CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210797Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 210797
Assessment # 1

Drug Product Name	Scenesse® (afamelanotide)
Dosage Form	Implant
Strength	16 mg
Route of Administration	Subcutaneous
Rx/OTC Dispensed	Rx
Applicant	CLINUVEL, INC
US agent, if applicable	(b) (4)

Submission(s) Assessed	Document Date	Discipline(s) Affected
Clinical and Nonclinical Overview and Reports	07/31/2017	Clinical
Proprietary Name Request	09/11/2017	All
Quality Information	10/30/2017	OPQ
Quality Information	11/21/2017	OPQ
Quality Information	12/04/2017	ONDP
Clinical Study Reports	06/21/2018	Clinical
Clinical Study Reports	07/23/2018	Clinical
Quality Information	07/25/2017	ONDP
Quality Information	08/03/2017	ONDP and OPF
Clinical Study Reports	08/07/2018	Clinical
Clinical Study Reports	08/10/2018	Clinical
Clinical Study Reports	08/13/2018	Clinical
Form 3674	08/15/2018	Clinical
NDA Submission	11/08/2018	OPQ and Clinical
Request for Advice (Quality)	12/14/2018	OPF
Response to Quality Information Request	01/16/2019	OPQ All

Response to Quality Information Request	01/18/2019	ONDP
Clinical Study Reports	01/18/2019	Clinical
Clinical Study Reports	01/23/2019	Clinical
Information for Clinical Pharmacology and Cardiac Safety	01/25/2019	Clinical
Clinical Study Reports	01/25/2019	Clinical
Response to Quality Information Request	01/28/2019	ONDP
Clinical Study Reports	01/30/2019	Clinical
Clinical Study Reports	02/11/2019	Clinical
Response to Clinical Information Request	02/13/2019	Clinical
Response to Clinical Information Request - Biometrics	02/21/2019	Clinical
Response to Quality Information Request	02/28/2019	ONDP
Response to Clinical Information Request	03/01/2019	Clinical
Response to Quality Information Request	02/28/2019	ONDP
Labeling	03/12/2019	All
Response to Quality Information Request	03/18/2019	CDRH
Follow-up to Teleconference 03/19/2019	03/22/2019	Clinical
Follow-up to Mid-cycle T-Con	04/02/2019	All
Response to Quality Information Request	04/10/2019	ONDP and CDRH
Labeling	04/17/2019	All
Response to Quality Information Request	04/23/2019	ONDP
Response to Quality Information Request	04/23/2019	DMA
Response to Quality Information Request	04/26/2019	DMA
Response to Quality Information Request	05/06/2019	ONDP and CDRH
Device Study	05/10/2019	CDRH
Response to Quality Information Request	05/10/2019	Biopharmaceutics

Response to Quality Information Request	05/14/2019	ONDP and CDRH
Response to Quality Information Request	05/15/2019	ONDP
Response to Quality Information Request	05/15/2019	ONDP and CDRH
Response to Clinical Information Request – Major Amendment	06/03/2019	Clinical - All
Response to Quality Information Request	06/04/2019	ONDP
Response to Quality Information Request	06/20/2019	ONDP
Labeling	06/24/2019	All
Response to Quality Information Request	07/16/2019	ONDP
Response to Quality Information Request	07/22/2019	ONDP, CDRH, and Clinical
Response to Quality Information Request	07/29/2019	ONDP
Response to Quality Information Request	08/01/2019	ONDP
Response to Quality Information Request	08/01/2019	Biopharmaceutics
Response to Quality Information Request	08/08/2019	ONDP
Response to Quality Information Request	09/10/2019	ONDP, CDRH and Clinical
Response to Quality Information Request	09/13/2019	ONDP and OPF
Response to Quality Information Request	09/18/2019	ONDP
Response to Quality Information Request	09/19/2019	OPF and DMA
Response to Quality Information Request	09/20/2019	ONDP, OPF, and DMA
Labeling	09/24/2019	All
Container and Carton Labels	09/27/2019	All
PMR/PMC General Correspondence	09/30/2019	Clinical
Container and Carton Labels	10/01/2019	All
PI Labeling and Container/Carton Labels	10/3/2019	All

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Joseph Leginus, Ph.D.	Donna Christner, Ph.D.
Drug Product	Hong Cai, Ph.D.	Moo-Jhong Rhee, Ph.D.
Manufacturing	Youmin Wang, Ph.D.	Yubing Tang, Ph.D.
Microbiology	Hemlata Tamta, Ph.D.	Nandini Bhattacharya, Ph.D.
Biopharmaceutics	Vidula Kolhatkar, Ph.D.	Tapash Ghosh, Ph.D.
Regulatory Business Process Manager	Bamidele (Florence) Aisida, Pharm. D., BCPS	
Application Technical Lead	Hamid R. Shafiei, Ph.D.	
Laboratory (OTR)		
Environmental	Hong Cai, Ph.D.	Moo-Jhong Rhee, Ph.D.

U.S. FOOD & DRUG ADMINISTRATION

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	Adequate	February 7, 2019	Reviewed by: Joseph Leginus, PhD
	III			---	---	Information provided in the NDA is sufficient
	III			---	---	Information provided in the NDA is sufficient
	IV			Adequate	April 19, 2019	Reviewed by: Hong Cai, PhD

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
N/A		

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH-ODE	N/A			
CDRH-OC	N/A			
Clinical	N/A			
Other	N/A			

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

- The applicant of this 505(b)(1) new drug application 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**.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The applicant, CLINUVEL, INC., has submitted this 505(b)(1) new drug application for Scenesse® (afamelanotide) implant,16 mg. Scenesse® is indicated for pain-fre (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.

EPP is a rare genetic disorder which arises from a deficiency in the enzyme ferrochelatase leading to accumulation of abnormally high levels of protoporphyrin IX (PPIX) in the red blood cells (erythrocytes), plasma, and tissues. Severe phototoxicity in EPP patients is caused by the light-induced excitation of PPIX which dissipates its excess energy by reacting with biological structures of human soft tissues. Indirect reaction of the activated PPIX with molecular oxygen leads to formation of excited oxygen states, such as singlet oxygen, causing acute symptoms described as deep burning sensations, at times accompanied by pruritus and edema in EPP patients.

The active ingredient, afamelanotide is a 13-amino acid linear peptide and is a structure analogue of the endogenous compound α-melanocyte

stimulating hormone (α-MSH). Afamelanotide for this drug product is produced as its acetate salt and has been classified as a new molecular entity (NME). Afamelanotide acts as a melanocortin-1 receptor (MC1R) agonist increasing the level of eumelanin that provides photoprotection through different mechanisms. Although afamelanotide is eliminated from the body within 7 to 10 days, the implant provides with a pharmacodynamic characteristics that persist for about 2 months.

Currently, there are no approved drugs for prevention of phototoxicity and anaphylactoid reactions in the EPP patients. Therefore, this application was granted fast-track designation and has been submitted as the rolling review application with a priority review status. The active ingredient afamelanotide has also been granted orphan-drug designation.

Implants are individually packaged into a 5 mL, 20 mm, USP Type I amber glass vials sealed with rubber stoppers with the aluminum overseal and stored at 2ºC - 8ºC.

