CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210797Orig1s000

OTHER REVIEW(S)

OFFICE OF DEVICE EVALUATION

DIVISION OF ANESTHESIOLOGY, GENERAL HOSPITAL,
RESPIRATORY, INFECTION CONTROL, AND DENTAL DEVICES

GENERAL HOSPITAL DEVICES BRANCH

INTERCENTER CONSULT MEMORANDUM

Date	September 26th, 2019
To	Cristina Atinello, Senior Regulatory Health PR CDER/OND/ODEIII/DDDP Shafiei, Hamid, Program Manager CDER/OPQ
Requesting Division	*CDER/OPQ/ONDP*
From	Peter Petrochenko CDRH/ODE/DAGRID/GHDB
Through (Team Lead)	Carolyn Dorgan, ICC Team Lead CDRH/ODE/DAGRID/GHDB
Through (Branch Chief)	CAPT Alan Stevens CDRH/ODE/DAGRRID/GHDB
Subject	Consult for Submission # NDA 210797 *ICCR2019-04358* *ICC1900087*
Recommendation	The labeling indicating the device for use with the drug product and device use instructions in the draft labeling are approvable.

Digital Signature Concurrence Table	
Reviewer	Peter E. Petrochenko -S 2019.09.26 14:56:14 -04'00'
Team Lead	Carolyn C. Dorgan -S Digitally signed by Carolyn C. Dorgan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001800814, cn=Carolyn C. Dorgan -S Date: 2019.09.26 15:07:42 -04'00'
Branch Chief	

1. Submission Overview

Table 1. Submission Information	
ICCR # (Lead)	ICCR2019-04358
ICC tracking # (Lead)	ICC1900087
Submission Number	NDA 210797
Sponsor	Clinuvel Inc.
Drug/Biologic	Afamelanotide implant
Indications for Use	SCENESSE® is indicated for (b) (4) adult patients with erythropoietic protoporphyria (EPP).
Device Constituent	NONE – clinical study performed with cleared and uncleared catcheter/stylus
Related Files	n/a

Table 2. Review Team	
CDER/CBER Lead Review Division	CDER/OPQ/
Submission RPM	Cristina Atinello
Lead Device Reviewer	Peter Petrochenko
The CDRH review is being managed under ICC #: ICC1900087	

Table 3. Important Dates	
Date Issued	1/31/2019
Internal Mid-Cycle	2/12/2019
CMC Internal Meeting	3/6/2019
IRs Sent	Multiple dates (See Interactive Review Section)

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2. PURPOSE/BACKGROUND

2.1. Scope

The Sharepoint ICCR contained the following consult request:

1.In the Section 2 "Dosage and Administration" of draft PI of NDA210797 (SN0005 dated 06/21/2018) the applicant is proposing (b) (4)

- (b) (4)

In clinical trials, stylets and needles were used to administer the implant. Stylets are not marketed in the US. We have concerns that use of needle to advance the implant through the catheter may damage the implant with consequent systemic and local safety implications. From CDRH perspective, is it acceptable to administer SCENSSE (afamelanotide implant) subcutaneously via (b) (4) *as proposed by the applicant?*

2.Please confirm that the (b) (4) *as proposed in Section 2 Dosage and Administration (NDA210797) is available in the US market.*

3.If using the (b) (4) *is deemed inappropriate for use, are there commercially available alternatives in the US market that could be used instead of the stylet proposed by the applicant?*

The CDRH reviewer performed an evaluation of the Sponsor's prior device approach and provided feedback to the Sponsor regarding acceptable device approaches. The Sponsor has indicated that they wish to proceed with one-way labeling indicating their product for use with a cleared implantation tool (cannula with stylet), which is marketed as an exempt device.

This review covered the following elements:

- Inspection of test methods and results of bench top testing completed by the NDA Sponsor
- Device-related labeling
- Sponsor's approach for ensuring access to the device indicated in the labeling

This review did not cover the following elements:

- Review of drug product
- Review of primary container closure-drug product interaction or biocompatibility/toxicology
- Usability and Human Factors of the combination product (deferred to DMEPA)
- Review of the marketed device itself

2.2. Prior Interactions

IND 103131

2.3. Background

Prior to initiating a consult to CDRH, the CDER quality review team had sent IRs to the Sponsor requesting additional information on the device used for implantation with the drug product. The IR and Sponsor's response is below (shaded in gray):

RESPONSE TO INFORMATION REQUEST, REFERENCE ID: 4376175 (January 15, 2019)

FDA QUESTION #1

1. Provide names and makers of the following devices: 14-gauge (1.6 mm inner diameter) catheter with needle and stylet used for implantation of your product in clinical trials CUV030 and CUV039. Provide information whether these devices are FDA cleared and currently available in the US.

