

Study 030 randomized 77 subjects, 39 who received afamelanotide and 38 who received placebo. Ten subjects discontinued the study (five afamelanotide and five placebo). Subjects discontinued due to the Applicant's decision, subject decision, or were lost to follow-up. See Table 50.

Table 50. Disposition of Subjects in Study 030

Subject Disposition	Afamelanotide	Placebo
Subjects randomized	39	38
Discontinued	5 (13%)	5 (13%)
Sponsor decision		1 (3%)
Subject decision	4 (10%)	4 (11%)
Other (lost to follow-up)	1 (3%)	

Source: pg 74 of CUV030 study report, and reviewer analysis.

Demographic Characteristics

Enrollment in Study 030 was generally balanced across demographic subgroups. The majority of subjects were less than 65 years of age and Caucasian. See Table 51.

Table 51. Baseline Demographics in Study 030 (Safety Population)

Characteristics	Afamelanotide N=39	Placebo N=38
Sex		
Male	23 (59%)	20 (53%)
Female	16 (41%)	18 (47%)
Age		
Mean years	38.1	42.6
Min, max (years)	18, 65	19, 72
Age group		
≥18–<65 years	38 (97%)	35 (92%)
≥65 years	1 (3%)	3 (8%)
Race		
Caucasian	39 (100%)	38 (100%)

Source: pg 77 of CUV030 study report and reviewer analysis.

Efficacy Results – Primary Endpoint

The protocol specified "median maximum severity score and median total severity score for all reported phototoxic reactions" as the primary endpoint. Phototoxic episodes were defined as consecutive days with Likert pain score ≥4.

Similarly to the datasets for Study 029, it is not clear how reliable the Applicant's ordering of the observations is, as there are examples of repeated dates for a given subject, and unusually written dates (for example dates that appear to be in July that represent the month with '04'.) The endpoints based on the maximum severity score and total severity score presented here are those reported by the Applicant. See Table 52. For both analyses, pain scores ≤3 are imputed as 0, rather than used in the analysis as observed (for example, a subject who had a maximum pain score of 3 during the study would be treated as having a maximum pain score of 0 for calculating means, medians, and standard deviations). These analyses have the same issues as those discussed for Study 029 regarding the bias introduced by imputing scores ≤3 as 0s. The Applicant's analysis excluded two subjects (one from each treatment arm) that discontinued the trial early and did not return any subject diaries. Neither endpoint was statistically significant.

Table 52. Phototoxic Episode Endpoints in Study 030 (ITT Population)

Endpoints		Afamelanotide N=38	Placebo N=37	p-value[a]
Maximum pain score	Mean (SD)	4.0 (3.0)	4.2 (3.5)	0.668
	Median	5.0	5.0	
	Range	0, 8	0, 10	
Total severity score (sum of pain scores ≥4)	Mean (SD)	27.9 (43.1)	37.2 (102.6)	0.833
	Median	9.0	8.0	
	Range	0, 164	0, 620	

ITT = intent-to-treat; SD = standard deviation
Source: pg 112 of CUV030 study report

Post hoc Endpoint – Pain-Free Sun Exposure

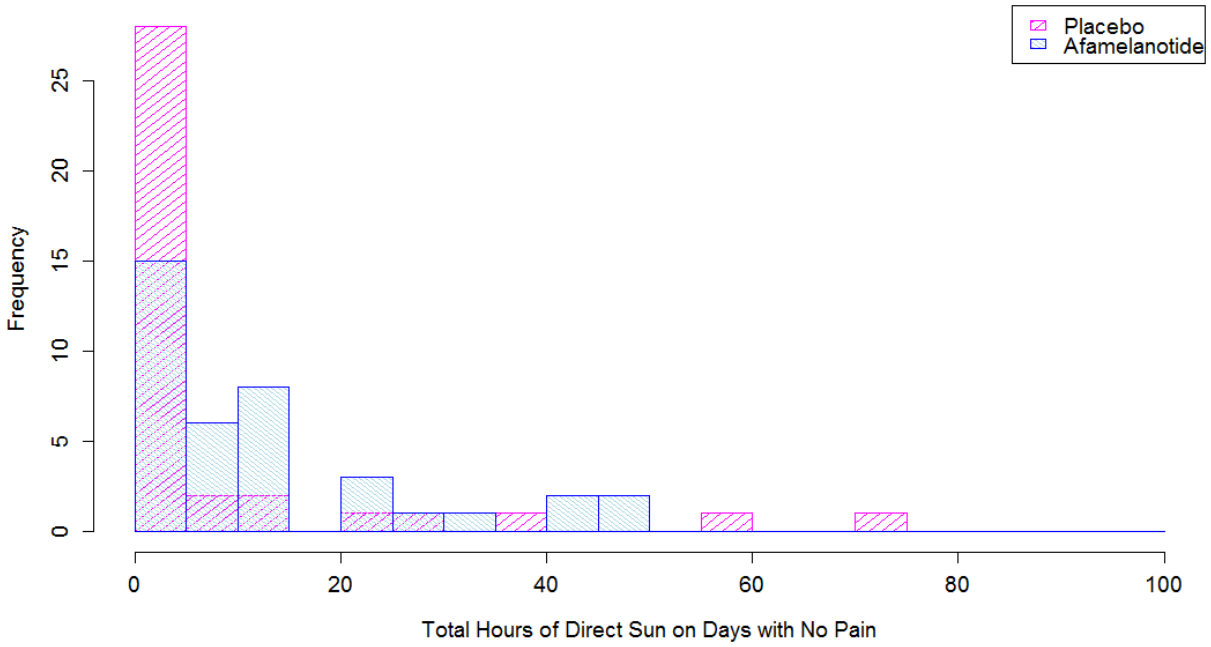
After analyzing the data in Study 030 and realizing the endpoints defined in the protocol based on the maximum and total severity scores did not show any benefit for afamelanotide, the Applicant developed a post hoc endpoint based on pain-free sun exposure. This endpoint is the same endpoint that was designated in the statistical analysis plan for Study 029 as the primary endpoint prior to the unblinding. Because for Study 030 the endpoint was only identified after analyzing the data, the endpoint cannot be used to support the efficacy of afamelanotide. However, the point estimates are of similar magnitude to those in Study 029 based on a subject diary of identical design (including the misprint for the time blocks). The key difference between the design of Study 029 and Study 030 was that Study 030 had a duration of 180 days, while Study 029 had a duration of 270 days. The results for the total hours spent outdoors between 10:00 and 15:00 on days with no pain and where most of the day was spent in direct sunlight are presented in Table 53 and Figure 32. The Applicant's ITT population excludes two subjects (one from each arm). While the Applicant did not provide a rationale for excluding these subjects, these two subjects did not have any recorded subject diary data and were likely excluded for that reason.

Table 53. Total Hours Outdoors Between 10:00 and 15:00 on Days With No Pain and Where Most of the Day was Spent in Direct Sun in Study 030 (ITT Population)

	Afamelanotide N=38	Placebo N=37	Estimate[a] 95% CI	p-value[b]
Mean (SD)	12.3 (14.4)	7.57 (16.5)	3.75	0.010
Median	8.25	0.75	(0, 9.25)	

[a] Hodges-Lehmann estimate
[b] Kruskal-Wallis test
ITT = intent-to-treat; SD = standard deviation
Note: this endpoint was defined after the data were unblinded and analyzed.
Source: pg 92 of CUV029 study report and reviewer analysis

Figure 32. Total Hours Outdoors Between 10:00 and 15:00 on Days With No Pain and Where Most of the Day was Spent in Direct Sun in Study 030 (ITT Population)



ITT = intent-to-treat
Source: Reviewer analysis.

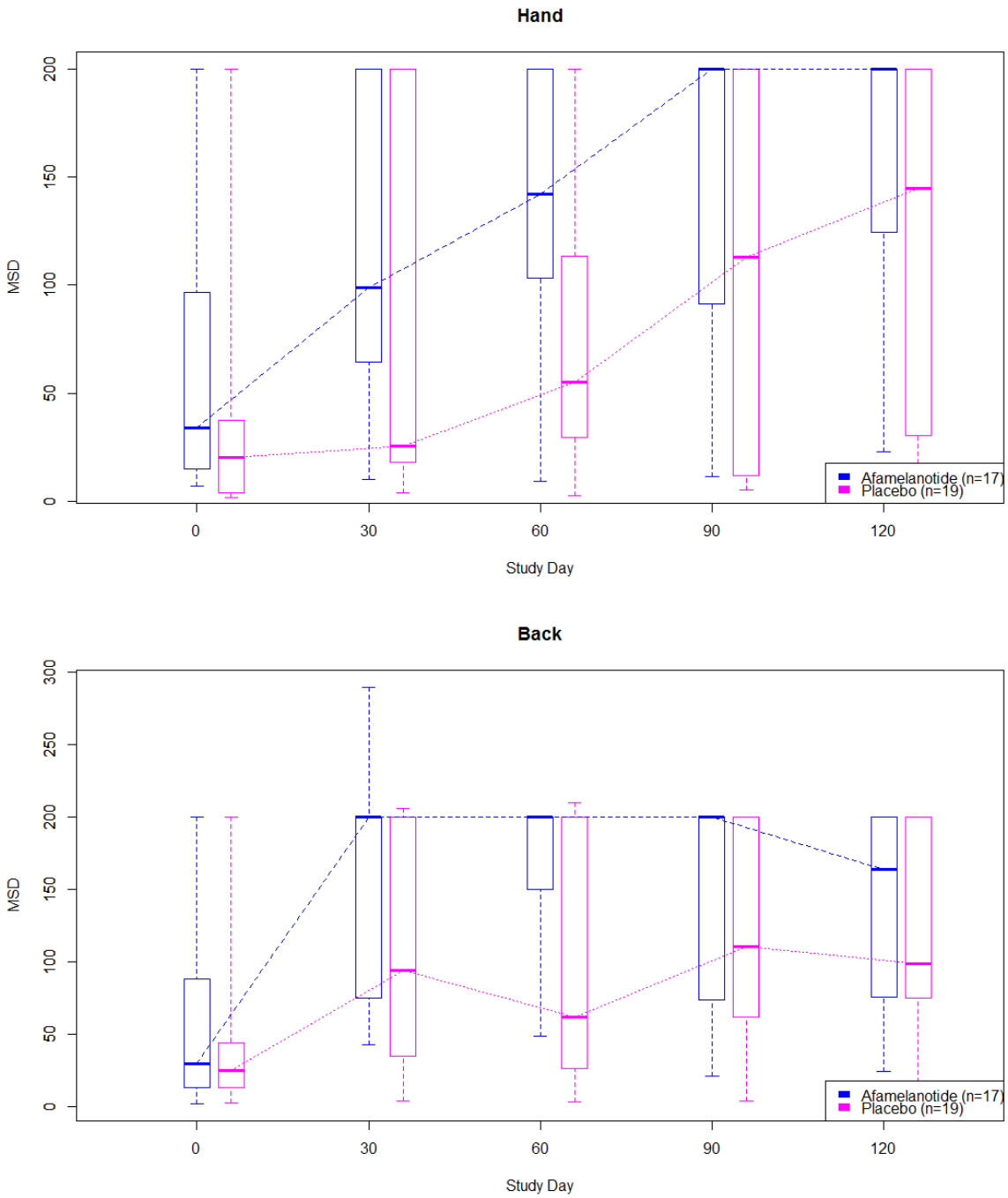
Photoprovocation

A photoprovocation sub-study was conducted at three sites: Site 1 (New York), Site 3 (Alabama), and Site 5 (Texas) in 36 subjects (17 afamelanotide and 19 placebo). For the photoprovocation, areas approximately 33 mm in diameter on the dorsal surface of the hand and on the back were irradiated with filtered light on Days 0, 30, 60, 90, and 120. The subjects were to be irradiated either until the subject experienced the first phototoxic symptoms or until a maximum dose of 200 J/cm^2 was received (one subject received a dose higher than 200 J/cm^2 on the back on Day 30). The minimum dose of radiation to induce the first symptom (minimum symptom dose or MSD) was recorded for the hand and the back for each visit.

When summarizing the MSD by visit across subjects, subjects treated with afamelanotide tended to have higher MSD values than subjects treated with placebo, though many subjects

were censored at 200 J/cm^2. See Figure 33. The median MSD was similar or higher on the afamelanotide arm than the placebo arm at each post-baseline timepoint on both the hand and back assessments.

Figure 33. Minimum Symptom Dose Following Photoprovocation in Study 029 (Photoprovocation Analysis Set)



Dashed lines connect the medians at each visit.
Source: Reviewer analysis

8.3.3. Assessment of Efficacy Across Trials

Endpoints Based on Phototoxic Reactions

The Applicant originally designed their development program with the objective of assessing the overall severity of phototoxic reactions in subjects with EPP. However, this endpoint was not sensitive to any treatment effect between afamelanotide and placebo. In addition, the Applicant's implementation of analyses based on the maximum pain severity and total severity of phototoxic reactions was flawed because the Applicant's analysis treated any phototoxic pain scores ≤3 as if they were equivalent to a pain score of 0, potentially biasing results and making any interpretation difficult. Consequently, the summary statistics (such as the mean) for the Applicant's analysis of the maximum severity score and total severity score do not represent the as-observed dataset, but are biased, relative to results that are based on the full observed values that do not use "0 imputation". The mean and median are biased downward, because observed values of 1 to 3 are replaced with 0s, compared with analyses that used all pain score data as observed. Endpoints based on the maximum severity and total severity failed to demonstrate efficacy in the clinical trials. For Studies 039 and 030, these endpoints failed to demonstrate statistical significance. The lack of significant findings in Study 030 for these protocol-specified primary endpoints made Study 030 a negative study that could not support any efficacy claims. For Study 029, where these endpoints were nominally significant, the biased nature of the Applicant's proposed analysis makes interpretation of the study findings difficult, and thus are not sufficient to support efficacy claims.

Pain-Free Direct Sun Exposure Endpoints

Studies 029 and 030 were originally designed with primary endpoints based on the maximum and total pain severity scores from phototoxic reactions. When Study 030 failed to detect a treatment effect for this endpoint, the Applicant worked with experts to devise an endpoint based on exposure to direct sunlight on days with no pain during late morning and afternoon hours. For Study 030, this endpoint was devised after the data had been analyzed, and thus Study 030 cannot be used to support efficacy for this endpoint. While Study 030 was being analyzed and explored for ways to describe an effect for afamelanotide, Study 029 was kept blinded. The statistical analysis plan for Study 029 was then modified prior to unblinding to define a new primary endpoint based on information that was collected in Studies 029 and 030 and was defined as the total amount of time spent outdoors from 10:00 to 15:00 on days with no pain and for which most of the day was spent in direct sunlight.