Proposed Indication(s) including Intended Patient Population	Pain-fre (b) (4) exposure in adult patients with erythropoietic protoporphyria
Duration of Treatment	As prescribed by the physician
Maximum Daily Dose	One implant every 2 months
Alternative Methods of Administration	None

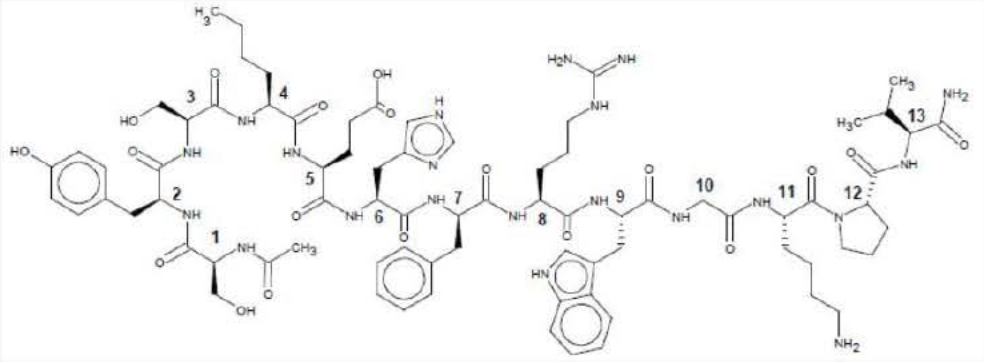
B. Quality Assessment Overview

Drug Substance: Adequate

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 is a white to off-white amorphous powder that melts/decomposes at 167ºC and has the optical rotation $[\alpha]_D^{20ºC} = -68º \pm 3º$ (C=1, water, 20ºC). It is hygroscopic and freely soluble in water, 1% acetic acid, and methanol, slightly soluble in ethanol, and practically insoluble in acetonitrile and 1-octanol.

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:



Afamelanotide acetate has the molecular formula of $C_{78}H_{111}N_{21}O_{19} \cdot xCH_3COOH$ with average x = 3.7 and the average molecular weight of 1868.85 g/mol.

Afamelanotide drug substance for this new drug application is manufactured by [redacted] (b) (4) It is tested and released according to a specification that includes testing and acceptance criteria for all physical and chemical attributes essential for the assurance of the identity, strength, purity and quality of the drug substance. The information regarding the manufacture of afamelanotide is provided in DMF [redacted] (b) (4) was reviewed by the Drug Substance Reviewer, Dr. Joseph Leginus on February 7, 2019 and was found to be adequate.

In summary, Dr. Leginus has found the information provided in DMF [redacted] (b) (4) and the drug substance module of the application adequate to support approval of this NDA.

Drug Product: Adequate

The drug product, SCENESSE®(afamelanotide) implant, 16mg is a white to off-white, sterile, biodegradable solid implant intended for subcutaneous administration. 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 15.3-19.5 mg of biodegradable/bioresorbable copolymers, poly (DL-lactide-co-glycolide) as inactive ingredients. Since the implant is

biodegradable, there will be no need for the removal of the implant from the patients. The implants are individually packaged in Type I amber glass vials sealed with rubber stoppers with aluminum overseal. The device intended for the implantation is not co-packaged with drug product. The proposed implantation device is currently being marketed in the United States and are available for use to the healthcare professionals. The information regarding the use of the proposed device and its compatibility with drug product has been reviewed by the CDRH Reviewer, Dr. Peter Petrochenko. Dr. Petrochenko has recommended that proposed implantation device is approvable. The information regarding the implantation device is described in the appropriate sections of the prescribing information (PI).

(b) (4)

The drug product, implant is manufactured and tested for release and stability by (b) (4) It is tested and released 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. The applicant has provided sufficient stability data in support of the proposed drug product expiration dating period, 48 months.

(b) (4)

Additionally, the applicant provided that the proposed new sterilization site has been previously approved for the release of the drug product to the European market. Although the information regarding the new sterilization site was submitted to the Agency late in the review cycle, because the drug product is for unmet medical need and currently the patients needing this drug have to travel to Europe to receive the treatment, the Agency decided to complete the review of the information regarding the new sterilization site during the current review cycle. The information regarding the new sterilization facility is captured in the Facilities Chapter of the IQA and the validation of the sterilization process at the new site is captured in the Microbiology Chapter of the IQA with "Acceptable" recommendation.

In summary, the drug product section of this application has been reviewed by the Drug Product Reviewer, Dr. Hong Cai. Dr. Cai has recommended the approval of this application with an expiration dating period of 48 months from the drug product perspective. Dr. Cai has also recommended granting the applicant's request for categorical exclusion from preparation of the environmental assessment based on the email recommendation from the Environmental Assessment Reviewer, Dr. James Laurenson (see Appendix IV of the Drug Product Chapter of IQA). Dr. Cai's review is provided in the Drug Product Chapter of the IQA.

Labeling: Adequate

The CMC sections of the Prescribing Information (PI) as well as the immediate container and carton labels have been reviewed by the Drug Product Reviewer, Dr. Hong Cai. Dr. Cai has found that the final PI as well as immediate container and carton labels submitted by the applicant have satisfactorily resolved all outstanding issues noted in her Labeling Review #1, and therefore, she has recommended approval of this application from the CMC labeling/labels perspective (see Dr. Cai's addendum dated October 3, 2019 to her Labeling Review # 1).

Manufacturing: Adequate

The drug product, Scenesse® (afamelanotide) implant,16 mg is manufactured (b) (4) All components of the drug

(b) (4)

(b) (4)

product. The manufacturing process of this drug product have been reviewed by the Process Reviewer, Dr. Youmin Wang. Dr. Wang has concluded that the manufacturing process and critical process steps are adequately controlled by the process parameters and in-process testing, and she has recommended that proposed manufacturing process is adequate to support the approval of this application. Dr. Wang's review of the manufacturing process is provided in the Process Chapter of the IQA.

The facilities involved in this application have also been reviewed by Dr. Youmin Wang. Dr. Wang has concluded that all facilities involved in this application, including the proposed new sterilization facilit (b) (4) submitted in the amendment dated September 13, 2019 are adequate, in compliance, and support the approval of this application from the facilities perspective.

Biopharmaceutics: Adequate

The Biopharmaceutics review of this application was mainly focused on the controlled-release aspect of the drug product, Scenesse® (afamelanotide) implant,16 mg through the evaluation of the proposed in-vitro release method and acceptance criteria. Based on the review of the in-vitro release data from the developmental and registration batches of the drug product, the following in-vitro release method and 3-tiered acceptance criteria were recommended by the Agency and agreed by the applicant:

Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Acceptance criteria
Screw capped glass bottles	120 oscillations per minute	0.05M phosphate buffer, pH 6.8 37 ± 2 °C	25 mL	2 Hours (b) (4)% 24 h (b) (4)% 96 h (b) (4)%

It should be noted that in-vitro release data from some of the stability time-points for some of the registration batches although met the in-vitro acceptance criteria that were in place at the time of testing, do not comply

with the agreed tightened in-vitro release acceptance criteria provided in the table above. However, based on review of entirety of the in-vitro-release data provided in the application and discussions with applicant, it was concluded that the tightened in-vitro release acceptance criteria in the table above should be used as the in-vitro release acceptance criteria for the release of commercial batches of drug product.

The Biopharmaceutics section of this application was reviewed by the Biopharmaceutic Reviewer, Dr. Vidula Kolhatkar. Dr. Kolhatkar has found the information submitted in Biopharmaceutics section of the application to be adequate to support the approval of this application. Dr. Kolhatkar review is provided in the Biopharmaceutics Chapter of the IQA.

Microbiology (if applicable): Adequate

The package integrity, sterilization method, and sterilization process validation at the original site where the registration batches of drug product were sterilized as well as the newly proposed site where commercial batches will be sterilized have been reviewed by the Microbiology Reviewer, Dr. Hemlata Tamta. Dr. Tamta has found the sterilization method, sterilization process validation at both sites and package integrity are adequate to support the approval of Scenesse® (afamelanotide) implant,16 mg, a sterile drug product intended for subcutaneous implementation. Dr. Tamta's review is provided in the Microbiology Chapter of the IQA.