CLINUVEL's response:

Following are details of the catheter with needle and the stylet used in the CUV030 and CUV039 clinical trials.

(b) (4)

(b) (4)

Attached are clearance documentation (b) (4) It is CLINUVEL's understanding that these (b) (4) are currently available in the US.

FDA QUESTION #2

2. (b) (4) described in Section 2 of labeling that can be used for (b) (4)

CLINUVEL's response:

CLINUVEL has searched the 510(k) Premarket Notification database and the internet for commercially available alternatives to those used during the CUV030 and CUV039 clinical trials. A number of alternative suppliers (b) (4) were identified including (b) (4)

Reviewer Comments:

The cited devices by the Sponsor have the following indications for use:

(b) (4)

These devices were deemed inappropriate for use by the Sponsor, since the devices are not indicated for subcutaneous implantation use per their cleared device labeling. Upon further review, the Sponsor has selected SFM Implantation Cannula (14G × 50 mm), Product Code: GEA, manufactured by SFM Medical Devices GmbH.

2.4. Indications for Use

Combination Product	Indications for Use
SCENESSE® afamelanotide (as afamelanotide acetate) 16 mg implant	SCENESSE® is indicated for [redacted] (b) (4) adult patients with erythropoietic protoporphyria (EPP).

3. ADMINISTRATIVE

3.1. Documents Reviewed

Document Title	Date - Version	Location in ANDA 211097
Response to Information Request, Reference ID_ 4376175	1/15/19	-
Clinical Summary		2.5 Clinical Overview
2019_04_02_Response to FDA Device Question	4/2/19	-
Response to Information Request Reference ID_ 4398899	3/5/19	-
RESPONSE TO INFORMATION REQUEST, REFERENCE ID: (IR # 4446141) Note: part 1 of 2	June 21, 2019	0047
RESPONSE TO INFORMATION REQUEST, REFERENCE ID: (IR # 4446141) Note: Part 2 of 2	July 22, 2019	0049

4. DEVICE DESCRIPTION AND PERFORMANCE REQUIREMENTS

4.1. Device Description

The SCENESSE®(afamelanotide) implant is a solid white to off-white, biodegradable and sterile rod approximately 1.7 cm in length and (b) (4) mm in diameter. Each implant contains 16 mg of afamelanotide, equivalent to 18 mg of afamelanotide acetate. It is supplied in a single-dose Type I amber glass vial sealed with a PTFE coated rubber stopper. SCENESSE® implants are not supplied (copackaged) with the device for subcutaneous administration. The drug labeling states that SCENESSE® implants should be administered using a separately marketed exempt surgical device, the *SFM Cannula for subcutaneous implant/pellet administration*; Implanter cannula (Product Code: GEA, Regulation 878.4800, Registered Establishment

4.2. Device Compatibility Testing with Implant Drug Product

The Sponsor used a different (b) (4) device in the clinical study performed outside of US (OUS). The (b) (4) device is not cleared or marketed in the US. The Sponsor, therefore, proposed bridging and providing compatibility testing of other implantation devices available on the US market (because of interactions with FDA regarding their approach). The compatibility testing provided did not address multiple issues wit (b) (4) (b) (4) and the Sponsor did not address this in their compatibility testing. During interactive review, (b) (4).

The device included in the final labeling is the SFM implantation cannula (green box above). The device is similar in its design and dimensions to the (b) (4) devices used in the clinical studies. The Sponsor has provided compatibility testing to bridge the use of the SFM device, however, the compatibility testing was not sufficient to bridge the (b) (4) (review and bench study summarized in the Interactive Review Section).

Only one device has been identified by the Sponsor and determined by FDA to be compatible: SFM Implantation Cannula (14G × 50 mm), Product Code: GEA, manufactured by SFM Medical Devices GmbH. (FDA Listing: https://www.accessdata.fda.gov/scripts/cdrh/Cfdocs/cfRL/rl.cfm?lid=536305&lpcd=GEA) (b) (4) The Sponsor projected the clinical demand and capacity per AEEC in the United States and anticipated clinical demand for treatment in the first three years post-approval for the device (covered in interactive review section). The Sponsor also confirmed that the device will be distributed to the trained and accredited American EPP expert centres for the reasons described in the NDA and has established a supply management strategy to secure access to the device.