For Study 039, the subject diaries were modified from the version used in Studies 029 and 030. The subject diary used in Study 039 was better able to distinguish between time spent in direct sunlight or shade, as subjects were asked to record time spent in direct sunlight and time spent in shade separately. The diary used in Studies 029 and 030 asked subjects to record time spent outdoors and then to mark whether "most of the day" was spent in direct sunlight, shade, or a combination. One other challenge with interpreting the results from Studies 029 and 030 was the fact that the subject diaries were misprinted and did not include pre-printed space for subjects to record time spent outdoors between 14:00 and 15:00. A proportion of subjects

recorded time spent outdoors between 14:00 and 15:00, but this time period was underreported because of the flawed diary design. Thus, the endpoint in Studies 029 and 030 primarily captures data from 10:00 to 14:00, with a portion of additional data from 14:00 to 15:00. In addition to the differences in diary design, the studies differed in the length of follow-up. Studies 030 and 039 followed subjects for 180 days, while Study 029 followed subjects for 270 days.

The pain-free direct sun exposure endpoints from Studies 039, 029 and 030 are summarized in Table 54. The primary endpoint for Study 039 is defined as the number of hours spent in direct sunlight from 10:00 to 18:00 on days with no pain. For Study 039, the reviewer analysis that includes all randomized subjects (rather than the Applicant's analysis that excludes subjects who did not return any subject diaries) is presented. This analysis imputes 0 hours of pain-free sun exposure for these subjects.

Table 54. Total Hours of Direct Sunlight on Days With No Pain (Studies 039, 029, 030)

Study		Afamelanotide	Placebo	Estimate[a] 95% CI	p-value[b]
Study 039 (all randomized)	N	48	45		
Protocol-specified	Mean (SD)	110.7 (139.6)	57.9 (60.5)	23.5	0.055
Primary endpoint[c]	Median	64.1	40.5	(0.0, 48.0)	
Study 029 (ITT)	N	38	36		
SAP-specified	Mean (SD)	20.4 (40.5)	5.6 (9.3)	2.75	0.005
Primary endpoint[d]	Median	6.0	0.75	(0.75, 6.5)	
Study 030 (ITT)	N	38	37		
Post hoc endpoint[e]	Mean (SD)	12.3 (14.4)	7.57 (16.5)	3.75	0.010
	Median	8.25	0.75	(0, 9.25)	

[a] Hodges-Lehman estimate
[b] Kruskal-Wallis test
[c] Hours of direct sunlight exposure (10:00 to 18:00) on days with no pain over 180 days (reviewer analysis including subjects who did not return any subject diaries)
[d] Hours spent outdoors from 10:00 to 15:00 on days with no pain in which most of the day was spent in direct sunlight over 270 days
[e] Hours spent outdoors from 10:00 to 15:00 on days with no pain in which most of the day was spent in direct sunlight over 180 days (Applicant analysis excluding subjects who did not return any subject diaries)
SD = standard deviation; ITT = intent-to-treat; CI = confidence interval

The p-value for the pain-free sun exposure endpoint in Study 039 was 0.055 in the reviewer's analysis and 0.044 in the Applicant's analysis that excluded subjects who did not return any subject diaries (see Table 26). Because the p-value is very close to the nominal significance level of 0.05, changes in assumptions (such as regarding missing data or time window for inclusion in the endpoint) frequently lead to supportive or sensitivity analyses that do not meet the 0.05 threshold for significance. Study 039 is the most reliable study conducted in the EPP development program; however, the study does not clearly meet the statistical significance threshold. The borderline statistical significance observed in Study 039 is supported by the results from Study 029. In addition, although the pain-free sun exposure endpoint in Study 030 was identified post hoc, and thus cannot be relied on to support efficacy, the results from Study 030 were very similar to those observed in Study 029 and Study 030 also provides some assurance that findings are consistent across multiple studies.

All of the studies suffered from challenges in collecting data on subjects' sunlight exposure and pain, such as poor diary design, challenges with reconciling inconsistent subject reports or missing data, and data handling practices that led to error in the databases. The Applicant also

ignored recommendations at the protocol stage on recommended statistical principles, such as including multiplicity adjustments for multiple endpoints or appropriately specifying methods to handle missing data. However, even with these significant issues, due to the replication of findings across multiple studies, we can conclude that the Applicant has demonstrated that afamelanotide can increase time spent in direct sunlight without pain relative to placebo in subjects with EPP.

Secondary and Other Endpoints

The secondary endpoints in the studies included quality of life assessments and photoprovocation to assess the minimum symptom dose. The Applicant has not submitted information to assess whether the quality of life tools are fit for purpose and they may not be clinically meaningful. Thus, the results from these endpoints are not considered in the overall assessment of efficacy.

Photoprovocation was conducted in a subset of subjects in Studies 039, 029, and 030. The studies were not powered to detect differences based on the minimum symptom dose nor were the endpoints included in any testing hierarchy or multiplicity control scheme. The protocols place an upper limit of exposure of 200 J/cm^2 for Studies 029 and 030 and 300 J/cm^2 for Study 039. Many subjects on both arms reached the maximum allowable exposure. Studies 039 and 030 had trends favorable to afamelanotide relative to placebo, however Study 029 did not demonstrate any trend differentiating the two treatments.

Subjects Participating in Multiple Studies

Because EPP is a rare disease and recruitment is challenging, there was some overlap between subjects enrolled in Study 030 and Study 039. When the Applicant was designing Study 039, they queried FDA regarding whether it would be acceptable to enroll subjects who received placebo in Study 030 in Study 039, as both studies were conducted in the US. FDA stated that that would be acceptable as long as the subjects were appropriately randomized in Study 039. The Applicant identified 23 subjects (based on initials, gender, date of birth, and medical history) treated with placebo in Study 030 that were also randomized into Study 039 (10 to placebo and 13 to afamelanotide). In addition, the reviewer identified 3 additional subjects with matched birthdates and genders that may represent additional subjects in common (1 randomized to placebo and 2 randomized to afamelanotide in Study 039). Because Study 030 is not adequate for assessing efficacy, that lack of independent enrollment between the two studies, has minimal impact on the assessment of efficacy in the overall database, with Studies 039 and 029 providing the primary evidence of efficacy.

8.4. Review of Safety

8.4.1. Safety Review Approach

The primary review of the safety of afamelanotide implant, 16 mg focused on pooled data from three Phase 3 trials, Studies CUV029, CUV030, and CUV039. The three trials were multicenter, randomized, double-blind, vehicle-controlled, Phase 3 trials of nearly identical design; Study CUV029 included treatment with five implants while Studies CUV039 and CUV030 included treatment with 3 implants. The Applicant's safety population included all subjects in Studies CUV010, CUV017, CUV029, CUV030, and CUV039 who received at least one dose of study medication. For our safety review, the safety population includes subjects in Studies CUV029, CUV030, and CUV039 who were randomized and who received at least 1 implant. Subjects who received vehicle in Study CUV030 could enroll in Study CUV039 and be randomized. The review team identified 26 subjects from Study CUV030 that enrolled in CUV039; 15 subjects were randomized to afamelanotide group and 11 subjects were randomized to the vehicle group. Thus, subjects who received vehicle in Study CUV030 and randomized to the afamelanotide group in Study CUV039 were unique afamelanotide subjects. The safety population did not include subjects from Studies CUV010 and CUV017 trials due to differences in the study design (e.g., open-label or cross-over design) and dose (20 mg implant). Refer to Section 7.1 for table of clinical studies for further details. Safety assessments from Studies CUV017 and CUV010 are reviewed separately under each section.

To determine the safety profile of afamelanotide implant, the review team analyzed the following types of pooled data: exposure, demographics, baseline characteristics, treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), adverse events (AEs) leading to discontinuation, laboratory results, vital signs, and findings from physical examinations.

The Applicant submitted safety data obtained from required European Medicines Agency (EMA) postmarketing safety studies (PASS) to support the safety information obtained from the clinical trials. EMA postmarketing data included patients treated with afamelanotide implant through Compassionate Use and Expanded Access programs. European postmarketing safety data was included in the review team safety analysis (postmarket safety population). Safety review of the postmarket safety data includes analyses from the submitted dataset (147 patients), information from the ISS (data cutoff of March 31, 2018), and copies of reports submitted to the EMA (CUV-PASS-001/CUV-PASS-002 Intermediate Report #3 and Periodic Safety Update Report/Periodic Benefit-Risk Evaluation Report dated February 28, 2019).

8.4.2. Review of the Safety Database

Overall Exposure

For the pooled Phase 3 trials (Studies CUV029, CUV030, and CUV039), the safety analysis set (safety population) included all randomized subjects who received at least one study implant.

In the safety population (Studies CUV029, CUV030, and CUV039), a total of 125 subjects received at least 1 afamelanotide implant. Among these subjects, 119 subjects received 3

implants administered every 2 months for a duration of 6 months of treatment. In safety population (Studies CUV029, CUV030, and CUV039), the Applicant evaluated extent of exposure by documenting the number of implants administered. No subject required surgical removal of the subcutaneous implant. One subject was discontinued due to protocol violation (Study CUV030, Subject (b) (6)) of implant self-removal and lost to follow-up. Two subjects had bleeding during the implantation procedure with successful implantation on the second attempt during the same visit (Study CUV029, Subjects (b) (6)). One subject reported the implant falling out 6 days after implantation; the subject received a replacement implant 3 days later (Study CUV029, Subject (b) (6)).

The overall exposure of the safety population (Phase 3 trials, Studies CUV029, CUV030, and CUV039) is summarized in the following table:

Table 55. Number of Afamelanotide Implants Administered in the Safety Population, (Studies CUV029, CUV030, and CV039)

	Number of Afamelanotide 16 mg Implants Q2M				
Study	**1 Implant**	**2 Implants**	**3 Implants**	**4 Implants**	**5 Implants**
CUV 039	48/48 (100%)	47/48 (97.9%)	46/48 (95.8%)	n/a	n/a
CUV 030	39/39 (100%)	39/39 (100%)	36/39 (92.3%)	n/a	n/a
CUV 029	38/38 (100%)	38/38 (100%)	37/38 (97.4%)	36/38 (94.7%)	34/38 (89.5%)
Total	**125/125 (100%)**	**124/125 (99.2%)**	**119/125 (95.2%)**	**36/38 (94.7%)**	**34/36 (89.5%)**

Q2M = every 2 months
Source: Reviewer's table, modified from ISS.

The EMA postmarketing exposure data included patients with EPP with up to 10 years of afamelanotide exposure. Per Applicant, 246 patients with EPP have been treated under the PASS protocols as of March 31, 2018. The Applicant also reports 323 patients treated with afamelanotide under Compassionate Use and Special Access programs. The table below summarizes the extent of exposure in the postmarket safety population.

Table 56. EMA Postmarketing[1]: Extent of Exposure in Patient With Erythropoietic Protoporphyria

	Number of Patients Exposed to Afamelanotide by Implant Number					
Dosage: Afa 16 mg Q2M	**>=1 Implant**	**13-20 Implants**	**21-30 Implants**	**31-40 Implants**	**41-50 Implants**	**51+ Implants**
Number of subjects	323	40	21	8	4	3
Approximate duration of exposure[2]						
Months	2	26-40	42-60	62-80	82-100	102+
Years	0.2	2.2-3.3	3.5-5	5.2-6.7	6.8-8.3	8.5

[1] PASS 1 and PASS 2 cutoff date of March 31, 2018
[2] Applicant estimates 12 implants =2 years of afamelanotide exposure
Q2M = every 2 months
Source: Reviewer's table, modified from ISS.

<u>Reviewer Comment</u>: The Integrated Summary of Safety (ISS) includes one adverse event of "device expulsion" (Table 10) that occurred in subjects from the clinical trials and PASS-1/-2 studies that received <12 afamelanotide implants while the PASS-1/-2 datasets include one report of "device expulsion" as an AE. In addition the single subject who experienced device expulsion in Study CUV029 (Subject (b) (6) an additional AE of device expulsion was reported in the postmarketing safety population. No further information was provided regarding the postmarketing population case.

Relevant Characteristics of the Safety Population

Demographic characteristics of subjects in the safety population are similar to the ITT population used in the efficacy analyses (see Section 8.1). In the safety population, most subjects were White (98%), female (53%), and between 18 to 65 years of age (97%). The demographic characteristics of both treatment groups were comparable. Most of the subjects enrolled in the Phase 3 trials resided in the United States (70%). The table below summarizes the baseline demographics of the safety population.

Table 57. Baseline Demographics in Safety Population (Studies CUV029, CUV030, and CUV039)

Demographics	Afamelanotide n (%) N=125	Vehicle n (%) N=119
Sex		
Male	68 (54%)	61 (51%)
Female	57 (46%)	58 (49%)
Age		
Mean years	39.1	40.1
Min, max (years)	18, 70	18, 74
Age group		
≥18–<65 years	124 (98%)	113 (95%)
≥65 years	1 (2%)	6 (5%)
Race		
Caucasian	124 (99%)	116 (98%)
Asian	1 (1%)	
African		1 (1%)
American Indian or Alaska Native or Pacific Islander		1 (1%)
Aboriginal/Torres Strait Islander		1 (1%)
Country		
United States	87 (70%)	83 (70%)
Outside United States	38 (30%)	36 (30%)
Fitzpatrick skin type		
(I) Never tans, always burns	28 (22%)	35 (29%)
(II) Tans less than average (with difficulty), mostly burns	51 (41%)	48 (40%)
(III) Tans about average, sometimes mild burn	35 (28%)	28 (24%)
(IV) Rarely burns, tans more than average (with ease)	11 (9%)	8 (7%)

Source: Reviewer's table.

The postmarket safety population was similar to the safety population (Phase 3 trials, Studies CUV029, CUV030, and CUV039) in sex and age. The CUV-PASS-001/CUV-PASS-002 Intermediate Report #3 did not include data relating to race or Fitzpatrick skin type.