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
[redacted] (b) (4)				Acceptable	None

D. List of Deficiencies: None

Application Technical Lead:
Hamid Shafiei, Ph.D.
Branch V/ DNDP II/OPND/OPQ

Hamid Shafiei

Digitally signed by Hamid Shafiei
Date: 10/03/2019 11:39:42AM
GUID: 507d824300005f344cf8b5e5989f0057

LABELING

I. Package Insert

1. *Highlights of Prescribing Information*

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SCENESSE® safely and effectively. See full prescribing information for SCENESSE®.

SCENESSE® afamelanotide (as afamelanotide acetate) 16 mg implant
Initial U.S. Approval: YYYY

----------DOSAGE FORMS AND STRENGTHS----------

- The implant contains 16 mg of afamelanotide. (3)

Item	Information Provided in NDA	Reviewer's Assessment
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))		
Proprietary name and established name	Scenesse ® afamelanotide (as afamelanotide acetate) 16 mg implant	**Not Satisfactory** Revise to "Scenesse ® (afamelanotide) Implant"
Dosage form, route of administration	implant	**Not Satisfactory** Route of administration is not provided. Add the following: "For subcutaneous use only"
Controlled drug substance symbol (if applicable)	N/A	**N/A**
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))		
Summary of the dosage form and strength	The implant contains 16 mg of afamelanotide. (3)	**Not Satisfactory** Revise to: "Implant: 16 mg of afamelanotide." To be concise per labeling review tool.

2. Full Prescribing Information

Section 2 Dosage and Administration

1 Page of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c) (12))		
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	See the applicant provided "Dosage and Administration" information above.	**Deferred to CDRH and Clinical for comments.** This NDA includes only the quality information of the proposed drug product Scenesse implant. It is not filed as the combination product. The dosing device is not co-packaged with the drug product. A dosing device consultation is requested to CDRH. Refer to the review comments from CDRH and the Clinical Team for Section 2 of PI.

3 DOSAGE FORMS AND STRENGTHS

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))		
Available dosage forms	Not provided	**Not Satisfactory** Add the dosage form "implant".
Strengths: in metric system	16 mg of afamelanotide (as afamelanotide acetate)	**Satisfactory**
Active moiety expression of strength with equivalence statement (if applicable)	16 mg of afamelanotide (as afamelanotide acetate)	**Not Satisfactory** The equivalency statement of afamelanotide acetate salt is not provided. It is recommended to include the acetate salt equivalency statement, such as " 16 mg of afamelanotide, equivalent to 18 mg of afamelanotide acetate." See review comments for the equivalency value (18 mg) recommended.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	SCENESSE® is a solid white to off-white rod approximately 1.7 cm in length an (b) (4) mm in diameter and contains 16 mg of afamelanotide (as afamelanotide acetate) and the biodegradable excipient poly(DL-lactide-co-glycolide).	**Satisfactory** The description of the identifying characteristics of the drug product dosage form is provided. The approximate length of 1.7 cm is not included in the drug product specification. The applicant should provide the justification or include the test for the implant rod in the release specification to support this statement.

11 DESCRIPTION

Afamelanotide acetate is a peptide containing 13 amino acids with molecular formula $C_{78}H_{111}N_{21}O_{19}$ (molecular weight 1645.84) · $(C_2H_4O_2)_x$ (b) (4)

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c) (12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))		
Proprietary name and established name	SCENESSE® afamelanotide 16 mg implant	**Not Satisfactory** Revise to: "SCENESSE® (afamelanotide) implant"
Dosage form and route of administration	SCENESSE® afamelanotide 16 mg implant is a controlled release implant for subcutaneous administration.	**Satisfactory**
Active moiety expression of strength with equivalence statement (if applicable)	Not provided.	**Not Satisfactory** Each SCENESSE® implant contains 16 mg of afamelanotide, equivalent to 18 mg of afamelanotide acetate.
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	The implant core comprises the drug substance admixed with a poly(DL-lactide-co-glycolide) bioresorbable copolymer (15.3-19.5 mg/dose).	**Not Satisfactory** Revise to the following: "Each implant core comprises the drug substance admixed with a poly (DL-lactide-co-glycolide) (b) (4) [redacted] 15.3-19.5 mg/implant."
Statement of being sterile (if applicable)	Not Provided.	**Not Satisfactory** Add sterile statement.
Pharmacological/ therapeutic class	Afamelanotide is a melanocortin 1 receptor agonist and structural analog of α-melanocyte stimulating hormone (α-MSH).	**Satisfactory**

Chemical name, structural formula, molecular weight	Afamelanotide acetate is a peptide containing 13 amino acids with molecular formula $C_{78}H_{111}N_{21}O_{19}$ (molecular weight 1645.84) · $(C_2H_4O_2)_x$ (b) (4) (b) (4)	**Not Satisfactory** Add "the active ingredient" in front of "Afamelanotide acetate" for clarity purpose. See the comment from the drug product reviewer Dr Joseph Leginus for the value of x (b) (4)
If radioactive, statement of important nuclear characteristics.	NA	NA
Other important chemical or physical properties (such as pKa or pH)	Not provide.	**Not Satisfactory** Add the important chemical or physical properties, such as the solubility, pKa or pH.

16 HOW SUPPLIED/STORAGE AND HANDLING

SCENESSE® (NDC XXXX-XXXX-XX) is supplied in (b) (4) Type I amber glass vial sealed with a PTFE coated rubber stopper.

(b) (4) Store in a refrigerator at 2°C – 8°C (36°F)

(b) (4)

Manufactured for:

CLINUVEL, INC.

CLINUVEL

Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))		
Strength of dosage form	The only available packaging configuration is of one pack of one vial containing one 16 mg afamelanotide implant.	**Satisfactory**
Available units (e.g., bottles of 100 tablets)	The only available packaging configuration is of one pack of one vial containing one 16 mg afamelanotide implant.	**Satisfactory**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	SCENESSE® (NDC XXXX-XXXX-XX) is supplied in a single-dose Type I amber glass vial sealed with a PTFE coated rubber stopper.	**Not Satisfactory** Add the description and the identification characteristics of the implant.
Special handling (e.g., protect from light)	Not provided.	**Not Satisfactory** Add the following statement: Protect from light.
Storage conditions	Store in a refrigerator at 2°C – 8°C (36°F).	**Not Satisfactory** The storage condition should use the USP standard storage language. Add "protect from light".
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Manufactured for CLINUVEL, IND.	**Not Satisfactory** Provide the manufacturer location (street address, city, state and zip code and the country).

Reviewer's Assessment of Package Insert: ***Inadequate***

Review comments are made based on the prescribing information submitted on April 17, 2019 (SN0034) and per 21 CFR Part 201 as well as the FDA Labeling Review Tool (October 2018 version).

The proposed drug product, Scenesse (afamelanotide implant, 16 mg) is designed to be an extended release dosage form with one implant dosed every 60 days. The active ingredient is afamelanotide acetate which is an NME. Per USAN definition, afamelanotide acetate molecule formula is $C_{78}H_{111}N_{21}O_{19}\cdot(C_2H_4O_2)_n$ and the exact number of acetates associated with each afamelanotide molecule is not defined. The

applicant, CLINUVEL, recommends usin (b) (4) mg of afamelanotide acetate as the equivalency statement value for 16 mg afamelanotide in each implant in the labeling/label (Response to FDA IR Item #2 dated August 03, 2018, SN0008). The drug substance reviewer, Dr. Joseph Leginus indicated that 16 mg afamelanotide is equivalent to 18.2 mg afamelanotide as the acetate salt based on the average number of acetates (b) (4) measured in 6 batches of the peptide provided in the NDA (via email on 1/31/2019). Therefore, Dr. Leginus recommends 18 mg instead o (b) (4) mg as the number value of the equivalent amount in the equivalency statement (Appendix I). Since the ratio of afamelanotide to acetate could vary from one batch to another, the recommended 18 mg of afamelanotide acetate equivalent to 16 mg of afamelanotide is deemed adequate as the salt to free base equivalency statement per implant for the labeling purpose.