4.3. Summary of Performance Testing

The Device Compatibility study is summarized below (the compatibility study was received interactively after sending an IR; the IR and response is also included under IR responses in the Interactive Review Section below). The information from the Sponsor is highlighted in gray, but has been edited into a summary format below:

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Reviewer Comments:
The compatibility study above looked at appearance qualitatively, with a visual and microscopic examination, as well as weight of the implant after delivery quantitatively. The Sponsor's study did not test certain parameters (b) (4) (b) (4) (b) (4) (b) (4) were appropriate for use with the implant. (b) (4) only keeping the SFM cannula which was very similar in design and function to the device used in the clinical studies outside of US. The reason for this was that primarily, the study did not address whether (b) (4) (b) (4) different than the clinical workflow in the instructions for use and in the prior clinical studies.

The Sponsor provided samples for the devices used in the study above as well as the original (b) (4) used in the OUS clinical study. Two of the devices, the (b) (4) appeared to (b) (4) and one of the devices (b) (4) thus supporting the conclusion from the compatibility study above that only the SFM device is compatible and does not introduce new risks due to a change in impantation procedure. The SFM device is similar in design and dimensions to the (b) (4) device used in the OUS study (b) (4) in comparison to the (b) (4) devices.

Additionally, the Sponsor was provided recommendations for including device specific language in the labeling and establishing a supplier management strategy to be notified of any discontinuations by the device manufacturer, since during approval only one device is determined to be compatible with the drug product. The Sponsor has agreed and provided draft labeling and has established a supplier management strategy.

5. CLINICAL DEVELOPMENT

5.1. Human Factors Studies

Clinical Summary (2.5 Clinical Overview):

- The final implant formulation implant which was capable of drug release along selected interval and being administered using (b) (4) (used in CUV006, CUV007, CUV009, CUV011, CUV015, CUV016, CUV017, CUV025, CUV028, CUV029, CUV030, CUV032, CUV038, CUV039 and subsequent studies). Pg 43/79
- The release profile and implant dimensions were refined over several years resulting in a final injectable formulation which could be administered (b) (4). Pg. 56/79
- CDER clinical team has concluded that no HF studies will be requested from the Sponsor. This decision was concurred by the CDER clinical team as well.

5.2. Labeling Review (as of 7/29/2019)

NOTE: The final device recommendation for Labeing is to indicate that the implant is not supplied with the administration device and directly indicate use of this implant with the SFM device. Language was added after discussions with CDER to allow the option for the Sponsor to add future compatible devices after performing compatibility testing and submitting a supplement. Device relevant sections are included below:

-DOSAGE AND ADMINISTRATION----------

(b) (4)

[redacted]

1 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Information

SCENESSE® should be administered by a health care professional. All healthcare professionals should be proficient in the subcutaneous implantation procedure and have completed the APPLICANT provided training prior to administration of the SCENESSE implant *[see Dosage and Administration (2.2)]*. Additional information, including a video, is available at www.xyz.com. The additional information has not been evaluated or approved by the FDA.

A single SCENESSE® implant is inserted subcutaneously above the anterior supra-iliac crest every 2 months. Use the SFM Implantation Cannula to implant SCENESSE. Contact <<drug manufacturer>> for other implantation devices that have been determined by the manufacturer to be suitable for implantation of SCENESSE.

2.2 Instructions for Implantation of SCENESSE

Insert a single SCENESSE® implant (containing 16 mg of afamelanotide) subcutaneously above anterior supra iliac crest.

Implant SCENESSE® observing an aseptic technique. The following equipment is needed for the implant insertion:

- SCENESSE® implant
- SFM Implantation Cannula; use of a device that has not been determined to be suitable could result in damage to the SCENESSE implant *[see Dosage and Administration (2.1)]*.

- Sterile gloves
- Local anesthetic, needle and syringe
- Blunt forceps suitable for removing the SCENESSE® implant from the glass vial and placement of the SCENESSE® implant
- Sterile gauze, adhesive bandage, pressure bandage

16 **HOW SUPPLIED/STORAGE AND HANDLING**

SCENESSE®(afamelanotide) implant, 16 mg, for subcutaneous administration (NDC XXXX-XXXX-XX) is supplied in a Type I amber glass vial sealed with a PTFE coated rubber stopper. Each vial contains one afamelanotide implant and packaged individually in a cardboard box. SCENESSE® implant is a solid white to off-white, biodegradable 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)]*.