Table 58. Demographics in Postmarket Safety Population (CUV-PASS-001/CUV-PASS-0021)

Demographics	Afamelanotide n (%) N=270
Sex	
Male	137 (51%)
Female	133 (49%)
Age	
Mean years	40.8
Min, max (years)	18, 77
Age group	
≥18–<65 years	252 (93%)
65–75 years	17 (6%)
>75 years	1 (0%)
Country	
United States	(0%)
Outside United States	270 (100%)

[1]: Cutoff date of June 30, 2018.
Source: Reviewer's table, modified from EU CUV-PASS-001/CUV-PASS-002 Intermediate Report #3

Adequacy of the Safety Database:

The total subject exposure to afamelanotide implant, 16 mg administered subcutaneously once every 2 months provides adequate data for the evaluation of safety. The demographics of the study population are sufficiently representative of the target population. Therefore, the safety database presented by the Applicant is sufficient to characterize the safety of afamelanotide implant, 16 mg to increase the duration of pain-free sun exposure in adults with EPP.

8.4.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Overall, the quality of the data submitted is adequate to characterize the safety and efficacy of Scenesse in adult subjects with EPP. Data quality and fitness were evaluated in conjunction with the statistics and JMP support teams. We discovered no significant deficiencies that would impede a thorough analysis of the data presented by the Applicant.

Categorization of Adverse Events

For the safety analysis set, the Applicant defined an adverse event (AE) 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 adverse event may be a symptom, sign, or abnormal finding or test result." For laboratory test results, if the laboratory value was outside the reference range and the investigator considered the laboratory value represented a clinically significant change from the baseline value, then the laboratory test result was reported as an adverse event. Expected phototoxic symptoms due to sun exposure was not documented as an adverse event.

AEs were categorized by system-organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.1. The coding of adverse events in the NDA submission appeared adequate and allowed for accurate estimation of AE risks.

Investigators monitored each subject regularly for AEs or serious AE (SAEs) occurring throughout the trial. AEs include spontaneously reported or elicited from the subject using non-specific questions ("have you noticed any problems?" or "do you feel different in any way?"). AEs and SAEs were recorded and reported from the time of signed and dated Informed Consent Form (ICF) was obtained until completion of the subject's safety follow-up visit.

Investigators categorized AE for seriousness, severity, causality, duration, and action taken with study drug. All AEs or SAEs were followed-up according to "good clinical practice." Serious adverse events occurring during the studies were to be reported by telephone report, recorded in the adverse event page of the case report form, and reported using the Serious Adverse Event Form.

The Applicant defined treatment-emergent AEs (TEAE) as:

- An event that was not present prior to or on the day of the first study medication administration but was present after study medication was administered
- An event that was present prior to first administration of study medication and continued to occur after the administration of the first dose at an increased level of severity
- An event that was present prior to administration of study medication and was documented as completely resolved and re-emerged after the administration of the first dose.

A SAE was defined as any untoward medical occurrence that at any dose:

- Death
- Is life-threatening
- Requires inpatient hospitalization or a prolongation of an existing hospitalization
- 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 hospitalization but may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed in the definition above

The investigator assessed severity for each AE and SAE reported during the trial. The severity of each AE and SAE was recorded on the eCRF and was assigned to one of the following categories: mild, moderate, or severe.

The investigator assessed the relationship between study product and the occurrence of each AE or SAE and categorized the potential relationship as follows:

- None: The event can be readily explained by the patient's underlying medical condition or concomitant therapy and no temporal relationship exists between the study drug and the event
- Unlikely: The temporal relationship between the event and the administration of the study drug is uncertain and it is likely that the event can be explained by the patient's medical condition or other therapies
- Possible: There is some temporal relationship between the event and the administration of the study drug and the event is unlikely to be explained by the patient's medical condition or other therapies
- Probable: The temporal relationship between the administration of the study drug is compelling, and the event cannot be explained by the patient's medical condition or other therapies
- Definite: The event follows a reasonable temporal sequence from administration of the medication, follows a known or suspected response pattern to the medication, is confirmed by improvement upon stopping or reducing the dosage of the medicine (dechallenge) and reappears upon repeated exposure (rechallenge)

The Applicant presented standard AE analyses. The definition of AE, TEAE, and SAE are acceptable. The classification system used by investigators to describe the severity of AE as well as the causal relationship between AE and study product are also acceptable.

The Postmarket Authorization Safety Studies (PASS) included the following AE assessments:

- Grading severity (mild, moderate, or severe)
- Outcome of the AE (resolved without sequelae, resolved with sequelae, or continuing)
- Serious AE
- Causality

Routine Clinical Tests

In the pooled safety analysis set (Studies CUV029, CUV030, and CUV039), investigators and site staff conducted safety monitoring during clinic visits at Screening, and Day 0, 60, 120, and 180 (or early termination). In Study CUV029, subjects received 2 additional implants, and thus, additional clinic visits were conducted on Day 240 and 270. Studies CUV029, CUV030 and CUV039 included photoprovocation testing cohorts. In Study CUV029, photoprovocation testing occurred on Day 0, 60, 120, 180, 240, and 270, while in Studies CUV030 and CUV039, photoprovocation testing occurred on Day 0, 30, 60, 90, and 120. Thus, subjects in the photoprovocation cohorts had additional clinic visits.

The evaluation of safety included laboratory tests (hematology, biochemistry, and urinalysis), vital signs, height and weight, pregnancy testing (urine and serum), abbreviated physical

examinations, concomitant medications, phototoxic reactions, and adverse events. In addition to the above assessments, in Studies CUV030 and CUV039, safety assessments included:

- Skin and oral mucosa examination by a dermatologist at Screening and Day 60, 120 and 360. Additional exam on Day 0 in Study CUV030
- Full physical examination including ophthalmologic examination at Screening and Day 180
- Full body photography at Screening and Day 180

Additionally, the safety assessments in Study CUV039 included 12-lead ECG on Day 60, 120, 180 and 360.

The protocols included clinical laboratory testing at Screening and Day 60, 120 and 180 (or early termination). The assessments included hematology, serum chemistry, and urinalysis. For women of childbearing potential, serum pregnancy was performed at Screening and urine pregnancy testing performed at Day 0, 60, 120, and 180 (or early termination).

In Studies CUV010 and CUV017, safety assessment included vital signs, weight, physical examination, laboratory tests (HIV, hepatitis B, and hepatitis C serology; hematology; biochemistry; and urinalysis), pregnancy testing (serum and urine), vital signs, weight, abbreviated physical examinations, concomitant medications, phototoxic reactions, and adverse events.

The Postmarket Authorization Safety Studies (PASS) included routine clinical testing as well as liver ultrasound.

8.4.4. Safety Results

Deaths

<u>Safety Population</u>

There were no deaths during the development program for afamelanotide implant. In Study CUV030, one subject who received 3 implants and terminated the study after the 3rd implant, died 8 months after the last implant while traveling (acute liver failure due to bile duct obstruction, considered by the investigator to be unrelated to study drug).

Narrative: Subject (b) (6)

42-year-old woman who received all three afamelanotide implants (last implant: (b) (6)) was traveling abroad when she was hospitalized for “rapid onset of motor neuron weakness” leading to respiratory distress. She died on (b) (6) while awaiting liver transplant. The SAE of death was considered “unlikely related to study medication.” The Applicant was notified on (b) (6) who then reported the death to the Agency on (b) (6) .

<u>Reviewer Comment</u>: I agree with the investigator that given the time period of 8 months between the last dose of study drug (b) (6) *and death* (b) (6) *that the death is unlikely related to study drug. The temporal relationship of the death to the treatment*

does not support a causal relationship. In addition, the subject had a history of elevated liver enzymes prior to cholecystectomy (2009). During the trial, the subject's alanine aminotransferase (63 to 90 U/L), aspartate aminotransferase (72 to 82 U/L), and gamma glutamyl transferase (56 to 83 U/L) was considered "outside of normal range/not clinically significant." The death summary from the treating foreign hospital identified the principal diagnosis as "respiratory failure secondary to proximal neuropathy secondary to erythropoietic protoporphyria" with diagnoses including chronic liver disease, renal failure – hepatorenal syndrome, and neuropathic pain. Email correspondence submitted by the Applicant includes the subject was awaiting liver transplant at the time of death. Of note, an estimated 1 to 3% of patients with EPP develop progressive liver failure.

Other Studies in Subjects With EPP

No deaths were reported in Studies CUV010 and CUV017.

Postmarket Safety Population

According to the Applicant, in the EMA post-authorization surveillance of Scenesse, five deaths were reported in patients receiving treatment with Scenesse (cardiac arrest secondary to arrhythmia, metastatic breast cancer, metastatic squamous cell carcinoma, brain tumor, and sepsis with multiorgan failure).

Table 59. Deaths During the Development Program and European Medicines Agency Postmarketing for Afamelanotide

Study or Program Study Product (Initial/Maint[1])	Number of Scenesse Implants Received	Subject Identifier	Narrative
CUV030 – post study	3	(b) (6)	A 41-year-old woman who received all three study implants (active) who was hospitalized and died of acute liver failure due to an obstructed bile duct. She had a history of idiopathic thrombocytopenic purpura, pelvic fracture, anemia, and elevated liver enzymes prior to cholecystectomy.
Rome Compassionate use	6		A 61-year-old man who died of cardiac arrest due to arrhythmia.
Rome Expanded access	14		An unknown aged woman who died of metastatic breast cancer.
Zurich Compassionate use	17		A 58-year-old man who died of metastatic squamous cell carcinoma arising from chronic wound attributed to underlying EPP.
Rotterdam Compassionate use	8		A 49-year-old woman who died of a progressive brain tumor.
United Kingdom Compassionate use	1		An unknown aged man who died of sepsis and multiorgan failure a "few" months after single Scenesse treatment.

Source: Modified from ISS Table 8.

Serious Adverse Events

Safety Population

In the safety population (Studies CUV029, CUV030, and CUV039), five subjects who received afamelanotide experienced six serious adverse events (SAEs) and three subjects who received vehicle experienced four SAEs. All subjects who experienced SAEs had resolution of the SAE without sequelae. All SAEs reported in subjects receiving afamelanotide were considered not related or unlikely to be related to study drug. The table below summarizes the reported SAEs.

Table 60. Treatment-Emergent Serious Adverse Events in the Safety Population (Studies CUV029, CUV030, and CUV039)

Preferred Term	Afamelanotide, 16 mg n (%)	Vehicle n (%)
Abdominal pain[1, 2]	2 (2%)	
Hospitalization[3]	1 (1%)	
Intervertebral disc protrusion	1 (1%)	
Melanocytic nevus[4]	1 (1%)	
Rectal hemorrhage[2]	1 (1%)	
Malignant melanoma in situ		1 (1%)
Dizziness		1 (1%)
Heart rate decreased		1 (1%)
Pulmonary embolism		1 (1%)
Subjects reporting SAEs, n(%)	5 (4%)	3 (3%)
Total number of SAEs	6	4

[1]: Subject (b) (6): Described above in Deaths – hospitalized for abdominal pain and died of acute liver failure due to obstructed bile duct.
[2]: Subject (b) (6) Hospitalized for abdominal pain and recurrent bright red blood per rectum after exercise
[3]: Subject Hospitalization to surgically repair humerus fracture.
[4]: Subject Compound nevus with mild dysplasia that was excised. Subject withdrew consent after receiving 2 afamelanotide implants.
SAE = serious adverse event
Source: Reviewer's own.

Narrative: Subject (b) (6), melanocytic nevus

56-year-old man a history of ">30 nevi, all <6mm but some with fried egg or slightly irregular in border consistent with atypical nevi." Subject had two nevi removed and recorded by the investigator in the Adverse Event summary as "compound nevus with atypical dysplasia" and "compound nevus," unknown severity, no action taken (already removed), and unlikely related to study drug. The subject discontinued due to inability to comply with protocol schedule. The Applicant has categorized the adverse event of compound nevus with mild dysplasia as serious.

Reviewer Comment: The subject appears to have a phenotype of multiple atypical nevi. For the SAE of melanocytic nevus, the subject was treated with "excisional biopsy" of a melanocytic nevus that showed compound nevus with mild dysplasia. The case report form notes that subject had an "ugly duckling" nevus but it is not clear if this lesion was one that was biopsied. Based on the mechanism of action of afamelanotide, it is reasonable that increased pigmentation in the skin and other pigmented skin lesions may occur; it is unclear whether afamelanotide contributed to dysplasia in melanocytic lesions. We recommend the prescribing information include skin monitoring in Section 5 Warnings and Precautions.

Other Studies in Subjects With EPP

In Study CUV017 (crossover), six subjects reported eight SAEs. No SAE was considered related to study drug. The subjects experiencing SAEs are summarized below:

- Subject (b) (6) thrombocytopenia - discontinued from the study by the investigator due to the SAE; the subject was later diagnosed with idiopathic thrombocytopenic purpura (see narrative in next section)
- Subject (b) (6): cholelithiasis
- Subject (b) (6): joint injury, dyskinesia, and post-procedural complication of instability of the knee – result of bike fall
- Subject (b) (6): spinal fracture – result of motor vehicle accident
- Subject (b) (6): diverticulitis – occurred 3 months after last afamelanotide implant
- Subject (b) (6): tonsillitis – occurred after receiving vehicle implant

Reviewer Comment: I agree with the investigator's determinations that the reported SAEs were reported in Study CUV017 are unlikely related to study drug.

No subjects in Study CUV010 (open-label) experienced an SAE.

No pregnancies were reported during the development program.

Postmarket Safety Population

In Study CUV-PASS-001/CUV-PASS-002, the Applicant reported that 5% of patients experienced one or more SAEs (27 SAEs in 14 patients). SAEs include the following: pain, pyrexia, abscess, appendicitis, peritonitis, hepatitis alcoholic, testicular germ cell tumor mixed, tumor fistulization, bone disorder, and transient ischemic attack. All these SAEs were considered unrelated and resolved.

Reviewer Comment: I agree with the investigator's assessment that the SAEs reported in the postmarket safety population were unlikely related to Scenesse.

Two SAEs in two patients were considered related to Scenesse (pneumonia influenzal and erythema). One patient with an unrelated SAE of testicular germ cell tumor mixed discontinued Scenesse treatment and registry participation. Narratives for these subjects follows.