As of this review, the Prescribing Information is not deemed satisfactory from the CMC labeling perspective (See "**List of the deficiencies**" at the end of this review).

II. Labels:

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size, prominence)	SCENESSE® Afamelanotide implant	**Satisfactory**
Dosage strength Active moiety expression of strength with equivalence statement (if applicable) in the side panel.	16 mg	**Not Satisfactory** The acetate salt equivalence statement is not included.
Net quantity of dosage form	Not provided	**Not Satisfactory** Add net quantity of one implant per vial.
"Rx only" displayed prominently on the main panel	Not provided	**Not Satisfactory** Add "Rx only"
Lot number and expiration date	BN Exp	**Satisfactory**
Storage conditions Special handling, e.g., "Dispense in tight and light resistant container as defined in USP".	Not provided.	**Not Satisfactory** Add storage condition
Bar code (21CFR 201.25)	Presented	**Satisfactory**
NDC number (21 CFR 207.35(b)(3)(i))	NDC XXXX-XXXX-XX	**Satisfactory** Space holder is provided.
Manufacturer/distributor's name	Manufactured for CLINUVEL, INC. by Evonik Corporation	**Satisfactory**
Quantitative ingredient information (injectables)	Not provided.	**Not Satisfactory** Add in the quantitative ingredient information for this subcutaneous route administration drug.
Statement of being sterile (if applicable)	Not Provided	**Not Satisfactory** Add in "Sterile"
Statement of Maximum level of aluminum present at expiry of all SVP's used in the preparation of TPN solutions per 21. CFR 201.323 (c).	N/A	**N/A**

2. Carton Label (SN0005, submitted on June 21, 2018).

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size, prominence)	SCENESSE® 16 mg afamelanotide implant	**Not Satisfactory** The format should be revised as the following: SCENESSE® 16 mg (afamelanotide) implant The font size of the established name afamelanotide should be at least half of the size of the proprietary name SCENESSE per 21 CFR 201.10(g)(2).
Dosage strength Active moiety expression of strength with equivalence statement (if applicable) in the side panel.	16 mg	**Not Satisfactory** Add the equivalent statement of acetate salt to the side panel as: Each implant contains 16 mg of afamelanotide (equivalent to 18 mg of afamelanotide acetate).
Net quantity of dosage form	1 implant	**Satisfactory**
"Rx only" displayed prominently on the main panel	Rx only	**Satisfactory**
Lot number and expiration date	Not provided.	**Not Satisfactory** Add the lot number and expiration date.
Storage conditions Special handling, e.g., "Dispense in tight and light resistant container as defined in USP".	Store at 2°C – 8°C (36 – 46°F).	**Not Satisfactory** Revise to be consistent with the approved storage condition statement in Section #16 of PI.
Bar code (21CFR 201.25)		**Satisfactory** Provided 2D code space holder
NDC number (21 CFR 207.35(b)(3)(i))	NDA XXXX-XXXX-XX	**Satisfactory** NDC number space holder is provided.

Manufacturer/distributor's name	Manufactured for CLINUVEL, INC. by: (b) (4) [redacted] (b) (4) [redacted]	**Satisfactory**
"See package insert for dosage information"	Usual Adult Dose; see package insert	**Satisfactory**
Quantitative ingredient information (injectables)	**Each implant contains:** **16 mg afamelanotide** (as afamelanotide acetate) **Poly(DL-lactide-co-glycolide):** **15.3–19.5 mg**	**Satisfactory**
Statement of being sterile (if applicable)	Not Provided.	**Not Satisfactory** Add the statement of "Sterile"

Reviewer's Assessment of Labels: ***Inadequate from CMC perspective***
The above review comments for the container and closure labels are based on the submission of NDA210797 on June 21, 2018 (SN0005), and as of this review, the labels for container and cartons are not deemed satisfactory from CMC perspective (see the following **List of deficiencies**).

List of Deficiencies:

A. Regarding Prescription Information:

1. *Revise the product title to include the route of administration: SCENESSE® (afamelanotide) implant, for subcutaneous administration.*

2. *Revise Section 3: DOSAGE FORMS AND STRENGTHS statement to include the dosage form of implant. It is recommended to include the salt equivalency statement of the active moiety afamelanotide.*

3. *Provide the justification and data for your statement of "SCENESSE® is a solid white to off-white rod approximately 1.7 cm in length" in Section #3 and*

#11. The length control is not included in the drug product release specification with the drug product release specification at present (SN0002 dated on October 30, 2017).

4. *In the "Description" section (#11):*

   a) *Include the presentation of the proprietary name and established name as SCENESSE® (afamelanotide) implant.*

   b) [redacted] (b) (4)

   c) *Add in the strength equivalency statement of afamelanotide per USP salt policy: Each implant contains 16 mg of afamelanotide, equivalent to approximately 18 mg of afamelanotide acetate.*

   d) *The statement of the excipients and their amount per implant should be revised as following: Each implant contains a total of 15.3-19.5 mg of poly (DL-lactide-co-glycolide) bioresorbable copolymer* [redacted] (b) (4) [redacted] (b) (4)

   e) *Add in the statement: "The active ingredient is afamelanotide acetate" for clarify purpose.*

   f) *Add sterile statement for the implant.*

   g) *Add the important physical and chemical properties for the drug substance afamelanotide acetate, such as the appearance, solubility, pKa and the polymorph form information.*

5. *In the "How supplied/storage and Handling "section (#16):*

   a. *Add the presentation of both the proprietary name and the established name.*

   b. *Per USP salt policy. add in the strength equivalency statement of afamelanotide to afamelanotide acetate per implant.*

   c. *Add in the description of the implant, such as the color, shape, sterility and size.*

   d. *Add "protect from light" to the storage condition statement.*

6. *Add in the manufacturer location information (street address, city, state and zip code and the country) at the end of PI (after Section 17 "Patient Counseling Information").*

B. Regarding Labels

For the vial label:

1. *The storage condition statement should be consistent with the statement in Section 16 of PI. Include "Protect from light".*

2. *Add the statement "See package insert for dosage information" to the carton label.*

3. *Add the net quantity of one implant per vial.*

For the carton label:

1. *Add the lot number and expiration date.*

For All Labels:

1. *The product title should be revised to*

   "SCENESSE® (afamelanotide) implant.

2. *The established name is not at least half the size of the proprietary name. Revise the established name to be in accordance with 21 CFR 201.10(g)(2).*

3. *Add "Sterile" to the container and carton labels.*

4. *Add the strength equivalency statement of afamelanotide to afamelanotide acetate per USP salt policy to the side panels of the carton and container labels.*

5. *The storage statement should be consistent with the content in Section 16 of PI.*

Overall Assessment and Recommendation:

From the ONDP perspective, this application is ***not*** deemed ready for approval in its present form per 314.125(b)(6) until the deficiencies delineated above are satisfactorily resolved.

Primary Labeling Reviewer Name and Date:

Hong Cai, Ph.D.
Drug product Reviewer
Branch V/DNDP II/ONDP/OPQ

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

I agree with Dr. Cai's assessment on the labeling and labels and concur with her recommendation that this NDA is not ready for approval as of this review.