The device language has been reviewed and developed interactively with the CDER review team and the Sponsor based on the appropriate regulatory approach and supporting compatibility bench testing with the selected device. Additionally, the sponsor has established a strategy for ensuring continued access to the device and to be notified in case of any potential shortages due to recalls/modifications/discuntinuations, etc., and may also intend to submit compatibility testing for other implantation devices in the future.

6. INTERACTIVE REVIEW

Agency Information Request 1 (sent on 3/5/19) - ADEQUATE – followed up and resolved below

1. We acknowledge you have provided the details of the catheter/needle and stylet used in the clinical studies as well as equivalent cleared devices on the US market. The devices you have used in the clinical studies (including [redacted (b) (4)]) are not indicated for placement of a subcutaneous implant [redacted (b) (4)] used is not cleared in the US. We additionally acknowledge that your [redacted (b) (4)]. Such use will result in an outstanding device issue. We recommend resolving this with one of the options below:
   a. [redacted (b) (4)] use of a US cleared device for which the indications for use encompasses subcutaneous implant placement. If the indications for use are broad, we ask you provide a justification for how these indications apply to use with your implant. Please note if the selection is appropriate, nonclinical compatibility testing of the device with your implant may be necessary to ensure the device is capable of properly implanting the drug product.
   b. Develop a device component specifically for your combination product under the current NDA if you intend to have a co-packaged device component. As the NDA holder, you would be responsible for establishing and ensuring all device-related essential performance requirements (EPRs) are maintained for use with the implant.

c. Partner with an existing device manufacturer to submit a new premarket application (ex. 510(k)) for a device with expanded indications for use which include subcutaneous implant placement. Please refer to Section "A. Labeling Changes" in the FDA Guidance titled "Deciding When to Submit a 510(k) for a Change to an Existing Device" (https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm514771.pdf). Updated performance testing may be necessary to ensure the device is suitable for the new intended use.

Sponsor Response (received on 03/12/19):

CLINUVEL's response:

In response to the question concerning the device to be used for the administration of SCENESSE®, the following comprehensive information on the subcutaneous administration of the SCENESSE® 16 mg implant formulation is provided.

(b) (4)

SCENESSE® implants should be administered using the following: (b) (4)

(b) (4)

(b) (4) No device will be included in the SCENESSE® packaging. Implant administration will be performed using one of the above named commercially available (b) (4) selected for the listed options at the discretion of the treating physician.

As part of the treatment regimen thus far, CLINUVEL has supplied the treatment centers with the

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Sent: Thursday, March 21, 2019 12:11 PM
To: Attinello, Cristina <Cristina.Attinello@fda.hhs.gov>
Cc: Nicoletta.Muner@secure.clinuvel.com
Subject: RE: New Scenesse IRs due March 12

Dear Ms. Attinello,

This is a follow up email to the teleconference held on Tuesday March 19, 2019 in which the device recommended by CLINUVEL for the administration of SCENESSE® was discussed. An equivalent letter has also been sent to Dr Marcus as eCTD sequence number 0031 to NDA 210,797.

It was our impression that there was some miscommunication during the teleconference so we wanted to provide in writing prior to the Mid-Cycle Communication later this week, CLINUVEL's current perspective as described by Dr Wolgen, on the device that is proposed to be used.

(b) (4)

In any event, we aim to complete the submission in the next weeks allowing the Division to proceed under the current NDA application and to adhere to the PDUFA date.

We ask that this email be appropriately circulated prior to the scheduled Mid-Cycle Communication teleconference on Friday March 22, 2019 so that FDA participants in that teleconference will have an understanding of CLINUVEL's intentions.

Yours sincerely
Kind regards,
Linda Teng
Director Clinical Compliance, CLINUVEL INC.
Tel: +1 415 341 5837 Fax: +1 650 618 1425

Follow on Agency Information Request # (sent on 3/21/2019)

The following feedback is related to the device constituent parts of your combination product. Following our phone conversation on 3/19/2019, if you intend to include a device component as part of your NDA, then we recommend you include the information described below.

Please provide documents to demonstrate alignment with the requirements established in 21 CFR Part 4. It appears that your company's CGMP operating system is based on 21 CFR 210/211 (the drug CGMPs). Please note that combination products manufactured under the drug CGMP operating system, the Applicant/Licensure must also fulfill the requirements under 21 CFR Part 4.4b, and the applicable 21 CFR 820 regulations (medical

device Quality System callouts), specifically 21 CFR 820.20, 21 CFR 820.30, 21 CFR 820.50, 21 CFR 820.100 to show compliance to 21 CFR Part 4 for the finished combination product. For more information regarding cGMP requirements for combination products please refer to the FDA Guidance titled Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products issued in January 2017 (https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM429304.pdf). To provide further clarity on meeting the Quality System Requirements (specifically the QS Callouts referenced above), you may reference the FDA Guidance 'Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff,' (2003) located at the link: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm

If you intend to refer to documentation (e.g. verification test reports) held within another submission and/or master file, be sure to provide a letter of authorization or right of reference alongside a detailed description of the location of the information within the file (i.e. volume, page number, section header, etc.). It is recommended that you provide a brief overview of how the referenced information is intended to support the review of your submission.