Narrative: Patient (b) (6) facial erythema

59-year-old woman developed facial erythema along with hematoma and an implantation site mass. The subject was hospitalized, and these events resolved. The adverse event of facial erythema was considered a related to study drug while hematoma and injection site mass were considered related to the implantation procedure.

Reviewer Comment: According to the Applicant, the facial erythema may have been flushing of the face, which was observed in subjects receiving the aqueous form of afamelanotide. Patient (b) (6) reportedly received subsequent treatment with Scenesse and did not have an adverse event "suggestive of further allergic reaction." No additional clinical information was provided

for this case. I agree with the Applicant's assessment that the adverse reaction of facial erythema was not a true allergic or hypersensitivity reaction given that the subject received additional treatments with Scenesse without recurrence. No further assessment of causality can be made based in the information provided.

Narrative, Patient (b) (6) ***pneumonia influenzal***

76-year-old woman developed pneumonia. The outcome was unknown at the time of reporting and considered serious due to hospitalization. No further clinical information was provided.

Reviewer Comment: Due to lack of information, this reviewer cannot make an adequate of assessment of potential causality for the SAE of influenzal pneumonia.

Dropouts and/or Discontinuations Due to Adverse Effects

Safety Population

In the safety analyses set (Studies CUV029, CUV030, and CUV039), fourteen subjects discontinued prior to study completion (afamelanotide =8, vehicle =6). Five subjects discontinued due to AEs. The table below summarizes the subjects who were discontinued from study. The reasons given for study discontinuation include withdrawal by subject (8), physician's decision (2), lost to follow-up (1), protocol violation (1), Applicant's decision (1), and other (1). The following adverse events were deemed by the Applicant to be related to study drug: nausea (3), fatigue (2), headache (2), melanocytic nevus (2), rash (2), blood creatinine phosphokinase increased (1), pain (1), and pigmentation disorder (1).

Table 61. Summary of Subjects Who Did Not Complete the Trial (Studies CUV029, CUV030, and CUV039)

Study	Subject	Serious	Severe Adverse Event (Preferred Term)	Reason for Withdrawal	Study Treatment
CUV029	(b) (6)	No	No	Withdrawal by subject	Active
		No	Yes (headache)	Withdrawal by subject	Active
		No	No	Withdrawal by subject	Vehicle
		No	Yes (migraine)	Physician's decision	Active
		No	No	Protocol violation	Active
CUV030		No	No	Withdrawal by subject	Vehicle
		No	Yes (Bowen's disease)	Sponsor's decision	Vehicle
		No	No	Other	Active
		No	No	Withdrawal by subject	Active
		No	Yes (fatigue)	Withdrawal by subject	Active
		No	No	Withdrawal by subject	Vehicle
CUV039		Yes[1]	Yes (arthralgia, migraine)	Physician's decision	Vehicle
		Yes[2]	No	Withdrawal by subject	Active
		No	No	Lost to follow-up	Vehicle

[1]: Subject diagnosed with melanoma in situ prior to receiving study drug, unrelated.
[2]: Subject reported compound nevus with mild dysplasia, resolved with removal, related.
Source: Reviewer's own.

Other Studies in Subjects With EPP

One subject in cross-over Study CUV017 (Subject (b) (6)) who received afamelanotide, discontinued due to SAE of thrombocytopenia detected on laboratory testing after the fourth

implant (the second afamelanotide implant). The subject was subsequently diagnosed with idiopathic thrombocytopenic purpura (ITP) which was considered unrelated to afamelanotide. The subject received treatment for ITP with reported subsequent stable platelet counts.

No subjects in Study CUV010 (open-label) discontinued or were withdrawn from the study due to adverse effects.

Reviewer Comment: Given the cross-over design of Study CUV017, we cannot make adequate assessments of potential causality of afamelanotide in relation to the above AEs.

Postmarket Safety Population

As mentioned above, the Applicant reported one patient (Subject (b) (6)) in the CUV-PASS-001/CUV-PASS-002 study with an unrelated SAE of testicular germ cell tumor mixed discontinued Scenesse and registry participation. The patient was a 26-year-old man hospitalized for suspected testicular cancer. The outcome was unknown at the time of reporting.

Reviewer Comment: Due to lack of information, this reviewer cannot make an adequate assessment of potential causality of testicular cancer, but given the proposed mechanism of action of Scenesse, the adverse of event of testicular cancer is unlikely related to Scenesse.

Significant Adverse Events

The categorization of adverse events used in the trials evaluating afamelanotide in subjects with erythropoietic protoporphyria (EPP) are summarized above in Section 8.4.3. No adverse events of special interest were defined specifically in the protocols for Studies CUV029, CUV030, and CUV039. Based on the pharmacologic action of afamelanotide and proposed mechanism of action in EPP, ophthalmologic and dermatologic examination (skin and mucosa) was included in the safety assessments to evaluate for new and existing pigmented lesions. Adverse reactions related to melanogenesis and skin cancer are discussed below. In addition, because afamelanotide implant requires subcutaneous administration, the safety review included evaluation of all injection site, administration site, and implant site reactions reported (see discussion below).

Treatment-emergent adverse events were also evaluated by severity. See discussion below.

Treatment-Emergent Adverse Events and Adverse Reactions

Safety Population

There were 1176 treatment-emergent adverse events (TEAEs) reported in the 213 subjects. Of these, 619 TEAEs were reported in 111 subjects (89%) in the afamelanotide group compared to 557 TEAEs in 101 subjects (85%) in the vehicle group. The most frequent TEAEs occurred in the system organ classes of Infections and Infestations , Nervous System Disorders, Gastrointestinal disorders, and General Disorders and Administration Site Conditions. The table below summarizes the frequency of TEAEs by system organ class in the safety population.

Table 62. Treatment-Emergent Adverse Events by System Organ Class in the Safety Population (Studies CUV029, CUV030, and CUV039)

Body System or Organ Class	Afamelanotide, 16 mg n (%) N=125	Vehicle n (%) N=119
Infections and infestations	51 (41%)	54 (45%)
Nervous system disorders	48 (38%)	46 (39%)
Gastrointestinal disorders	40 (32%)	38 (32%)
General disorders and administration site conditions	37 (30%)	25 (21%)

Source: Reviewer's own.

The table below summarizes TEAEs by preferred term that occurred more frequently in the afamelanotide group in descending order of frequency in the safety population.

Table 63. Treatment-Emergent Adverse Events That Occurred in More Than 2 Subjects in the Safety Population and at a Higher Rate Than the Vehicle Group (Studies CUV029, CUV030, and CUV039)

Preferred Term	Afamelanotide, 16 mg n (%) N=125	Vehicle n (%) N=119
Nausea	24 (19%)	16 (13%)
Implant site discoloration	13 (10%)	0 (0%)
Oropharyngeal pain	9 (7%)	5 (4%)
Abdominal pain	7 (6%)	5 (4%)
Cough	6 (5%)	3 (3%)
Fatigue	6 (5%)	1 (1%)
Dizziness	5 (4%)	4 (3%)
Dyspepsia	5 (4%)	3 (3%)
Musculoskeletal pain	3 (2%)	1 (1%)
Pigmentation disorder	3 (2%)	0 (0%)
Upper respiratory tract infection	3 (2%)	1 (1%)
Eczema	2 (2%)	1 (1%)
Melanocytic naevus	2 (2%)	1 (1%)
Nasal congestion	2 (2%)	1 (1%)
Procedural pain	2 (2%)	0 (0%)

Source: Reviewer's own.

Reviewer Comment: The five melanocortin receptors subtypes are distributed differently throughout the body. Melanocortin 1 receptor (MC1R) is present on melanocytes and leukocytes, while MC3R and MC4R are located in the central nervous system and MC5R is located in skeletal muscle and the brain. αMSH interacts with MC1R, MC4R, and MC5R.[2] *As an a-MSH structural analogue, afamelanotide may interact with MC1R, MC4R, and MC5R. Given the presence of melanocortin receptors in the central nervous system, afamelanotide may have a causal role in the adverse events of nausea, dizziness, and somnolence.*

[2] Wolf Horrell EM, Boulanger MC and D'Orazio JA. Melanocortin 1 Receptor: Structure, Function, and Regulation. Front. Genet. 106:7(95). doi: 10.3389/fgene.2016.00095

Other Studies in Subjects With EPP

In Study CUV017 (cross-over), 97 subjects (97%) experienced 1333 TEAEs. In Study CUV010 (open-label), five subjects (100%) experienced 38 TEAEs.

Postmarket Safety Population

In Study CUV-PASS-001/CUV-PASS-002 , the Applicant reported that 64% of patients experienced at least one TEAE (904 TEAEs in 174 patients), with 82% of those experiences a TEAE considered related to Scenesse.

Table 64. Treatment-Emergent Adverse Events (TEAEs) by System Organ Class in the Postmarket Safety Population (CUV-PAS-001/CUV-PASS-002)

Body System or Organ Class	# of TEAEs	Scenesse 16 mg n (%) N=270
General disorders and administration site conditions	179	86 (32%)
Gastrointestinal disorders	178	84 (31%)
Nervous system disorders	145	70 (26%)
Skin and subcutaneous tissue disorders	114	53 (20%)
Infections and infestations	66	44 (16%)
Vascular disorders	51	30 (11%)

Source: Reviewer's own, modified from PASS Study Report 3.

The most common preferred terms reported in the postmarket safety population are: nausea (21%), headache (18%) and fatigue (13%).

Treatment-Emergent Events by Severity

Safety Population

The majority of TEAEs were mild to moderate in the afamelanotide group (556/619, 90%) and the vehicle group (520/557, 93%). Twenty-eight of the 1176 TEAEs did not include a severity rating (afamelanotide: 23, vehicle: 5). In the safety population, 17 subjects in the afamelanotide group experienced 40 severe AEs and 16 subjects in the vehicle group experienced 32 severe AEs. The following table summarizes the severe TEAEs that occurred in one or more subjects in the afamelanotide group and occurred more frequently in the afamelanotide group than in the vehicle group. The subjects who discontinued due to severe AEs are summarized in the Section 8.4.4 Dropouts and/or Discontinuations Due to Adverse Effects.

Table 65. Severe Treatment-Emergent Adverse Events That Occurred More Frequently in the Afamelanotide Group: Safety Population (Studies CUV029, CUV030, and CUV039)

Preferred Term	Afamelanotide 16 mg n (%) N=125	Vehicle n (%) N=119
Migraine	3 (2%)	2 (2%)
Fatigue	2 (2%)	0
Abdominal distension	1 (1%)	0
Abdominal pain upper	1 (1%)	0
Back pain	1 (1%)	0
Ear pain	1 (1%)	0
Flatulence	1 (1%)	0
Foot fracture	1 (1%)	0
Foreign body in eye	1 (1%)	0
Injection site pain	1 (1%)	0
Intervertebral disc protrusion	1 (1%)	0
Joint swelling	1 (1%)	0
Musculoskeletal pain	1 (1%)	0
Nausea	1 (1%)	0
Somnolence	1 (1%)	0
Swollen tongue	1 (1%)	0

Source: Reviewer's own.

Reviewer Comment: Subject (b) (6) *in the afamelanotide group had a history of migraines with 11 reported as adverse events (eight severe and 3 moderate) and eventually discontinued due to migraines.*

Other Studies in Subjects With EPP

In Study CUV017 (crossover), 32 subjects reported 87 severe TEAEs. Most TEAEs were classified as mild (659 AEs) or moderate (481 AEs) in severity. There were a further 106 AEs for which no severity grading was provided by the investigator. One serious adverse event (thrombocytopenia) was reported and classified as severe; see discussion above on Subject (b) (6) in section on Discontinuations.

In Study CUV010 (open-label), five subjects experienced 38 TEAEs. Most of the TEAEs were mild or moderate in severity (93%). One subject experienced two severe AEs (fibula fracture and joint injury) considered not related to afamelanotide.

Reviewer Comment: Given the cross-over design of Study CUV017 and open-label design of Study CUV010, we cannot make adequate assessments of potential causality of afamelanotide in relation to the above AEs.

Postmarket Safety Population

In Study CUV-PASS-001/CUV-PASS-002, the Applicant reported that of patients experiencing TEAE (N=174), 74% were mild in severity and 61% had an outcome of TEAE reported as recovered/resolved. Eleven patients experienced severe TEAEs: pain, pyrexia, implant site pruritus, swelling, nausea, abdominal pain upper, abdominal pain, transient ischemic attack, photosensitivity reaction, influenza, abscess, appendicitis, peritonitis, back pain, depression, hepatitis alcoholic, testicular germ cell tumor mixed and tumor fistulization. For three of the

eleven patients with severe TEAEs, the investigator considered one or more severe TEAEs as related (nausea, pain, implant site pruritus, swelling, and photosensitivity reaction).

Adverse Reactions

Safety Population

Per Applicant, the following adverse events were considered related to study drug:

- CUV029: headache, pigmentation of implant site, and sensitivity in area of implant
- CUV030: no specific adverse reactions are noted, but the Applicant remarks that few than 50% reported any TEAE related to study drug.
- CUV039: half of subjects reported at least one TEAE considered related to study drug.

Our review for adverse reactions related to afamelanotide included pooling subjects from Studies CUV029, CUV030, and CUV039, as well as grouping related preferred terms to better capture adverse reactions (e.g., abdominal pain, skin pigment changes, implant site reactions, headache). The table below summarizes the adverse reactions that occurred in more than two subjects.

Table 66. Proportion of Subjects With Adverse Reactions Occurring in More Than 2% of Subjects (Studies CUV029, CUV030, and CUV039)

Adverse Reaction	Scenesse n (%) N=125	Vehicle n (%) N=119
Implant site reaction[1]	26 (21%)	12 (10%)
Nausea	24 (19%)	17 (14%)
Oropharyngeal pain	9 (7%)	5 (4%)
Cough	7 (6%)	4 (3%)
Fatigue	7 (6%)	3 (3%)
Skin hyperpigmentation[2]	5 (4%)	0 (0%)
Dizziness	5 (4%)	4 (3%)
Melanocytic nevus	5 (4%)	2 (2%)
Respiratory tract infection	5 (4%)	3 (3%)
Somnolence	3 (2%)	1 (1%)
Porphyria non-acute	2 (2%)	0 (0%)
Skin irritation	2 (2%)	0 (0%)

[1]: Implant site reaction include the following MedDRA preferred terms: implant site bruising, discoloration, erythema, hemorrhage, hypertrophy, irritation, nodule, pain, pruritus, and swelling; injection site bruising and erythema; and administration site reaction, as well as the narrative report of implant expulsion (Clinical Study Report Study CUV029).
[2]: Skin hyperpigmentation includes skin hyperpigmentation, pigmentation lip (subject also had skin hyperpigmentation), and pigmentation disorder.
Source: Reviewer's own.