Moo-Jhong Rhee, Ph.D.
Chief
Branch V/DNDP II/ONDP/OPQ

Appendix I:

From: Leginus, Joseph
Sent: Thursday, January 31, 2019 2:17 PM
To: Cai, Hong <Hong.Cai@fda.hhs.gov>
Subject: RE: NDA 210797 Label

Hi Hong:

Here is a version of the DS portion of the Description in the PI for afamelanotide that you might consider:

> Afamelanotide is a white to off-white powder with a molecular formula of $C_{78}H_{111}N_{21}O_{19}$•x$CH_3COOH$ isolated as the acetate salt with a molecular weight of 1646.9 (free base).
>
> The amino acid sequence of afamelanotide is:
> Ac-Ser-Tyr-Ser-Nle-Glu-His-(D)Phe-Arg-Trp-Gly-Lys-Pro-Val-NH_2•xCH_3COOH where x = (b) (4)
>
> Each SCENESSE® (afamelanotide) implant contains 16 mg afamelanotide (equivalent to 18 (b) (4) mg afamelanotide as the acetate salt)…

(the equivalency factor (b) (4) was based on the average number of acetates (b) (4) measured in 6 batches of afamelanotide DS provided in the NDA).

Joe

From: Leginus, Joseph
Sent: Thursday, February 07, 2019 12:48 PM
To: Cai, Hong
Cc: Shafiei, Hamid
Subject: RE: NDA 210797 Label

My recommendation would be to use 18 mg as the equivalency value. Since the strength of the drug is 16 mg, the equivalency should also only have 2 significant digits. This should solve the problem.

From: Cai, Hong
Sent: Thursday, February 7, 2019 12:39 PM
To: Leginus, Joseph <Joseph.Leginus@fda.hhs.gov>
Cc: Shafiei, Hamid <Hamid.Shafiei@fda.hhs.gov>
Subject: RE: NDA 210797 Label

Joe,
I am fine to convey at the labeling review stage.
Can you please clarify whether you would accept the applicant proposed number value of (b) (4) mg?
I need a clarification since this peptide acetate salt number is a range. As we communicated before, I thought you prefer to use the average number value instead of the range due to the Agency previous experience. Thanks.
Hong

Hong Cai

Digitally signed by Hong Cai
Date: 4/26/2019 02:36:52PM
GUID: 55919d6500e16bdaad5825645e4f22ff

Moo Jhong Rhee

Digitally signed by Moo Jhong Rhee
Date: 4/26/2019 03:21:06PM
GUID: 502d0913000029f9798ca689a802fa55

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: **October 3, 2019**

From: **Hong Cai, Ph.D.**
Drug Product Reviewer
Office of New Drug Products
Branch V/DNDP II

Through: **Moo-Jhong Rhee, Ph.D.**
Chief, Branch V
Office of New Drug Products
Branch V/DNDP II

To: **CMC Labeling Review #1 of NDA210797**
for SCENESSE® (afamelanotide) implant, 16 mg

Subject: **Final Recommendation - APPROVAL**

At the time when Labeling Review #1 of NDA210797 was completed on April 26, 2019, this NDA was not recommended for approval in its present form per 21 CFR 314.125(b)(8). Specifically, it was noted that labeling (Prescribing Information, container/carton) negotiations had not been completed, and in its present form, the labeling did not comply with the requirements under 21 CFR 201.

This addendum is to document the most updated Prescribing Information of the CMC related sections: the product title in Highlights of Prescribing Information Section and Section #3, #11 and #16 in Full Prescribing Information (**Attachment-1**) and container/carton labels (**Attachment-2**), which were submitted on October 3, 2019 with all CMC labeling/label issues addressed. The documents are on the FDA share point with the link provided by RPM Cristina Attinello via email on October 3, 2019. Afamelanotide is an NME. The conversion equivalency between the drug substance afamelanotide acetate to afamelanotide anhydrous free base is per the recommendation from the drug substance reviewer, Dr. Joseph Leginus via email (**See Attachment-3**). The labeling and labels are now acceptable from the CMC labeling perspective.

Recommendation:

The outstanding CMC label/labeling issues have been satisfactorily resolved. This application is now recommended for **approval** from the labeling/label perspective.

Hong Cai, Ph.D.
Drug Product Reviewer
Branch V, Division II, ONDP

Moo-Jhong Rhee, Ph.D.
Branch Chief
Branch V, Division II, ONDP

Attachment-1:

Sections reviewed in the Package Insert (PI):

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SCENESSE safely and effectively. See full prescribing information for SCENESSE.

SCENESSE® (afamelanotide) implant, for subcutaneous use
Initial U.S. Approval: 2019

----------DOSAGE FORMS AND STRENGTHS----------
Implant: 16 mg of afamelanotide. (3)

Contents in Full Prescribing Information: Contents

3 DOSAGE FORMS AND STRENGTHS

Implant: 16 mg of afamelanotide as a solid white to off-white, bioresorbable, sterile rod approximately 1.7 cm in length and 1.45 mm in diameter.

11 DESCRIPTION

SCENESSE (afamelanotide) implant is a controlled-release dosage form for subcutaneous administration. Afamelanotide is a melanocortin 1 receptor (MC1-R) agonist. The active ingredient afamelanotide acetate is a synthetic peptide containing 13 amino acids with molecular formula $C_{78}H_{111}N_{21}O_{19} \cdot xC_2H_4O_2$ ($3 \leq x \leq 4$). The molecular weight of afamelanotide is 1646.85 (anhydrous free base). Afamelanotide acetate has the following structure:

Ac-Ser-Tyr-Ser-Nle-Glu-His-(D)Phe-Arg-Trp-Gly-Lys-Pro-Val-$NH_2 \cdot$ xCH_3COOH.

Afamelanotide is a white to off-white powder, freely soluble in water. Each SCENESSE implant contains 16 mg of afamelanotide (equivalent to 18 mg of afamelanotide acetate), and 15.3-19.5 mg of poly (DL-lactide-co-glycolide). SCENESSE implant is a single, solid white to off-white, bioresorbable and sterile rod approximately 1.7 cm in length and 1.45 mm in diameter. The implant core comprises of the drug substance admixed with a poly (DL-lactide-co-glycolide) bioresorbable copolymer.

16 HOW SUPPLIED/STORAGE AND HANDLING

SCENESSE (afamelanotide) implant, 16 mg, for subcutaneous administration (NDC 73372-0116-1) is supplied in a Type I amber glass vial sealed with a PTFE coated rubber stopper. Each vial contains one afamelanotide implant and is packaged individually in a cardboard box. SCENESSE implant is a solid white to off-white, bioresorbable and sterile rod approximately 1.7 cm in length and 1.45 mm in diameter.

Store in a refrigerator at 2°C – 8°C (36°F-46°F). Protect from light.

SCENESSE implants are not supplied with an implantation device for subcutaneous administration *[see Dosage and Administration (2)]*.

Manufactured for:

CLINUVEL, INC.
2419 Sharon Oaks Dr
West Menlo Park, CA 94025

Attachment-2:
Carton Labels

(b) (4)

Container (b) (4)

(b) (4)

Attachment-3:

Below is the email from drug substance reviewer Dr. Joseph Leginus. His recommendation regarding the drug substance properties are in Red.