Device information should be located in the appropriate eCTD module, as recommended in the FDA's eCTD Technical Conformance Guide: Technical Specifications Document: "Guidance for Industry Providing Regulatory Submissions in Electronic Format —Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications" (https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM465411.pdf).

1) Device Description Documentation
   a) Provide a description of your device constituent design, including any novel features and/or functionalities. This may include engineering drawings and detailed descriptions of the individual device constituent components.
   b) Describe the principles of operation of your device.
2) Design Control – We recommend that the design control information provided in your application include the following:
   a) Design Input Requirements
   b) Design Output Specifications (e.g., device description, drawings, specifications, bill of materials, etc.)
   c) Design Verification Plan/Summary Report and supporting data
   d) Design Validation Plan/Summary Report and supporting data
   e) Risk Management File
   f) Traceability Matrix
3) Essential Performance – Describe the device's essential performance requirements that you have determined necessary to achieve clinical performance of the product, where loss or degradation beyond your specified limits may result in an unacceptable risk.

   We recommend that your marketing application describe how you have determined that the EPR specifications are acceptable and describe product reliability and level of risk associated with failure.

The following are example EPRs for your device type. The final set of device essential performance requirements and product-specific specifications should be based on the design control process for the combination product.

Example EPRs for subdermal implant kits with applicators:

- Applicator Dimensions

4) Control Strategy – Propose and justify a control strategy that ensures that the final finished combination product maintains its essential performance requirements. The control strategy may consist of, but is not limited to, lot release, in-process, control of incoming materials, purchasing controls, etc.
5) Considerations specific to your device constituent
   a) Based on your previous responses to questions issued by the Agency and your feedback during a phone call on 3/19/2019, your clinical studies were conducted with devices which you do not intend to select for marketing with the drug product in the US. In this case, you should develop and perform a comprehensive compatibility evaluation of the implant with the new proposed device constituent. You should consider including a side by side comparison of the devices used in the clinical studies with the devices you intend to market with the drug product. The evaluation should examine implant integrity after placement, any necessary changes to labeling instructions, and other considerations, as applicable.
   b) Sterility Evaluation – You have indicated that the possible device constituent of the combination product is intended to be provided sterile. In this case, we recommend you provide information about sterilization methods, sterility assurance level or verification of the sterility method (i.e. bioburden testing). You should provide documentation to support the sterility of the device constituent including test reports and protocols to ensure that the system components are sterile.

Reviewer Comments:
The Sponsor's approach may require coordination with CDER regarding the timeframe (the issue of timing/CR/Major Ammendments is deferred to CDER). Based on the available feedback from the Sponsor, it appears the Sponsor wants to

(b) (4)

(b) (4)

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d) Please note that all the testing recommendations above may be completed through nonclinical bench testing. Complete test reports (with methods, result, conclusions) should be provided for all device performance testing to ensure that your proposed device will perform as intended with your implant and the proposed device constituent does not introduce and new risk as compared to the devices used in the clinical trials.

Sponsor Response (received on 5/10/19)

The below information is summarized from the submitted report titled "DEVICE - Study ICPQN1431 Non-clinical Bench Performance Testing"

NON-CLINICAL BENCH PERFORMANCE TESTING FOR COMPATIBILITY EVALUATION OF MEDICAL DEVICES IDENTIFIED AS SUITABLE FOR THE ADMINISTRATION OF SCENESSE® (AFAMELANOTIDE 16MG IMPLANT) IN THE US

Date: 10 May 2019

2 ABSTRACT

The objective of this study was to provide *in vitro* evidence to demonstrate the suitability (i.e. performance) of 3 selected medical devices for the subcutaneous administration of SCENESSE® implants as well as the maintenance of the integrity of SCENESSE®
implants throughout the administration procedure (i.e. compatibility), compared to the devices used in clinical studies and commercial distribution in Europe.
The medical devices were:

Reference Devices:

(b) (4)

Test Devices:

(b) (4)

- **SFM Implantation Cannula (14G × 50 mm) (FDA Listing: https://www.accessdata.fda.gov/scripts/cdrh/Cfdocs/cfRL/rl.cfm?lid=536305&lpcd=GEA**

The proposed experiments were aligned with the principles of the 'least burdensome provisions' outlined in the relevant FDA guideline for medical devices.