Reviewer Comment: The safety analysis for implant site reactions identified that implant site discoloration was the most frequent implant site reaction reported. Thus, we have recommended its inclusion as a specific adverse reaction to highlight this potential risk.

As discussed above (Table 64), given the presence of melanocortin receptors in the central nervous system, afamelanotide may have a causal role in the adverse events of nausea, dizziness, and somnolence.

Other Studies in Subjects With EPP

In Study CUV017 (cross-over), the Applicant concluded that adverse reactions of implant site reactions and changes in skin pigment were similar in afamelanotide and vehicle groups.

In Study CUV010 (open-label), three subjects reported adverse reactions related to the implant site (see table below). There were no reports of new or changing pigmented lesions.

Table 67. Proportion of Subjects With Adverse Reactions Related to Implant Site Reactions in Study CUV010

Adverse Reaction	Afamelanotide, 20 mg n (%) N=5
Dermatitis contact	2 (40%)
Implant site pain	2 (40%)
Implant site pruritus	1 (20%)

Source: Reviewer's own.

Postmarket Safety Population

In Study CUV-PASS-001/CUV-PASS-002, the Applicant included summaries of adverse events related to pigment expression changes, administration site reactions, and administration errors.

- 12% of patients (32/270) reported TEAEs associated with pigment expression changes (implant site discoloration, pigmentation disorder, pigmentation lip, melanocytic nevus, birth mark, hair color changes, nail pigmentation, skin hyperpigmentation, post inflammatory pigmentation change, skin depigmentation, skin discoloration). Twenty-eight of the patients reported the pigment change within the first 6 months of treatment, four patients reported pigment change in the 2nd 6-month interval, and no patient-reported pigment change after more than 52-weeks of treatment.
- 4.3% of administrations (56/1293) were reported to have administration site reactions. Fifty-five administration site reactions were considered mild with one considered severe (Patient (b) (6): implant site pruritus). One administration site reaction was considered serious (Patient (b) (6) injection site mass) and is described above in Serious Adverse Events.
- Four administration errors (0.3% of administrations) were reported. Three administration errors were from one healthcare provider who implanted Scenesse at a site not specified in the labeling (Patients (b) (6)). One administration error was due to the implant administered "not deep enough" but was "adjusted" with "sterile glove and cloth." Of note, the Applicant describes two cases (Patients (b) (6)) of "administration at inappropriate site" and thus considered "off-label use" and not as administration errors.

Reviewer Comment: Review of the postmarketing data submitted did not identify additional adverse reactions regarding pigment change or implant site reactions. Thus, the prescribing information does not include a section 6 Adverse Reactions Postmarketing subsection. In addition, we are working with the Applicant to modify section 2 Dosage and Administration of labeling to mitigate administration errors.

In addition to the above adverse events, the Applicant reported 21 allergy and hypersensitivity reactions involving 1.6% of Scenesse administrations. One patient (Patient (b) (6), erythema) required hospitalization and is described above in Serious Adverse Events.

Reviewer Comment: Adverse events related to allergy and hypersensitivity were not observed in the drug development program. Routine pharmacovigilance will include surveillance for allergy and hypersensitivity reactions.

Laboratory Findings

Safety Population

Laboratory testing (hematology, biochemistry, and urinalysis) was conducted routinely in the safety population (Studies CUV029, CUV030, and CUV039). A central laboratory was not used. Investigators reviewed laboratory test results and evaluated the result as normal, abnormal/clinically not significant, or abnormal/clinically significant.

There were no clinically meaningful changes in laboratory parameters such as renal function tests, liver enzymes, and hematology tests in subjects exposed to afamelanotide implant, 16 mg compared to vehicle.

Other Studies in Subjects With EPP

In Study CUV017 (cross-over): Subject (b) (6) experienced low plate count. Subsequently stabilized after diagnosis and treatment for idiopathic thrombocytopenic purpura. Refer to subject narrative in Section 8.4.4 Serious Adverse Events.

In Study CUV010 (open-label): Subject 2 reported a clinically significant urinalysis findings of increased ketones and attributed to the subject's calorie reduced diet. The laboratory finding was not reported as an AE. Three subjects ((b) (6) reported "abnormal, not clinically significant" hematology laboratory results while four subjects reported "abnormal, not clinically significant" biochemistry results. No subject reported clinically significant hematology or biochemistry results.

Postmarket Safety Population

Laboratory testing and liver ultrasound were routinely conducted in Study CUV-PASS-001/CUV-PASS-002. No data was submitted in the PASS Study Report #3.

Vital Signs

Safety Population

As discussed in Section 8.4.3 of this review, vital signs were included as part of the safety assessments. There were no clinically significant changes in weight, temperature, pulse rate, and blood pressure in the safety population (Studies CUV029, CUV030, and CUV039).

Other Studies in Subjects With EPP

In Studies CUV017 (cross-over) and CUV010 (open-label), vital signs were included as part of the safety assessments. There were no clinically significant changes in weight, temperature, pulse rate, and blood pressure identified in the trials.

Postmarket Safety Population

Vitals signs were routinely conducted in Study CUV-PASS-001/CUV-PASS-002. No data was submitted in the PASS Study Report #3.

Physical Examination

As discussed in Section 8.4.3 of this review, physical exam, including skin, mucosa and ophthalmologic examination, were included as part of the safety assessments. There were no clinically significant changes in physical examination findings in the safety population (Studies CUV029, CUV030, and CUV039).

Other Studies in Subjects With EPP

In Studies CUV017 (cross-over) and CUV010 (open-label), clinically significant physical examination findings were reported as AEs, and reviewed in the respective section.

Postmarket Safety Population

Physical examination, skin and mucosal examination, and full body photography were routinely conducted in Study CUV-PASS-001/CUV-PASS-002. No data was submitted in the PASS Study Report #3.

Electrocardiograms (ECGs)

In the safety analysis set (Studies CUV029, CUV030, and CUV039), ECG evaluation was conducted only in Study CUV039 on Day 60, 120, 180. ECG evaluation was performed at screening and any time during the study at the discretion of the investigator. No clinically significant ECG changes were noted during the study or reported as an AE.

Review of the submitted case report forms for Study CUV039 revealed two subjects who had abnormal ECGs.

- Subject (b) (6): 4-year-old woman with an adverse event of “incidental left atrial enlargement on ECG” dated (b) (6) recorded in the case report form. No action was taken. The AE was considered not related and resolved.
- Subject (b) (6): 56-year-old man without baseline or study ECG with ECG done at early termination visit (b) (6) reported as “borderline abnormal left anterior hemiblock.” The ECG abnormality was not reported as an adverse event. Last dose of study drug received (b) (6). Subject discontinued study due to inability to comply with protocol schedule. Note, subject discussed above under serious adverse events.

Other Studies in Subjects With EPP

ECGs were not routinely conducted in Studies CUV010, CUV017, or in CUV-PASS-001/CUV-PASS-002.

QT

The Applicant did not conduct a thorough QT Study during the trials in the development program. The Applicant submitted a tQT waiver to the NDA. The QT-IRT team was consulted and provided the following conclusions:

The Applicant's request to not conduct a QT study is not acceptable because the available nonclinical and clinical data are not adequate for the characterization of afamelanotide' s effect on the QT interval.

1. In the pivotal Study CUV039, safety ECGs were collected every 60 days after implant. Most of these ECG data were collected predose when afamelanotide was not systemically available (i.e., afamelanotide concentrations are BLQ by 96 h post-implant). These ECG data are not sufficient to characterize the effects of afamelanotide on cardiac repolarization.
2. Based on legacy clinical study report submitted under NDA 210797, none of the studies EP006, CUV006, CUV007, CUV009, CUV011, CUV015, or CUV038 would be adequate to serve as an alternative to a TQT study. These studies do not have adequate dose/exposure, PK/ECG sampling schedule, and/or appropriate placebo control for QTc assessment.
3. The Applicant did not provide any information related to the in vitro characterization of afamelanotide effect on cardiac ion channels.

Afamelanotide is a new molecular entity. To characterize the effect of afamelanotide on cardiac repolarization is recommended as per ICH E14 and ICH E14 Q & A (R3) guidelines, approval will include a PMR to conduct a tQT study. See Section 13. See Section 6 Clinical Pharmacology for further discussion.

Immunogenicity

As the proposed product is not a therapeutic protein, the Applicant did not assess the potential immunogenicity.

8.4.5. Analysis of Submission-Specific Safety Issues

Evaluation for Melanoma and Pigmentary Skin Changes Due to Afamelanotide Mechanism of Action

During the development program, additional safety monitoring including dermatologic examination (skin and mucosa) and ophthalmologic examination was recommended and

conducted. The safety assessments were reviewed as part of the safety review and analyses results are included throughout Section 8.

8.4.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

No clinical outcome assessment (COA) analyses informing safety or tolerability was performed as part of the safety review. In preparation for a Type C meeting, a COA consult was requested by the Division during early development of afamelanotide (see review by Nikunj Patel, PharmD, dated September 30, 2015) requesting input on the proposed patient-reported outcome-based primary efficacy endpoint. No specific comments were provided because COA-related information was not complete for the purpose of formal COA review.

8.4.7. Safety Analyses by Demographic Subgroups

The review team conducted multiple analyses to evaluate the safety profile of afamelanotide implant, 16 mg in different populations. The results indicated that there were no substantial differences in treatment-emergent adverse events (TEAEs) in demographic subgroups.

Overall, a greater proportion of female subjects 95% who received afamelanotide implant, 16 mg reported TEAEs compared to 84% of male subjects who received afamelanotide. In comparison 86% of female subjects and 85% of male subjects in the vehicle group reported TEAEs. For serious TEAEs (SAEs), three female subjects (5%) and two male subjects (3%) in the afamelanotide group compared to two female subjects (3%) and one male subject (2%) reported SAEs. The table below summarizes the severity of TEAEs by gender.

Table 68. TEAE Severity by Gender in the Safety Population (Studies CUV029, CUV030, and CUV039)

	Afamelanotide, 16 mg n (%) N=125		Vehicle n (%) N=119	
TEAE Severity	Female n (%) N=57	Male n (%) N=68	Female n (%) N=58	Male n (%) N=61
Mild	49 (86%)	48 (71%)	46 (79%)	38 (62%)
Moderate	29 (51%)	24 (35%)	28 (48%)	25 (41%)
Severe	12 (21%)	5 (7%)	8 (14%)	8 (13%)

TEAE = treatment-emergent adverse event
Source: Reviewer's own.

For TEAEs that were reported by 2 or more subjects, female subjects in the afamelanotide group were more likely to report the following selected TEAEs compared to male subjects:

- Nausea: 40% compared to 15%
- Nasopharyngitis: 25% compared to 12%
- Arthralgia: 16% compared to 1%
- Migraine: 12% compared to 3%
- Implant site pain: 5% compared to 0%

- Joint swelling: 5% compared to 0%
- Pigmentation disorder: 5% compared to 3%

For TEAEs that were reported by 2 or more subjects, male subjects in the afamelanotide group were more likely to report the following selected TEAEs compared to female subjects:

- Implant site discoloration: 13% compared to 7%
- Implant site bruising: 3% compared to 0%
- Implant site reaction: 3% compared to 0%
- Fatigue: 9% compared to 7%
- Musculoskeletal pain: 4% compared to 2%
- Myalgia: 4% compared to 2%
- Pyrexia: 6% compared to 0%

Studies CUV030 and CUV039 were conducted in the United States while Study CUV029 was conducted in the European Union (EU). Approximately 70% of subjects were from the United States while 30% of subjects were from different countries through the EU (refer to Section 7.1 for study details). The demographic characteristics between the American and non-American populations were similar.

Approximately 99% of subjects in the safety population were Caucasian.

Reviewer comment: Due to the small number of subjects of non-Caucasian race, no meaningful conclusions could be drawn regarding ARs and race.

Approximately 98% of subjects were between 18 and 65 years of age.

Reviewer comment: Due to the small number of subjects of age over 65 years, no meaningful conclusions could be drawn regarding ARs and age.

8.4.8. Specific Safety Studies/Clinical Trials

The Applicant did not conduct additional specific study or clinical trials to evaluate a potential safety concern as part of the development program. The Applicant is conducting postmarketing safety studies as required under the EMA approval “under exceptional circumstances” pathway. The submitted EMA postmarketing safety study data is discussed throughout Section 8.

Photoprovocation testing was conducted in a subset of subjects in each trial (Studies CUV010, CUV017, CUV029, CUV030, and CUV039). The photoprovocation testing was conducted as part of the efficacy assessment of afamelanotide and was not related to the safety assessment of afamelanotide.

8.4.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant did not conduct a specific clinical trial to evaluate human carcinogenicity or tumor development. During the development of afamelanotide implant, the trial designs did not include specific assessments to evaluate for carcinogenicity but did include dermatologic examination to screen for cutaneous malignancies (melanoma and non-melanoma). Refer to Section 8.4.3.

The Applicant submitted a nonclinical carcinogenicity study waiver request which was granted by the Agency on March 1, 2017. Refer to Section 5.5.5 of this review for a discussion of the nonclinical data.

Human Reproduction and Pregnancy

Requirements for women of childbearing potential who were enrolled in the afamelanotide development program included the use of effective forms of contraception, negative pregnancy tests at screening, and urinary pregnancy testing at select clinic visits. Requirements for men who were enrolled included barrier contraception during the trial and 3 months after trial participation.

Among subjects receiving afamelanotide in the development program, there were no documented pregnancies. The EMA postmarketing surveillance identified 12 pregnancies in patients with history of treatment with Scenesse. DPMH review of these pregnancies determined that the pregnancies occurred while patients were not receiving Scenesse treatment, and therefore, no data on Scenesse in pregnant women is available to evaluate for any drug associated risk of major birth defects, miscarriages, or adverse maternal or fetal outcomes.