From: Leginus, Joseph
To: Cai, Hong
Subject: RE: INTERNAL Labeling Meeting #1: NDA 210797 Scenesse (afamelanotide) implant, 16 mg (b) (4)
Date: Wednesday, July 10, 2019 8:15:28 AM

Hi Hong:

The recommendations below for the label of afamelanotide are based on the similar peptide, bremelanotide, which was recently approved (NDA 210557):

> **11 DESCRIPTION**
>
> VYLEESI (bremelanotide injection) contains bremelanotide, a melanocortin receptor agonist for subcutaneous administration via an autoinjector. Bremelanotide acetate is a synthetic, cyclic heptapeptide with a free acid at the carboxyl terminus and an acetylated amino group at the amino terminus of the peptide with the following structure:
>
> Ac-Nle-cyclo-(Asp-His-D-Phe-Arg-Trp-Lys-OH) • xCH_3COOH
>
> The molecular formula of bremelanotide acetate is $C_{50}H_{68}N_{14}O_{10} \bullet xCH_3COOH$ (1= x = 2) and the molecular weight is 1025.2 (free base).
>
> …Each pre-filled syringe contains 1.75 mg of bremelanotide (equivalent to 1.89 mg bremelanotide acetate) in 0.3 mL solution.

Joe

From: Cai, Hong
Sent: Tuesday, July 9, 2019 6:55 PM
To: Leginus, Joseph <Joseph.Leginus@fda.hhs.gov>
Subject: RE: INTERNAL Labeling Meeting #1: NDA 210797 Scenesse (afamelanotide) implant, 16 mg (b) (4)

Hi Joe,

Can you please review my edit in Description (Section 11) of PI (link below) for the content related to the API afamelanotide acetate? My modification has been tracked. Please comment as needed. Thanks.

Mainly for the following:

1. Molecular formula of afamelanotide acetate,

   $C_{78}H_{111}N_{21}O_{19} \bullet xCH_3COOH$ (3 = x = 4)

2. Molecular Weight of afamelanotide. Should it be (b) (4) as the

applicant proposed?

The molecular weight of the afamelanotide free base, anhydrous is 1646.85.

3. Is the number of acetate "x = (b) (4) correct?

The average number of acetates is (b) (4) therefore: "x = 3 to 4" is more accurate (as indicated in the molecular formula described in #1).

4. The peptide sequence. Would you agree with my comment on the side?

I agree with your comment about the amino acid sequence. It should be Ac-Ser-Tyr-Ser-Nle-Glu-His-(D)Phe-Arg-Trp-Gly-Lys-Pro-Val-NH_2 • xCH_3COOH.

I don't see the need for chemical/physical properties of the drug substance.

5. Confirm the equivalency statement of afamelanotide to afamelanotide acetate. The current statement of "16 mg of afamelanotide, equivalent to (b) (4) 18 mg of afamelanotide acetate" was based on your recommended before. Also would you recommend to keep " (b) (4) before "18mg " in the statement? Thanks.

SCENESSE® (afamelanotide) implant contains 16 mg of afamelanotide (equivalent to 18 mg of afamelanotide acetate) and ...

The link for PI:

UPDATED Draft Label: Scenesse

Hong Cai

Digitally signed by Hong Cai
Date: 10/03/2019 10:29:58AM
GUID: 55919d6500e16bdaad5825645e4f22ff

Moo Jhong Rhee

Digitally signed by Moo Jhong Rhee
Date: 10/03/2019 10:31:16AM
GUID: 502d0913000029f9798ca689a802fa55

BIOPHARMACEUTICS

Product Background: ORIG-1

NDA/ANDA: NDA 210797

Drug Product Name / Strength: Scenesse (afamelanotide) implant/16 mg

Route of Administration: Subcutaneous

Indication (b) (4) **adult patients with erythropoietic protoporphyria (EPP)**

Applicant Name: Clinuvel Inc.

Review Recommendation: *Adequate*

Review Summary: The proposed product contains a new drug substance, Afamelanotide, a structural analogue of the endogenous compound α-melanocyte stimulating hormone (α-MSH). Afamelanotide 16 mg Implant is formulated as a sterile bioresorbable controlled release implant intended for subcutaneous administration. The implant core comprises the drug substance admixed with a poly(DL-lactide-coglycolide) bioresorbable copolymer (b) (4) (b) (4)

The biopharmaceutics review is focused on the evaluation of the proposed in vitro release method and acceptance criteria and bridging to support a level -2 site change. The following table represents the approved in vitro release method and acceptance criteria:

Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Acceptance criteria
Screw capped glass bottles	120 oscillations per minute	0.05M phosphate buffer, pH 6.8 37 ± 2 °C	25 mL	2 Hours (b) (4)% 24 h (b) (4)% 96 h (b) (4)%

The applicant provided adequate information to bridge the manufacturing site change.

NDA 210797 for Scenesse (afamelanotide) implant/16 mg is Adequate from Biopharmaceutics perspective.

List Submissions being reviewed (table):

10/30/2017	Application 210797 - Sequence 0002 - 0002 (3) 10/30/2017 ORIG-1 /Quality/Quality Information
07/25/2018	Application 210797 - Sequence 0007 - 0007 (8) 07/25/2018 ORIG-1 /Quality/Response To Information Request
08/03/2018	Application 210797 - Sequence 0008 - 0008 (9) 08/03/2018 ORIG-1 /Quality/Response To Information Request
11/08/2018	Application 210797 - Sequence 0013 - 0013 (14) 11/08/2018 ORIG-1 /New/NDA
03/04/2019	Application 210797 - Sequence 0028 - 0028 (29) 03/04/2019 ORIG-1 /Quality/Response To Information Request
05/102019	Application 210797 - Sequence 0040 - 0040 (41) 05/10/2019 ORIG-1 /Quality/Response To Information Request
06/04/2019	Application 210797 - Sequence 0045 - 0045 (46) 06/04/2019 ORIG-1 /Quality/Response To Information Request

Highlights of Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: None

BCS Designation

Reviewer's Assessment: The proposed product is a subcutaneous implant, BCS designation is not pertinent.

Solubility: According to the applicant the drug substance is freely soluble in water.

Permeability: N/A

Dissolution:

The following table represents the originally proposed in vitro release method and acceptance criteria:

In vitro release Method and Acceptance Criteria

Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Sampling Times	Acceptance criteria
Screw capped glass bottles	120 oscillations per minute	0.05M phosphate buffer, pH 6.8 37 ± 2 °C	25 mL	(b) (4)	

The applicant initially did not provide detailed method development report. The following summarizes the applicant's justification submitted in response to the Information Requests received November 08, 2018 and March 04, 2019.

(b) (4)

Discriminating ability

The applicant submitted data obtained from several laboratory scale batches. Based on the proposed commercial formulation data obtained from the most relevant batches is included below.

(b) (4)

1 Page has been Withheld in Full as b4 (CCI/TS) immediately following this page

Validation of the in vitro release method

The applicant evaluated robustness of the method for changes in shaker bath speed (120 opm ± 15 opm) and temperature (37° C ± 3° C). Samples were prepared and tested under the respective experimental conditions with data collected up to day 7. The results demonstrated that the method is robust for small variations in the shaker speed but temperature is a critical parameter. The water-shaker bath is maintained at a set temperature ± 0.5° C which ensures the temperature is tightly controlled within the limits of 37 ± 2° C required for the assay.

Refer to Drug Product review for validation of analytical method.

[1] Application 210797 - Sequence 0028 - Response to Information Request, Biopharmaceutics - FDA Question #4
[2] Application 210797 - Sequence 0040 - Response to Information Request - FDA Question #2

Reviewer's Assessment: ***Adequate***

- The applicant did not provide in vitro release method development report or detailed justification for selection of media and other conditions. However, afamelanotide is freely soluble in water. Considering all the provided data selection of pH 6.8 media is acceptable.
- The applicant initially did not provide information on discriminatory ability of the in vitro release method. Subsequent information provided determined that the mentod can discriminate between products with and withou (b) (4) as well as changes in th (b) (4) parameters to some degree. The produc (b) (4) under optimal condi emonstrate less variability than the product (b) (4) under non-standard conditions.
- (b) (4)

Acceptance criteria

The applicant had originally proposed the following acceptance criteria:

(b) (4)

The applicant collected data for 336 hours. However (b) (4) % or more release was observed at 96 hours. Based on the available data the originally proposed acceptance criteria were not appropriate. Several IRs were communicated to the applicant about acceptance criteria. These IRs outlined Agency's general thinking that a middle time-point should be a range rather than of keeping it open ended (e.g., NLT and NMT) for all 3 points. Also, complete release was observed for Phase 3 batches at 96 hours. This should be reflected the in the acceptance criteria.