The integrity of the implant was assessed following passage through the device and forwarding and guiding with the stylet, (if applicable) into a medical gel tissue model.

For performance evaluation the administration procedure was simulated *in vitro* by injecting the device into the tissue model to mimic the *in vivo* administration procedure. After injection into the tissue model, the tissue model will be dissected to allow retrieval of the implant.

Three (3) SCENESSE® implants were tested with each device model (reference and test devices). A new device was used for the administration of each implant to reflect the disposable nature of the device. Plastic forceps were used to retrieve the implant.

The following tests will be used to assess implant integrity before and after passage through the device:

- **Appearance before and after insertion into the tissue model**
- **Microscopic examination before and after insertion into the tissue model**
- **Weight before and after insertion into the tissue model**
- **Placement of Implant after insertion into the tissue model**

Under the conditions of this study, the performance evaluation showed a pass for appearance, microscopic and weight tests using each of the reference and the 3 test devices for the SCENESSE® test item implants

4 TEST/REFERENCE ITEM AND TEST SYSTEM

To evaluate the performance and compatibility of the test devices proposed for use with the SCENESSE® implant in the US in comparison to the reference medical devices under simulated clinical conditions.

Three (3) SCENESSE® implants were tested with each device model (reference and test devices). A new device was used for the administration of each implant to reflect the disposable nature of the device. Three (3) devices of each model were thus tested. Plastic forceps were used to retrieve the implant.

4.5. Identification of Test Item Implant by code or name

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(b) (4)

[redacted]

Follow on Agency Information Request # (sent on 6/10/19) - ADEQUATE

1. We acknowledge you have provided compatibility testing for three devices you selected: (b) (4) [redacted] SFM Implantation Cannula. As part of your compatibility testing report (STUDY NUMBER - ICPQN1431), you provided "a qualitative assessment

determining that the implant could be successfully delivered by the administration device without fracture, damage or lesion and remaining in place after the device was withdrawn." Although you used a transparent gel tissue model, you did not quantify the ability of these devices (b) (4) . You have only provided a qualitative visual evaluation that the implant was delivered "without fracture, damage or lesion and remaining in place after the device was withdrawn," which is insufficient to ensure these devices do not raise any new questions of safety and effectiveness compared to the ones used in your clinical studies. Therefore, based on this limited qualitative evaluation and different device design, two of your selected devices may have risks not previously present with the device used in your clinical studies and not accounted for in your compatibility testing. (b) (4)

2. Additional issues with the devices are noted below:

(b) (4)

(b) (4)

It should be noted, that the third device choice, the SFM Implantation Cannula, does not share these issues and the compatibility testing you provided is sufficient to ensure bridging its use with your implant to the devices used in your clinical studies. The comments below are provided for the SFM Implantation Cannula only:

- Your labeling should clearly indicate that the implant is designed for use with an application device. It should further include a statement that the SFM Implantation Cannula has specifically been evaluated for compatibility with the implant. Your labeling should also include any relevant warnings/precautions against using the implant with devices not evaluated for implanting your product and note any possible associated risks with such off-label use. Any specific instructions for the SFM Implantation Cannula should be added to your instructions for use, if necessary.
- You should have a proper management strategy in place to ensure that you are notified immediately in the event the manufacturer for the SFM Implantation Cannula modifies, recalls, discontinues or performs any other

action that may restrict or prevent your customers from having access to this device, which is required to administer your drug product. This may be performed through an agreement with the device manufacturer.

We request that you respond to these requests by the following dates:
By June 24, 2019 provide your labeling modifications and whether you concur with (b) (4) [redacted] or provide a new proposed approach for ensuring safe and effective use of these devices with your product.
By July 22, 2019 provide your response for establishing a strategy for ensuring continued access to the device indicated in your labeling as compatible for use with your drug product to address the comments above.

NOTE: Dates above were requested based on discussions with the CDER RPM on this file.

Sponsor Response (received on 6/24/19 and Part 2 on 7/22/19)

FDA Request #1
By June 24, 2019 provide your labeling modifications and whether you concur with (b) (4) [redacted]
or provide a new proposed approach for ensuring safe and effective use of these devices with your product.