In addition, there is no data on the presence of afamelanotide in human or animal milk, the effects on breastfed infant, or the effect on milk production. Afamelanotide is unlikely to be transferred into maternal milk due to the large molecular size, and as a tridecapeptide, afamelanotide is likely to be denatured in the breastfeeding infants' gastrointestinal tract. Therefore, it is unlikely that any afamelanotide that transfers to maternal milk will result in systemic exposure to the breastfeeding infant.

Regarding effects of afamelanotide on human fertility, DPMH review concluded that there is no data to support effects of afamelanotide on human fertility.

Based on the above conclusions, modifications to the proposed Prescribing Information were made to reflect the known risks of afamelanotide on pregnancy, lactation, and human fertility. Refer to the DPMH review by Leyla Sahin, MD dated July 15, 2019.

Pediatrics and Assessment of Effects on Growth

Clinical studies CUV010, CUV017, CUV029, CUV030, and CUV039 did not enroll any subjects less than 18 years of age, and thus did not evaluate the safety or efficacy of Scenesse in the pediatric population or the effect of Scenesse on growth.

The Applicant received an Orphan designation for afamelanotide on July 17, 2008. Therefore, this application is not a subject to the Pediatric Research Equity Act of 2007, and the Applicant will not be required to conduct studies in pediatric patients. No PMR or PMC will be issued for the conduct of studies in children for afamelanotide in the treatment of EPP.

Of note, the European Medicines Agency (EMA) Pediatric Investigation Plan (PIP) waived studies in patients less than 2 years. The EMA is requiring the following juvenile toxicology, bioequivalence and pediatric clinical studies:

- A juvenile repeat dose toxicity study in rats followed by 4-week recovery
- A comparative study to evaluate the pharmacokinetics of afamelanotide and the pharmacodynamic response to afamelanotide between subcutaneous administration of solid implant and the age appropriate prolonged release formulation in healthy adults.

An open-label, multicenter, multiple dose, dose-escalation pharmacokinetic and pharmacodynamic study of afamelanotide age appropriate prolonged release formulation in children from 6 years to less than 18 years with EPP.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There were no cases of overdose, drug abuse, withdrawal, or rebound effect reported in clinical studies of Scenesse in subjects with EPP. Based on the mode of action, there is no reason to assume that there is a potential for abuse or dependency for afamelanotide.

8.4.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience and Expectations on Safety in the Postmarket Setting

Afamelanotide implant, 16 mg was authorized for marketing in the European Union on December 22, 2014 with commercial marketing of Scenesse beginning on June 22, 2016.

The comprehensive analysis of the afamelanotide implant safety data identified no safety signals. Review of postmarketing from the European market has not identified additional safety concerns. Safety analysis of submitted EMA postmarketing data is discussed above, throughout Section 8. Thus, we do not expect a change in the favorable risk/benefit assessment or increased risk with administration of afamelanotide implant in the postmarket setting.

8.4.11. Integrated Assessment of Safety

The safety profile for afamelanotide implant was adequately characterized during the drug development program. The primary safety database consisted of 244 subjects from Studies

CUV029, CUV030, and CUV039 (the pooled safety analysis set). All randomized subjects who received at least one implant were included in the safety analysis set.

Review of the safety data did not reveal any contraindications to treatment with afamelanotide implant to be included in section 4 of product labeling. Adverse reactions related to increased skin pigmentation and pigmented lesions, as well as subcutaneous administration, are consistent with the mechanism of action of afamelanotide. The data support advising patients to undergo routine skin examination in section 5 Warnings and Precautions of labeling. Postmarket data from the European market supports the adverse reactions identified in the development program.

Treatment with afamelanotide implant was not associated with an increased risk of mortality or serious adverse events. There were no deaths in the development program for afamelanotide implant and there were no serious adverse events assessed as related to either study product. In the safety population, serious adverse events occurred in 4% subjects in the afamelanotide implant group and 3% subjects in the vehicle group. No afamelanotide-exposed pregnancies occurred during the development program or European Union postmarketing surveillance program.

The currently available safety data from Studies CVU029, CUV030, and CUV039 demonstrate that afamelanotide implant appears safe to increase the duration of pain-free sun exposure in erythropoietic protoporphyria patients 18 years of age and older. The Applicant included European postmarketing surveillance data to support the long-term safety demonstrated in the development program. The postmarketing safety profile of Scenesse is consistent with the safety profile of afamelanotide during development.

Postmarketing risk management will include professional labeling and routine pharmacovigilance. As this is a new chemical entity, the review team recommends postmarketing requirements to better characterize the potential for afamelanotide to prolong QT. In addition, given the small safety population, the review team recommends a postmarketing study to further evaluate the safety of afamelanotide regarding skin cancer, administration and implant site reactions, pregnancy, and device failure or malfunction.

8.5. Statistical Issues

Refer to Sections 8.1, 8.2, and 8.3 for relevant discussion.

8.6. Conclusions and Recommendations

To establish the effectiveness of afamelanotide implant, 16 mg, the Applicant submitted data from three randomized, multicenter, vehicle-controlled, Phase 3 trials (Studies CUV029, CUV030, and CUV039), one cross-over design trial (Study CUV017), and one open-label proof of concept trial (Study CUV010). The trials enrolled subjects 18 years of age and older with erythropoietic protoporphyria. Enrolled subjects had clinical symptoms of phototoxic reactions and biochemical confirmation of erythropoietic protoporphyria.

In the Phase 3 trials, subjects were randomized in a 1:1 ratio to receive afamelanotide implant, 16 mg or vehicle implant, administered subcutaneously every 2 months. Studies CUV039 and CUV029 demonstrated the efficacy of afamelanotide implant relative to vehicle in increasing the duration of pain-free direct sun exposure. The primary endpoint in Studies CUV039 and CUV029 was the duration of direct sunlight exposure on days when no pain was experienced. Although Study CUV030 was a negative study, and the findings regarding the duration of pain-free sun exposure were identified post hoc and thus cannot support efficacy, the results were very similar to those observed in Study 029 and provide some assurance that findings are consistent across multiple studies.

The Applicant conducted a comprehensive assessment of the safety of afamelanotide implant, 16 mg in the target population, including European postmarketing data. The size of the safety database and the safety evaluations were adequate to identify local and systemic treatment-emergent adverse reactions.

Submitted safety and efficacy data support approval of this NDA for afamelanotide implant, 16 mg to increase (b) (4) pain-free (b) (4) exposure (b) (4) in adult patients with EPP.

9. Advisory Committee Meeting and Other External Consultations

No advisory committee was held for this NDA because the application did not raise significant safety or efficacy issues in the intended population.

The NDA and results submitted by the Applicant in support of approval was presented to the CDER Medical Policy and Program Review Council on February 22, 2019. The council determined that the Applicant had provided adequate efficacy information to support approval of Scenesse for the following indication: to increase (b) (4) pain-free (b) (4) exposure in adults with EPP.

10. Pediatrics

Pediatric subjects were not included in the development program for afamelanotide implant, 16 mg.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, the Applicant is exempt from this requirement.

11. Labeling Recommendations

11.1. Prescription Drug Labeling

The Applicant submitted proposed Prescribing Information (PI) and carton/container labels for afamelanotide implant, 16 mg. The proposed PI reflected sections included in the EMA-authorized Summary of Product Characteristics. The review team provided labeling recommendations throughout this review; to fulfill labeling requirements. Madhuri R. Patel, PharmD from the Division of Medication Error Prevention and Analysis reviewed the proposed PI for Scenesse (afamelanotide) implant, 16, mg and the carton and container labels and provided comments. DMEPA concluded that vulnerabilities exist in PI and carton and container labels that may lead to medication error and provided recommendations to promote safe use of the product. DMEPA's recommendations were conveyed to the Applicant. Dr. Patel reviewed the revised container labels and carton labeling for Scenesse and found them acceptable from a medication error perspective. The Office of Prescription Drug Promotion (OPDP) reviewed and provided comments regarding the proposed PI and carton/container. Refer to the OPDP review by Laurie Buonaccorsi, PharmD dated September 26, 2019. These comments are reflected in final labeling. Information regarding post-procedure implant site care will be included in sections 2.2 and 17.

The following table provides the location of the labeling discussion for each section.

Table 69. Summary of Significant High-Level Labeling Changes

Section	Location of Reviewer Comments on Proposed Labeling
1 INDICATIONS	Section 8
2 DOSAGE AND ADMINISTRATION	Section 8
3 DOSAGE FORMS AND STRENGTHS	Section 4
4 CONTRAINDICATIONS	Section 8.4.11
5 WARNINGS AND PRECAUTIONS	Section 8.4.4 and 8.4.5
6 ADVERSE REACTIONS	Section 8.4.4
7 DRUG INTERACTIONS	Section 6.3.2
8 USE IN SPECIFIC POPULATIONS	Section 8.4.9
11 DESCRIPTION	Section 4
12 CLINICAL PHARMACOLOGY	Section 6
13 NONCLINICAL TOXICOLOGY	Section 5
14 CLINICAL STUDIES	Section 7.1
17 PATIENT COUNSELING INFORMATION	Section 8.4.4 and 8.4.5

Patient Labeling

The Applicant submitted a proposed Medication Guide for afamelanotide implant 16 mg. The review team concluded that revision of section 17 Patient Counseling Information would adequately mitigate risks associated with the use of Scenesse in adults with EPP; thus, no separate patient labeling for Scenesse is recommended.

12. Risk Evaluation and Mitigation Strategies (REMS)

The Applicant submitted a postmarketing risk mitigation plan, based on the drug's EMA postmarketing risk mitigation plan, that resembled Risk Evaluation and Mitigation Strategies (REMS). The proposed risk mitigation plan and submitted safety and efficacy data was presented to the Office of New Drug REMS Oversight Committee (ROC). Upon review, risk mitigation measures beyond labeling and postmarketing requirement and commitment are not warranted at this time. See Section 11 Labeling Recommendations.

13. Postmarketing Requirements and Commitment

Clinical postmarketing requirements are intended to characterize the risks of afamelanotide implant use in special populations and address the long- term safety of this novel drug product in the target population.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, the Applicant is exempt from this requirement.

Based on review of the data in this submission, the following postmarketing requirements (PMRs) and commitments (PMCs) were conveyed to the Applicant:

<u>Postmarketing Requirements Under 505(O)</u>

The following PMR is recommended by the clinical pharmacology team. Refer to Section 6 for further discussion.

1. Conduct a thorough QT clinical study to adequately characterize the effect of afamelanotide on cardiac repolarization.

The following PMR is recommended by the clinical team:

2. Conduct a prospective, longitudinal, registry based observational exposure cohort study to collect information on long-term safety of afamelanotide in patients with erythropoietic protoporphyria (EPP) in the United States. Patients will be followed for a minimum of eight years from initiation of treatment with afamelanotide. The primary adverse events of interest are:
    - Skin cancer (melanomas and non-melanomas)
    - Administration/injection/implant site reactions

Secondary adverse events of interest are:

- Changes in pigmentary expressions
- Pregnancy outcomes (including major birth defects and other adverse pregnancy outcomes such as spontaneous abortions, stillbirths, preterm deliveries, and small for gestational age)
- Exposure during lactation and adverse reactions in breastfed infants
- Implantation device malfunction or failure

At the time of this review, final milestone dates were under discussion. Refer to the Approval Letter for the final PMR and PMC with milestone dates.

14. Division Director (DHOT) Comments

15. Division Director (OCP) Comments

16. Division Director (OB) Comments

17. Division Director (Clinical) Comments

See Section 18

18. Office Director (or Designated Signatory Authority) Comments

NDA 210797 for Scenesse (afamelanotide) implant, 16 mg, a new molecular entity (NME), was submitted by the Applicant in support of an indication for the [redacted] (b) (4) patients with erythropoietic protoporphyria (EPP). Scenesse implant, 16 mg, is subcutaneously administered to the patient by a healthcare provider proficient in implantation. The implant is biodegradable eliminating the need for removal. The proposed dosing schedule is one implant subcutaneously administered every two months during periods when photoprotection is required.

EPP is an inherited disorder caused by a deficiency in ferrochelatase, the final enzyme in the heme biosynthetic pathway. This deficiency leads to an accumulation of the final precursor to heme, protoporphyrin IX (PPIX), in red blood cells, plasma, and tissues such as skin. Reactive

oxygen species are produced when PPIX in the skin is exposed to light in the range of 380 nm to 420 nm, leading to damage of adjacent cutaneous tissue and blood vessels. Phototoxic reactions resulting from the generation of reactive oxygen species are manifested by pain, pruritis, erythema, edema, blistering, and petechiae of the skin; symptoms can last from hours to weeks. For many patients, the pain is extreme and debilitating, causing them to lead severely restricted lives because of the necessity of sun/light avoidance.

Afamelanotide, a 13-amino acid linear peptide, is an agonist of the melanocortin-1 receptor (MC1R) and a structural analogue of the endogenous hormone α-melanocyte stimulating hormone (αMSH). Afamelanotide's primary pharmacological activity results in the increased synthesis, release, and transfer of eumelanin through stimulation of the MC1R. The Applicant's proposed mechanism of action is reduced PPIX excitation due to increased absorption of light by the increased epidermal eumelanin. Eumelanin may also confer photoprotection against the DNA damaging effects of sun exposure by its ability to quench reactive oxygen radicals.

Afamelanotide pharmacokinetics were assessed in eight Phase 1 healthy volunteer studies, and pharmacodynamic effects were assessed through measurement of melanin density (MD) in nine healthy volunteer studies and in two EPP patient studies. Evaluation of data from these studies led to selection of the 16 mg dose utilized in the Phase 3 studies. An overall increase in MD across different anatomical sites was observed following administration of afamelanotide, although high intersite variability was observed. In general, MD would rise following implantation reaching a plateau sometime between Day 7 through Day 28 and decline sometime thereafter. In Study 017 in which subjects received afamelanotide implants alternating with vehicle implants, the changes in mean MD followed a cyclical pattern.

The Applicant submitted data from one adequate and well-controlled trial (Study 039), which provided evidence that afamelanotide increases the duration of pain-free sun exposure time in adults with erythropoietic protoporphyria (EPP). They submitted two additional trials (Studies 029 and 030) that were supportive of the conclusions of Study 039.