The applicant did not accept Agency's recommended and provided following justification:

The key factors taken into consideration during development of the controlled-release implant dosage form were to achieve:

- continuous releas (b) (4) to maintain stimulation of the melanocortin-1 receptors with the consequent enhancement of dermal eumelanin, and
- near complete drug release withi (b) (4), limiting the overall period of exposure to afamelanotide while not compromising the duration of its pharmacodynamic effect over the proposed dosing interval (60 days).

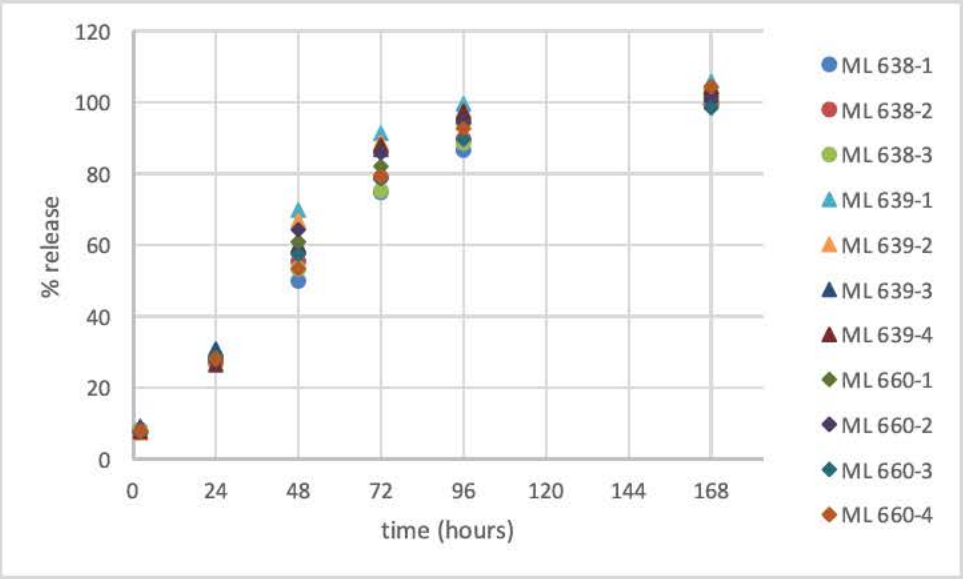
The applicant had conducted studies using the aqueous solution and had identified that adverse reactions including headache, nausea and fatigue needed to be minimized. The 2 hour (b) (4) (b) (4) specification was introduced to limit the initial burst release to reduce the likelihood of the adverse reactions.

The applicant stated that the Agency's recommendation is both unnecessarily restrictive and suggests a more rapid release than would occur with the existing specifications.

The applicant proposed the following revised acceptance criteria:

Reviewer's Assessment:

- The applicant submitted four sets of data for Phase 3 batches. One set (6 samples) were tested as per the product specification and process validation protocol. These data are reported on the CoA. The other three sets (18 samples – beginning, middle and end) were tested as per the process validation protocol. Based on these four sets, Batch ML639 appears to have higher variability and released afamelanotide faster than the other two batches. It should be noted that there was no burst release up to 24 hours. The following represents mean % release for each set tested for the three batches used in Phase 3 study (CUV 039).



- The applicant has stated that the photoprotective properties of afamelanotide are associated with its pharmacodynamic effect rather than its pharmacokinetics. As long as drug exposure occurs over a number of days, the pharmacodynamic effect will be maintained over the proposed dosing interval of 60 days. The study report for CUV038 states that for most subjects, the last measurable concentration was at 96 hours post-dose. There were no measurable levels (b) (4) days post-dose in any subjects.
- The applicant did not accept the Agency recommend acceptance criteri (b) (4) The applicant's assertion that the Agency recommended acceptance criteria are restrictive and suggests a more rapid release than would occur with the existing specifications is not accurate. Agency's recommendation is based on the data obtained from the Phase 3 batches.
- The Agency acknowledges that the activity of the proposed product is associated with pharmacodynamic effect rather than pharmacokinetics. In vitro release method and acceptance criteria are part of the routine QC tests for the product to be used at release and stability. As discussed earlie (b) (4) is an important step in product manufacturing (b) (4) In vitro release test conducted with appropriate acceptance criteria is critical to (b) (4) Products manufactured under non-optimum conditions demonstrated faster release. Hence, it is important to have a range (upper and lower

limit) for in vitro release test at the middle time-point. Therefore, applicant's newly proposed acceptance criteria are not acceptable.

- After further communication via IRs (see Appendix for details) and responses from the applicant, the Agency recommended the following acceptance criteria:
  2 hours (b) (4)%
  24 hours (b) (4)%
  96 hours (b) (4)%
- The applicant accepted the Agency recommended acceptance criteria.

EXTENDED RELEASE DOSAGE FORMS –Extended Release Claim

Reviewer's Assessment: ***{Adequate/Inadequate}***

Bridging of Formulations

The applicant changed manufacturing site during product development. All Phase 3 batches were manufactured at the proposed commercial site (Site 2). Batches used in two pivotal clinical pharmacology studies CUV 028 and CUV 038 were manufacture at Site 1 which is not proposed commercial site. The site change from Site 1 to site 2 is considered a level -2 change.

The proposed drug product can be considered a modified release product. Therefore, per request from the Clinical Pharmacology team to bridge batches used in these studies and based on the principles outlined in the SUPAC-MR Guidance (SUPAC-MR: Modified Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation) the applicant submitted comparative in vitro release data for batches used in these clinical studies and the batches manufactured at the proposed commercial site to support this site change. the applicant was asked to submit the most recent multi-point data from the old site if data from an unexpired batch from the old site is not available.

In response to the information request the applicant submitted in vitro release data for Batch ML594 (the last batch from manufacturing site 1) and ML638, ML639, ML660 and ML755 (all process validation batches from manufacturing site 2).

Batch Number	Date of Manufacture	Site of Manufacture
ML594	25 June 2010	(b) (4)
ML638	25 March 2011	
ML639	15 April 2011	
ML660	1 July 2011	
ML755	28 September 2012	

The applicant calculated similarity factor (f2) comparing data obtained from batch ML 594 (data from n = 12 units, 6 units tested at release and 6 from stability at t = 3 months) and four other batches ML 638, ML639, ML660, ML755 and obtained the following results:

Reference Batch*	Test Batch**	f1	f2
ML594	ML638; t=0 set 1 and set 2	3	85
ML594	ML638; t=0 set 3 and set 4	3	84
ML594	ML639; t=0 set 1 and set 2	16	49
ML594	ML639; t=0 set 3 and set 4	10	59
ML594	ML660; t=0 set 1 and set 2	9	60
ML594	ML660; t=0 set 3 and set 4	3	80
ML594	ML755; t=0 set 1 and set 2	6	67
ML594	ML755; t=0 set 3 and set 4	4	73

*The 12 implants for the reference batch are the six implants tested at t=0 and six implants from stability at t=3 months
**For process validation (PV) batches, 24 implants (four sets of 6 each) were tested at t=0, thus sets 1, 2, 3 and 4

Compared with the reference batch (ML594) from manufacturing site 1, the f2 for all implant batches from manufacturing site 2 exceeded 50 except for batch ML639 (t=0 set 1 and set 2) where the f2 was 49. The applicant stated that for these batches, there was a limited burst release with less than (b)(4)% release at 2 hours and more than (b)(4)% released by Da (b)(4) Hence, from a biological significance perspective, these implants are considered to be eq ivalent.