CLINUVEL's response:

CLINUVEL agrees with the FDA's request to (b) (4) [redacted] and to modify the associated labeling accordingly. The modified Prescribing Information document (in Microsoft Word format) is provided with this response.

Concerning the **SFM Implantation Cannula**, CLINUVEL has the following comments:

The revised labeling indicates that the SCENESSE® implant is to be used with an administration device and that the SFM Implantation Cannula has been evaluated for compatibility with the implant. The labeling further (b) (4) [redacted]
CLINUVEL is providing with its label a step by step guidance on the administration procedure. In addition, the medical staff at each treatment center will be trained and accredited in the implant administration procedure prior to use of the product, to conform to the procedures used in the European Union and Switzerland. As part of CLINUVEL's risk management plan, pharmacovigilance and quality systems, communication with our suppliers and third party contractors will be in place to ensure that modifications, changes in manufacturing and any issue on supply of devices to the centers will be managed in a timely manner.

(b) (4) [redacted]

(b) (4)

[redacted]

FDA REQUEST #2

You should have a proper management strategy in place to ensure that you are notified immediately in the event the manufacturer for the SFM Implantation Cannula modifies, recalls, discontinues or performs any other action that may restrict or prevent your customers from having access to this device, which is required to administer your drug product. This may be performed through an agreement with the device manufacturer. By July 22, 2019 provide your response for establishing a strategy for ensuring continued access to the device indicated in your labeling as compatible for use with your drug product to address the comments above.

CLINUVEL's response:

CLINUVEL agrees with the notion that a supply management strategy is required to secure access to the SFM Implantation Cannula (**"device"**) in United States. (b) (4)

[redacted]

The identification of 'customers', in CLINUVEL's case, patients suffering from EPP, was deemed essential prior to supply of SCENESSE®. Projecting the clinical demand and capacity per AEEC in the United States, CLINUVEL has determined the anticipated clinical demand for treatment in the first three years post-approval as summarized in the table below:

(b) (4)

(b) (4)

. Similar to the distribution of the drug product in the Europe, CLINUVEL does not allow nor facilitate distribution or off-label use by prescribing physicians other than those trained and accredited porphyria expert physicians in the United States.

The American Porphyria Foundation has stated that not more than 400 patients would be expected to seek treatment with SCENESSE® across the 8 US states.

The following measures - part of the supply management strategy - taken by CLINUVEL are key to secure access to the device:

(b) (4)

[redacted]

Summary

CLINUVEL has described the key elements of the US supply management strategy to ensure that any potential shortage in access to the SFM implantation cannula is mitigated. Essential parts of the supply management strategy with regard to the device required for implant administration of SCENESSE® are:

- [redacted]

Reviewer Comments:

The Sponsor agrees that the "Placement of Implant" parameter in the bench testing is qualitative in nature. The Sponsor further states [redacted] device which was used during the clinical trials." [redacted] This labeling has been reviewed by the CDRH reviewer, but the document is in draft and currently being reviewed and actively edited by CDER reviewers. The revised labeling states that the SCENESSE® implant is to be used with an administration device and that the SFM Implantation Cannula has been evaluated for compatibility with the implant. The labeling further [redacted]

The Sponsor agrees with the second part of the IR to establish some form of a "supply management strategy" is required to secure access to the SFM Implantation Cannula ("device") in United States. The distributor of the device is [redacted] (b) (4) and has concurred and cooperated with the NDA Sponsor, CLINUVEL, on each of the measures included in the supply management strategy. The outline of the Strategy is provided and is reasonable. No further questions or concerns remain and no further IRs have been issued after review of these responses. All outstanding deficiencies on the CDRH review side have been resolved and the device labeling is pending review and approval by CDER.

7. OUTSTANDING DEFICIENCIES

None

8. RECOMMENDATION

The compatibility study bridging the devices used in the Sponsor's clinical studies and the language citing SFM Implantation Cannula as the device recommended for use in the draft labeling is approvable. The device-related language in the labeling is appropriate and the Sponsor's supply management strategy is thorough and ensures the continued supply of devices for use with the implantable drug product. CDRH has also interactively conveyed informal labeling recommendations to CDER during internal meetings.