Study 039 was a randomized, parallel group, vehicle-controlled study conducted in the U.S. Subjects in Study 039 received 3 implants 2 months apart and were followed for 180 days. The primary endpoint was prespecified as the number of hours that subjects were able to spend outdoors in direct sunlight on days with no pain. Efficacy information was collected from subject diaries regarding the level of phototoxic pain and the amount of time spent outdoors in direct sun or in shade. Earlier studies, including 029 and 030, were designed to assess primary endpoints based on the number and total severity of phototoxic reactions during the study. However, because the earlier studies were unable to detect a treatment effect related to the total severity of phototoxic reactions, the Applicant designed Study 039 to assess efficacy in terms of the number of hours of sun exposure on days with no pain.

In Study 039, a total of 94 subjects were randomized, 48 to afamelanotide and 46 to vehicle. Most subjects (95%) received all three doses. Afamelanotide-treated subjects spent a median of

64.1 hours in direct sunlight with no pain as compared to a median of 40.5 hours for vehicle subjects during the 180 day treatment period. The Applicant conducted an analysis that excluded subjects who did not have any post-baseline efficacy data and calculated a p-value of 0.044. An analysis including all randomized subjects with imputation for missing data conducted by FDA has a p-value of 0.055.

The primary efficacy endpoint for Study 039, the number of hours that subjects were able to spend outdoors in direct sunlight on days with no pain, is complex, requiring both behavioral aspects (spending time outdoors, and in direct sun rather than shade) and physiological response (having no pain on days where time was spent outdoors in direct sunlight). The nesting definitions of total hours spent outdoors, total hours spent outdoors in direct sunlight, and total hours spent outdoors in direct sunlight on days with no pain were explored graphically to evaluate the varying impacts of the different components. For each component, the afamelanotide group is shifted to the right of the vehicle group, representing longer durations on afamelanotide. The difference is the greatest for the primary endpoint, which includes all the components.

Although Study 029 had some data quality issues, afamelanotide was statistically superior to vehicle (p=0.005) for the pain-free direct sun exposure endpoint, thus providing support for the findings in Study 039. Study 030 did not demonstrate statistical significance on the prespecified endpoint of the severity of phototoxic reactions. The endpoints based on pain-free sun exposure in Study 030 were defined post hoc and thus not able to support efficacy for pain-free direct sun exposure; however, the results from Study 030 were very similar to those observed in Study 029 and Study 039 and thus provide some assurance that findings are consistent across multiple studies.

The Applicant originally designed their development program with the objective of assessing the overall severity of phototoxic reactions in subjects with EPP. However, this endpoint was not sensitive to any treatment effect between afamelanotide and vehicle. Thus, the indication granted reflects the primary endpoint demonstrating a significant treatment effect between afamelanotide and vehicle.

The safety profile of afamelanotide implant was adequately characterized during the development program. One afamelanotide-treated subject died of liver failure secondary to an obstructed bile duct eight months after receiving her last implant. Her death is considered unlikely to be related to afamelanotide due to the time period of eight months between the last dose of study drug and death. In the pooled safety analysis set (Studies 029, 030, and 039), serious adverse events (SAEs) were reported in five subjects who received afamelanotide. All SAEs resolved without sequelae and were considered not related or unlikely to be related to afamelanotide. Three afamelanotide-treated subjects discontinued from the clinical trials for adverse events, one each for the events of headache, migraine, and fatigue. The subject who discontinued for migraine had a prior history of migraine at the time of enrollment. Adverse reactions that occurred in at least 2% of afamelanotide-treated subjects included implant site

reactions (21%), nausea (19%), fatigue (6%), skin hyperpigmentation (4%), dizziness (4%), and somnolence (2%). Given the presence of melanocortin receptors in the central nervous system, it is plausible that afamelanotide may have a causal role in the adverse events of nausea, dizziness, and somnolence.

Because afamelanotide stimulates melanogenesis there is a safety concern for pigmentation disorders and melanoma. In nonclinical studies, afamelanotide inhibited the growth of cultured melanoma cells and showed no stimulating effects on primary melanoma or lung metastasis in mice bearing malignant melanoma. Currently, there is no accurate animal model to address the potential of afamelanotide to induce melanomas. During the development program, targeted safety monitoring included dermatologic examination of the skin and mucosa and ophthalmologic exam to evaluate for new and existing pigmentary lesions. Skin hyperpigmentation was reported as an adverse reaction by 4% of afamelanotide-treated subjects as compared to none receiving vehicle. Melanocytic nevi were reported by 4% of afamelanotide-treated subjects and 2% of vehicle-treated subjects. One vehicle-treated subject was discontinued after receiving two doses for an adverse event of malignant melanoma in situ. One afamelanotide-treated subject was discontinued after receiving two doses for an adverse event of compound nevus with mild dysplasia.

Scenesse was granted marketing authorization in the European Union in December 2014. The Applicant submitted safety data obtained from required European Medicines Agency (EMA) postmarketing safety studies to support the safety information obtained from the clinical trials. The EMA postmarketing exposure data included patients with EPP with up to 10 years of afamelanotide exposure. The most common adverse events reported in the postmarket safety population were nausea, headache, and fatigue. No cases of melanoma have been reported.

I concur with the review team that the available evidence of efficacy and safety supports the approval of Scenesse (afamelanotide) implant, 16 mg to increase the duration of pain-free light exposure in adults with a history of phototoxic reactions from EPP. Scenesse (afamelanotide) implant, 16 mg will be an important addition to the management strategies currently utilized by EPP patients. Because of the limited patient population available to participate in the development program and fully characterize the safety profile of the product, and because of the potential of afamelanotide to affect melanogenesis, postmarketing safety data collection will be required through conduct of a voluntary patient registry.

19. Appendices

19.1. References

The references are included throughout the document as footnotes.

19.2. Financial Disclosure

In compliance with 21 CFR Part 54, the Applicant provided Certification/Disclosure Forms from clinical investigators and sub-investigators who participated in covered clinical studies for afamelanotide. Prior to trial initiation, the investigators certified the absence of certain financial interests or arrangements or disclosed, as required, those financial interests or arrangements as delineated in 21 CFR 54.4(a)(3)(i-iv).

The covered clinical studies as defined in 21 CFR 54.2(e) were studies CUV010, CUV017, CUV029, CUV030, and CUV039, which provided the primary data to establish effectiveness and safety of this product. Refer to Section 8.1 for the study designs.

The Applicant adequately disclosed financial interests involving clinical investigators. Because the number of investigators with financial disclosures was limited and assessments were blinded, the strategies employed by the Applicant to minimize potential bias arising from investigator financial interests/arrangements appear reasonable.

Table 70. Financial Disclosure for Study CUV010

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): _____		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		

Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Table 71. Financial Disclosure for Study CUV017

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 40		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): _____		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Table 72. Financial Disclosure for Study CUV029

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 32		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): _____		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Table 73. Financial Disclosure for Study CUV030

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 31		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): _____		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Table 74. Financial Disclosure for Study CUV039

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 32		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): _____		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

19.3. Nonclinical Pharmacology/Toxicology

19.3.1. Multiples of Human Exposure Calculation

The proposed maximum recommended human dose (MRHD) is one implant (16 mg afamelanotide) given to a 60 kg patient (0.27 mg/kg or 9.9 mg/m^2) once every 2 months. The highest dose of afamelanotide tested subcutaneously in the reproductive and developmental toxicity studies in rats was 20 mg/kg/day or 120 mg/m^2/day, which is at least 12 times the MRHD, based on a body surface area comparison.

19.3.2. Nonclinical Labeling

Recommended Revisions to the Nonclinical Portions of Labelling

Revisions to the Applicant's proposed wording for the nonclinical and related sections of the labeling are provided below. It is recommended that the underlined wording be inserted into and the ~~strikethrough~~ wording be deleted from the Scenesse label proposed by the Applicant. The subheadings in section 8.1 should be in underlined format which has been proposed by the Applicant. The pharmacologic class for afamelanotide is melanocortin 1 receptor agonist.

INDICATIONS AND USAGE

Scenesse is a melanocortin 1 receptor (MC1-R) agonist indicated for (b) (4) adult patients with erythropoietic protoporphyria (EPP).

8.1 Pregnancy

Risk Summary

(b) (4)

Limited available data with Scenesse use in pregnant women are insufficient to evaluate a drug associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcome.

In animal reproductive and development toxicity studies, no adverse developmental effects were observed with afamelanotide administration during the period of organogenesis to pregnant rats at subcutaneous doses up to 12 times the maximum recommended human dose (MRHD) *(see Data).*

(b) (4)

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

[redacted] (b) (4)

[redacted] (b) (4)

In embryofetal development studies in Sprague Dawley and Lister Hooded rats, afamelanotide was administered subcutaneously to pregnant rats at doses of 0.2, 2, or 20 mg/kg/day throughout the period of organogenesis. No adverse embryofetal developmental effects were observed at doses up to 20 mg/kg/day (12 times the MRHD, based on a body surface area comparison).

In an oral pre- and post-natal development study in Sprague Dawley rats, afamelanotide was administered subcutaneously at doses of 0.2, 2, or 20 mg/kg/day during the period of organogenesis through lactation. No treatment-related effects were observed at doses up to 20 mg/kg/day (12 times the MRHD, based on a body surface area comparison).

12.1 Mechanism of Action

Afamelanotide is a synthetic tridecapeptide and a structural analog of α-melanocyte stimulating hormone (α-MSH). Afamelanotide is a melanocortin receptor agonist and binds predominantly [redacted] (b) (4)

13 Nonclinical Toxicology

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

[redacted] (b) (4)

Carcinogenicity studies have not been conducted with Scenesse.

Afamelanotide was negative in the Ames test, in vitro mouse lymphoma assay, and in vivo mouse bone marrow micronucleus assay.

No effects on (b) (4) male or female fertility and reproductive performance (b) (4) were observed in rats at subcutaneous doses (b) (4) up to 20 mg/kg/day afamelanotide (12 times the MRHD, based on a body surface area comparison) (b) (4)

(b) (4)

19.4. OCP Appendices (Technical Documents Supporting OCP Recommendations)

19.4.1. Bioanalytical Methods for PK Studies

In PK studies, the concentration of afamelanotide in plasma samples was determined using LC/MS/MS. The methods used to support PK studies are summarized in Table 75. Among the five methods, three methods, ALM MT01, BACG-3734 A and ALM AFM.3, were used to support pertinent studies for Clinical Pharmacology review. The validation and performance results of these three methods are summarized in Table 76, Table 77, and Table 78, respectively. They appear reasonable and do not bring up significant concerns about the validity of measured values.

Table 75. Summary of Bioanalytical Methods for Plasma Sample Analyses of Afamelanotide

Analytical Method	Associated Studies	Linearity Range
ALM 007/1	EP001	2.00 to 500 ng/mL
ALM M-008/1	EP004	0.25 to 50 ng/mL
ALM MT01	EP006, CUV006, CUV007, CUV009	0.250 to 50.0 ng/mL
BACG-3734 A	CUV028	0.25 to 50 ng/mL
ALM AFM.3	CUV038	0.025 to 5.00 ng/mL

Table 76. Summary of Method Validation and Performance Results for ALM MT01

Method Validation	
Matrix	Human plasma
Extraction procedure	Solid phase extraction
Analyte	MT1 (afamelanotide)
Internal standard	(b) (4)
Linearity (calibration curve range)	0.250 to 50.0 ng/mL
LLOQ	0.250 ng/mL
Specificity	Retention times of analyte and internal standard were 9.0 min and 8.5 min, respectively. There were no peaks that interfered with the analyte or the internal standard.
Precision (% CV)	
Intra-day	Lower limit of quantification (LLOQ): 19 Quality Control Low (QCL) concentration: 14.4 Quality Control Mid (QCM) concentration: 3.5 Quality Control High (QCH) concentration: 1.5
Inter-day	LLOQ: 6 QCL: 12.8 QCM: 2.0 QCH: 4.0
Accuracy (Mean % difference from actual conc.)	
Intra-day	LLOQ: 5 QCL: -4.2 QCM: 3.9 QCH: 2.4
Inter-day	LLOQ: 3 QCL: -4.4 QCM: 2.0 QCH: 3.3
Stability of afamelanotide in plasma	Long term at -70°C: 64 days[1] Long term at -20°C: 72 days Freeze/Thaw: 3 Cycles[1] Room temperature: 24 hours[1]
Stability of afamelanotide in solution	50 days at -20°C
Stability of processed extract	50 hours at room temperatre[1]
Performance – Study CUV006	
Incurred sample reanalysis	Not conducted
Duration of sample storage[2]	First sample drawn: Nov 22, 2006 Last sample analysis: Feb 21, 2007
Sample storage temperature	-20°C
Performance – Study CUV007	
Incurred sample reanalysis	Not conducted
Duration of sample storage[2]	Within the validated 72 days First sample drawn: Jan 15, 2007 Last sample analysis: Mar 1, 2007
Sample storage temperature	-20°C
Performance – Study CUV009	
Incurred sample reanalysis	Not conducted
Duration of sample storage	66 days (Within the validated 72 days)
Sample storage temperature	-20°C

[1] Validation was conducted for method ALM M-008/1.
[2] Sample duration was not reported.

Reviewer's Comment: For studies CUV006, CUV007 and CUV009, which supported the dose selection, incurred sample reanalysis was not conducted. In addition, the duration of sample storage was not reported for CUV006. The samples from CUV006 were analyzed on multiple days but it is unclear whether each sample was analyzed with the validated 72 days.

While the results of these three studies were used to support the dose selection, in addition to efficacy and safety data, these studies are considered supportive and not pivotal from Clinical Pharmacology perspective and thus the noted deficiencies do not pose significant concerns.

Table 77. Summary of Method Validation Results for BACG-3734 A

Matrix	Human plasma
Extraction procedure	Solid phase extraction
Analyte	Afamelanotide
Internal standard	(b) (4)
Linearity (calibration curve range)	0.25 to 50 ng/mL
LLOQ	0.25 ng/mL
Recovery of analyte (mean, %)	97.6
Accuracy (mean, %)	
Intra-day	Ranged from 95.5 to 108
Inter-day	Ranged from 101 to 104
Precision (% CV)	
Intra-day	Ranged from 2.86 to 14.2
Inter-day	5.88 to 11.0
Stability	Not conducted under the current validation; Reference is made to method validation for ALM MT01

LLOQ = lower limit of quantification; CV = coefficient of variation

Reviewer's Comment: The bioanalysis report for CUV028 was not submitted. For accuracy and precision validation, the FDA guidance recommends at least five replicates in at least three runs. For BACG-3734 A, only 3 replicates from two runs were used. In addition, bioanalysis report for CUV028 is not available.