Reviewer's Assessment: Adequate

- It should be noted that Batch ML594 was used in study CUV038, one of the pivotal studies from clinical pharmacology perspective.
- This reviewer calculated similarity factor f2 using data obtained from 6 units at release for batch ML594 (manufactured at site 1) and 6 units each for batches manufactured at the proposed commercial site (site 2) ML638, ML639 and ML660. Note that these batches were used in pivotal phase 3 study CUV039.

Reference batch	Test batch	Similarity factor f2
ML594	ML638	82
ML594	ML639	48
ML594	ML660	65

- The results obtained by this reviewer are similar to those reported by the applicant. Two batches ML638 and ML660 demonstrated similar in vitro release. Similarity factor f2 was slightly less than 50 for Batch ML639. Release from Batch ML639 was faster than the other batches. However, this batch did not demonstrate burst release in in vitro study (b)(4) % release at 2 hours and (b)(4)% at 24 hours), one of the important factors considered during development. The applicant has stated that the photoprotective properties of afamelanotide are associated with its

pharmacodynamic effect rather than its pharmacokinetics. As long as drug exposure occurs over a number of days, the pharmacodynamic effect will be maintained over the proposed dosing interval of 60 days. While the applicant has not established an in vitro in vivo correlation considering lack of burst release in the first 24 hours a similarity factor slightly less than 50 for Batch ML 639 is not a concern.

- The applicant has provided adequate information to bridge the manufacturing site change.

R Regional Information

Post-Approval Commitments (For NDA only)

Reviewer's Assessment: *{Adequate/Inadequate} None*

Lifecycle Management Considerations

List of Deficiencies: None

Primary Biopharmaceutics Reviewer Name and Date:

Vidula Kolhatkar, Ph.D.

Secondary Reviewer Name and Date (and Secondary Summary, as needed):
Tapash Ghosh, Ph.D.

Appendix I

The following IRs related to acceptance criteria were communicated to the applicant

May 28, 2019

We recommend the following in vitro release acceptance criteria for your product:

(b) (4)

2 hours %
48 hou
96 hou %

We request that you acknowledge your acceptance of the recommended in vitro release specifications for your drug product and update your drug product release and stability specifications accordingly. In addition, please be advised, that all proposed exhibit batches are expected to meet these revised dissolution specifications in your stability program through your proposed expiry period.

July 10, 2019

The Agency acknowledges that the activity of the proposed product is associated with pharmacodynamic effect. However, in vitro release test is a part of the routine QC testing to ensure batch to batch product quality encompassing all the formulation and manufacturing variables. In light of that, the Agency continues to recommend a range for 48 hour time-point instead of keeping it open ended (e.g., NLT and NMT) for all 3 points.
We recommend the following in vitro release acceptance criteria for your product:

(b) (4)

2 hours %
48 hou
96 hou %

We request that you acknowledge your acceptance of the recommended in vitro release specifications for your drug product and update your drug product release and stability specifications accordingly. In addition, please be advised, that all proposed exhibit batches are expected to meet these revised dissolution specifications in your stability program through your proposed expiry period.

July 24, 2019
We acknowledge your response dated July 16, 2019 to the Agency's IR dated July 10, 2019.

You have mentioned that the following in-vitro release acceptance criteria are more appropriate for batch to batch control as they are representative of the batches used in the development program, including the pivotal clinical safety and efficacy study.

(b) (4)

2 hours
24 hou %
96 hou

(b) (4)

You have confirmed that all exhibit batches (ML638, ML639, ML660 and ML755) meet your proposed in-vitro release acceptance criteria throughout the drug product's proposed shelf-life.

However, based on review of the data you have submitted from the batches used in the Phase 3 studies, your proposed in-vitro release range o (b) (4) % in 24 h is considered permissive and therefore, not acceptable. The data also shows (b) (4) or greater in-vitro release in 96 hours. Similarly, the proposed acceptance criteria of NL (b) (4) % in 96 hours is not acceptable.
Based on the data from the Phase 3 batches, the FD recommends the following 3-time-point in-vitro release acceptance criteria: :
2 hours (b) (4)
24 hou
96 hou %
Update t product specification with the FDA-recommended in-vitro release acceptance criteria and resubmit by Monday August 29, 2019.

If you have any question, we will be amenable to discuss with you via T-con.

Vidula Kolhatkar

Digitally signed by Vidula Kolhatkar
Date: 8/08/2019 10:31:02AM
GUID: 5424aeae00c3274f93e50573f7ca407e

Tapash Ghosh

Digitally signed by Tapash Ghosh
Date: 8/08/2019 10:40:02AM
GUID: 508da7230002a2433ddcef616ca190df

QUALITY ASSESSMENT

MICROBIOLOGY

Product Background:

NDA: 210797

Drug Product Name / Strength: SCENESSE (Afamelanotide implant/ 16 mg)

Route of Administration: Subcutaneous implant

Applicant Name: Clinuvel, Inc.

Manufacturing Site (b) (4)

Method of Sterilization (b) (4)

Review Recommendation: Adequate

Review Summary: The submission is **recommended** for approval on the basis of sterility assurance.

List Submissions Being Reviewed:

Submit	Received	Review Request	Assigned to Reviewer
11/08/2018	11/08/2018	N/A	11/08/2018
03/04/2019	03/04/2019	N/A	03/04/2019
04/23/2019	04/23/2019	N/A	04/23/2019
04/26/2019	04/26/2019	N/A	04/26/2019
08/08/2019	08/08/2019	N/A	08/08/2019
09/13/2019	09/13/2019	N/A	09/13/2019

Highlight Key Outstanding Issues from Last Cycle: NA

Remarks: This is an eCTD submission. This is an eCTD submission. Information request was conveyed to the applicant on 02/15/2019 (IR1), 04/19/2019 (IR2), 04/25/2019 (IR3), and 08/06/2019 (IR4). The response to IR 1, IR 2, IR 3 and IR 4 received on 03/04/2019, 04/23/2019, 04/26/2019, and 08/08/2019 respectively, were incorporated in the review. The applicant submitted a Courtesy notification letter (dated 09/02/2019) on 09/13/2019 proposing change (b) (4)

Concise Description Outstanding Issues Remaining: None

Supporting Document (b) (4)

List Number of Comparability Protocols (ANDA only): NA

31 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Package Insert

Storage temperature: 2-8°C (36-46°F); Route of administration: Subcutaneous implant; Container: Single administration dose

- **Post-dilution/constitution hold time- N/A**

Reviewer's Assessment: ***Adequate***
No storage of the reconstituted drug product is proposed in the labeling. The applicant provided adequate instructions in the package insert to maintain product sterility.

Post-Approval Commitments:

Reviewer's Assessment: ***N/A***
List of Deficiencies:

NDA: 210797 APPLICANT: Clinuvel, Inc.

DRUG PRODUCT: Scenesse (Afamelanotide implant/ 16 mg)

The Division of Microbiology Assessment has no comments at this time.

Primary Microbiology Reviewer Name and Date:
Hemlata Tamta, Ph.D.
Microbiologist
CDER/OPQ/OPF/DMA/BII
Date: 09/18/2019

Secondary Reviewer Name and Date (and Secondary Summary, as needed):
Nandini Bhattacharya, Ph.D.
Microbiologist
CDER/OPQ/OPF/DMA/BII
Date: 09/18/2019

Hemlata Tamta

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Nandini Bhattacharya

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