Table 78. Summary of Method Validation and Performance Results for ALM AFM.3

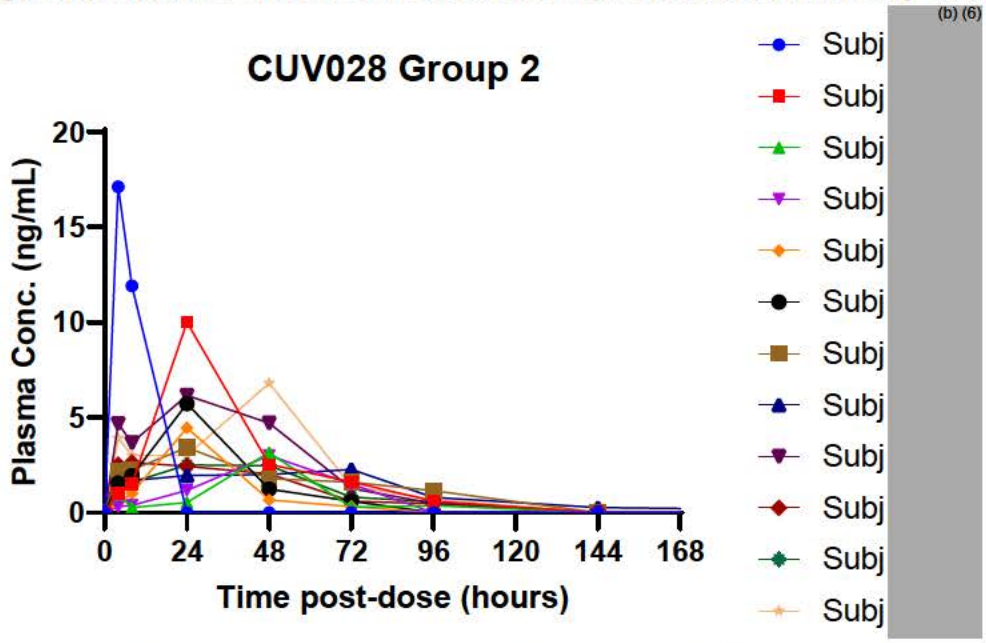
Method Validation	
Matrix	Human plasma
Extraction procedure	Solid phase extraction
Analyte	Afamelanotide
Internal standard	(b) (4)
Linearity (calibration curve range)	0.025 to 5.00 ng/mL
LLOQ	0.025 ng/mL
Recovery of analyte (mean, %)	71.4%
Accuracy (mean, %)	
Intra-day	Ranged from 91 to 110
Inter-day	Ranged from 95 to 108
Precision (% CV)	
Intra-day	Ranged from 1 to 6
Inter-day	Ranged from 5 to 13
Stability in human plasma	Freeze/thaw cycles: 3 cycles Benchtop at room temperature: 4 hours Long-term at -80°C: 68 days Long-term at -20°C: 4 days

Method Validation	
Stability of stock solution in dilution solution (10% methanol/0.1% TFA)	Afamelanotide: Room temperature: 6 hours 4°C: 83 days -20°C: 13 days -80°C: 7 days Internal standard: Room temperature: 6 hours 4°C: NA -20°C: 13 days -80°C: 43 days
Performance – Study CUV038	
Incurred sample reanalysis	
Total no. of incurred sample reanalysis	23
Total no. of sample whose % differences are within 20%	19
% of total no. of samples whose % differences are within 20%	83
Duration of sample storage	Within the validated 72 days First sample drawn: Jul 15, 2011 Last sample analysis: Aug 30, 2011
Sample storage temperature	-80°C

Reviewer's Comment: The method, ALM AFM.3, used to analyze samples from study CUV038 is acceptable.

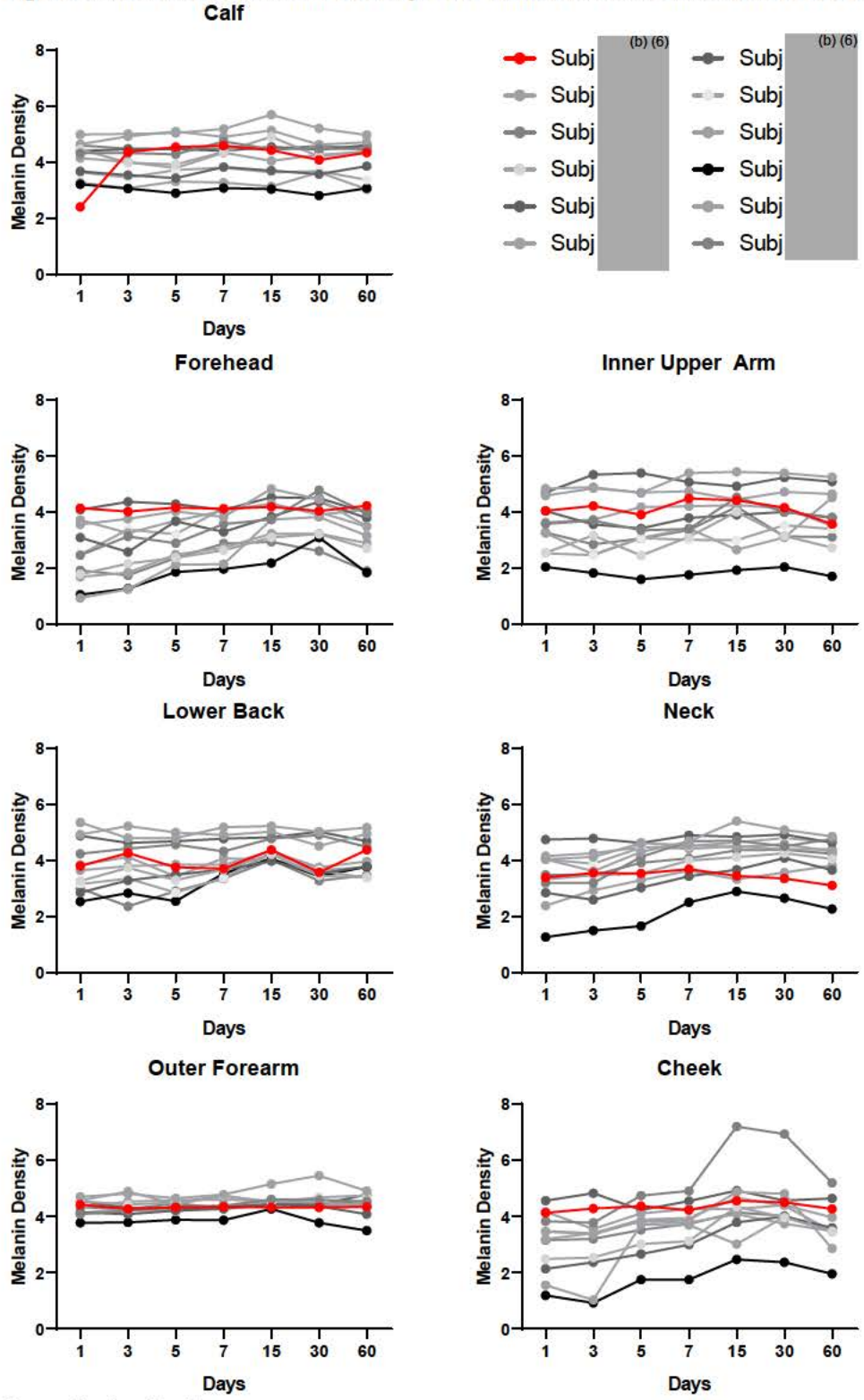
19.4.2. Supporting Graphs

Figure 34. Individual Plasma Concentrations of Afamelanotide From Study CUV028, Group 2



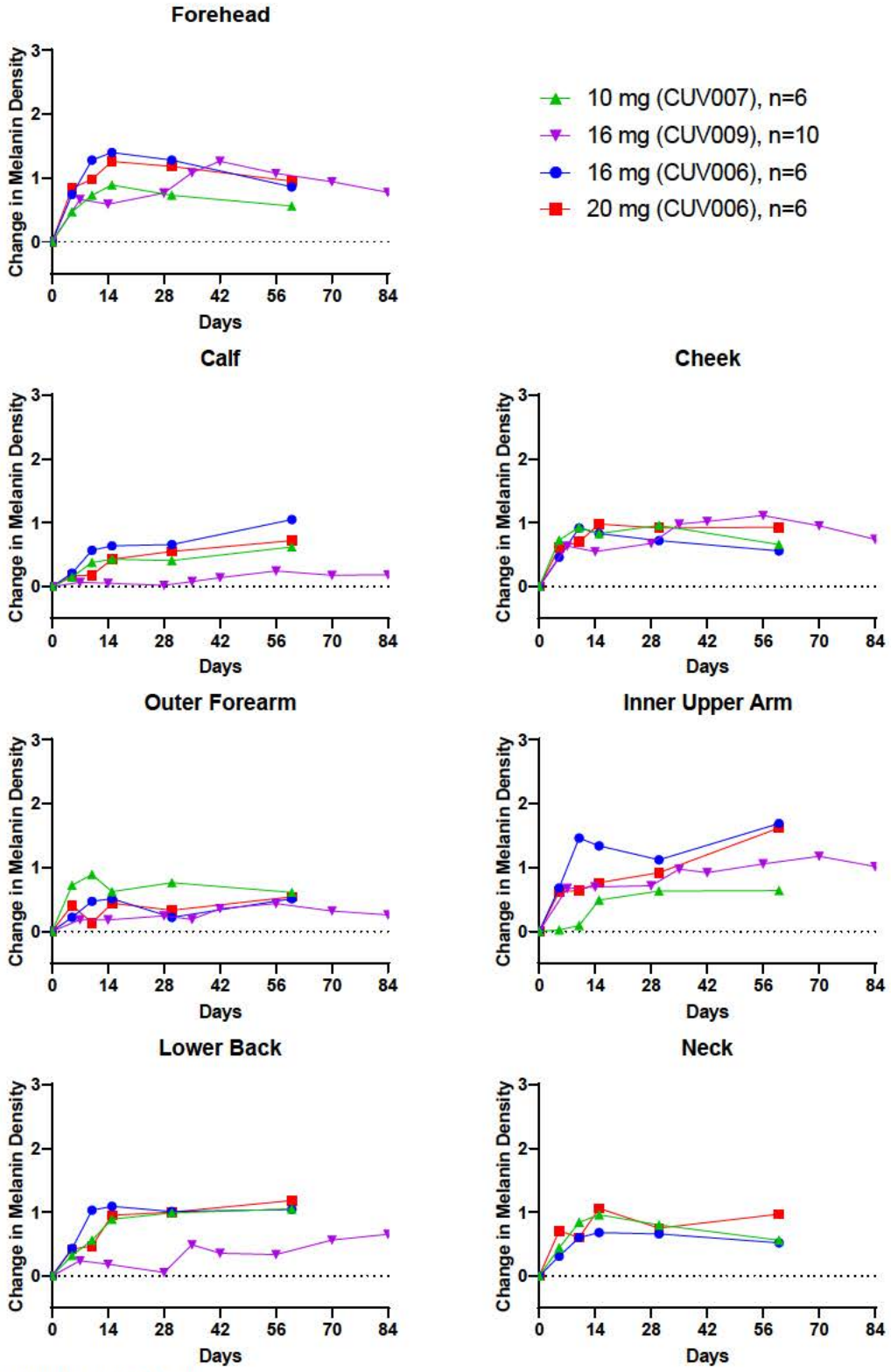
Source: Reviewer's plot; the initial spike of concentration observed in Subj (b) (6) suggests an initial burst release of afamelanotide.

Figure 35. Individual Melanin Density Over Time Per Anatomical Site From Study CUV028, Group 2



Source: Reviewer's plot

Figure 36. Comparison of Change in Melanin Density From Baseline Following Administration of 10 mg, 16 mg, and 20 mg of Afamelanotide Implants Per Anatomical Site



Source: Reviewer's plot

19.5. Clinical/Biostatistics Supporting Data

The following instrument was used to assess EPP Quality of Life in Study 039.

Figure 37. EPP-QoL Questionnaire

1. Over the last two months, how has your well-being been affected by EPP? I have been:	Much better Better Same Worse	-2 -1 0 1
2. Over the last two months, how much has your EPP symptoms influenced your capacity to go to work or school?	Very much A lot A little Not at all	3 2 1 0
3. Over the last two months, how often did you feel the need to seek out shade?	More than usual Same as usual Less than usual Much less than usual	1 0 -1 -2
4. Over the last two months, how much has EPP influenced the choice of the clothes you wear on a sunny day?	Very much A lot A little Not at all	3 2 1 0
5. Over the last two months, how often did you feel you were at risk of developing EPP symptoms?	Very often Often A little Not at all	3 2 1 0
6. Over the last two months, how much has EPP affected any social or leisure activities on a sunny day?	Very much A lot A little Not at all	3 2 1 0
7. Over the last two months, how much has EPP influenced your need to plan before leaving your house?	Very much A lot A little Not at all	3 2 1 0

8. Over the last two months, has EPP limited your ability to undertake activities in a spontaneous manner?	Very much A lot A little Not at all	3 2 1 0
9. Over the last two months, how often have you not worn protective clothing on a sunny day?	Very often Often Not often Not at all	-3 -2 -1 0
10. Over the last two months, how much has EPP interfered with your going shopping or looking after your home (indoors and outdoors) or garden on a sunny day?	Very much A lot A little Not at all	3 2 1 0
11. Over the last two months, how much has EPP prevented you from attending outdoor social activities with family and friends?	Very much A lot A little Not at all	3 2 1 0
12. Over the last two months, how much has EPP limited your amount of outdoor activities?	Very much A lot A little Not at all	3 2 1 0
13. Over the last two months, how often did you experience typical EPP skin complaints?	Very often Often Not often Not at all	3 2 1 0
14. Over the last two months, how much has your quality of life improved?	Very much A lot A little Not at all	-3 -2 -1 0
15. Over the last two months, how much has EPP influenced your method of transportation or seating preference during transportati	Very much A lot A little Not at all	3 2 1 0

EPP = erythropoietic protoporphyria; QoL = quality of life

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CRISTINA Petruccelli Attinello
10/08/2019 09:12:11 AM
Please sign on behalf of Dr. Beitz, if appropriate

KENDALL A MARCUS
10/08/2019 09:33:09 AM