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/s/

CRISTINA Petruccelli Attinello
10/02/2019 03:06:16 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 1, 2019
Requesting Office or Division:	Division of Dermatology and Dental Products (DDDP)
Application Type and Number:	NDA 210797
Product Name and Strength:	Scenesse (afamelanotide) implant, 16 mg
Applicant/Sponsor Name:	Clinuvel Inc
OSE RCM #:	2018-1326-1
DMEPA Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on October 1, 2019 for Scenesse. Division of Dermatology and Dental Products (DDDP) requested that we review the revised container label and carton labeling for Scenesse (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Patel M. Label and Labeling Review for Scenesse (NDA 210797). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JUL 02. RCM No.: 2018-1326.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON OCTOBER 1, 2019

Container label

Carton labeling

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/s/

MADHURI R PATEL
10/01/2019 01:02:21 PM

SEVAN H KOLEJIAN
10/01/2019 01:31:39 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

REVIEW DEFERRAL MEMORANDUM

Date:	September 26, 2019
To:	Kendall Marcus, MD Director **Division of Dermatology and Dental Products (DDDP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Ruth Mayrosh, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Laurie Buonaccorsi, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review Deferred: Medication Guide (MG)
Drug Name (established name):	SCENESSE (afamelanotide)
Dosage Form and Route:	implant, for subcutaneous use
Application Type/Number:	NDA 210797
Applicant:	Clinuvel Inc.

1 INTRODUCTION

On June 21, 2018, Clinuvel Inc. submitted for the Agency's review the final part of a rolling review for original New Drug Application (NDA) 210797 for SCENESSE (afamelanotide) implant. The proposed indication for SCENESSE (afamelanotide) implant is for (b) (4) adult patients with erythropoietic protoporphyria.

On August 12, 2019, the Division of Dermatology and Dental Products (DDDP) requested that the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) review the Applicant's proposed Medication Guide (MG) for SCENESSE (afamelanotide) implant.

This memorandum documents the DMPP and OPDP review deferral of the Applicant's proposed MG for SCENESSE (afamelanotide) implant.

2 CONCLUSIONS

The Agency does not plan to take action on approval of patient labeling during this review cycle. Therefore, DMPP and OPDP defer comment on patient labeling at this time. Please send us a new consult request for review of patient labeling for SCENESSE (afamelanotide) implant if submitted in a future application.

Please notify us if you have any questions.

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/s/

RUTH I MAYROSH
09/26/2019 08:16:54 AM

LAURIE J BUONACCORSI
09/26/2019 08:23:51 AM

BARBARA A FULLER
09/26/2019 09:43:29 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: September 24, 2019

To: Melissa Reyes/Clinical Reviewer, M.D.
Division of Dermatology and Dental Products (DDDP)

Christina Attinello, Regulatory Project Manager, (DDDP)

Barbara Gould, Regulatory Project Manager, (DDDP)

Nancy Xu, Associate Director for Labeling, (DDDP)

From: Laurie Buonaccorsi, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matthew Falter, Team Leader, OPDP

Subject: OPDP Labeling Comments for SCENESSE® (afamelanotide) implant, for subcutaneous use

NDA: 210797

In response to DDDP's consult request dated August 12, 2019, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for SCENESSE® (afamelanotide) implant, for subcutaneous use (Scenesse).

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DDDP on September 19, 2019.

Patient Labeling: DDDP will request a patient package insert (PPI) as a postmarketing commitment. Therefore, a draft PPI was not provided by DDDP and was not reviewed by OPDP.

Carton and Container Labeling: OPDP has reviewed the proposed carton and container labeling submitted by the Sponsor to the electronic document room on September 24, 2019, and we have no comments.

Thank you for your consult. If you have any questions, please contact Laurie Buonaccorsi at (240) 402-6297 or laurie.buonaccorsi@fda.hhs.gov.

21 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

LAURIE J BUONACCORSI
09/24/2019 11:28:00 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Pregnancy and Lactation Labeling Review

Date: 7-11-2019 **Date Consulted:** 2-13-2019

From: Leyla Sahin, M.D.
Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Through: Tamara N. Johnson, M.D., M.S.
Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, M.D.
Director,
Division of Pediatric and Maternal Health

To: Division of Dermatology and Dental Products

Drug : Scenesse (afamelanotide) implant; NDA 210797

Proposed Indication: To increase pain free (b) (4) exposure in adult patients with erythropoietic protoporphyria

Subject: Pregnancy and Lactation Labeling as Part of Original NDA Review

Applicant: Clinuvel Inc.

Materials Reviewed:
- Applicant's proposed labeling and Safety Submission
- Literature review

Consult Question: Please evaluate adequacy of Pregnancy and Lactation Labeling

INTRODUCTION

The applicant submitted an original NDA for Scenesse (afamelanotide) implant on 11-8-2018 for a proposed indication to increase pain free (b) (4) exposure in adult patients with erythropoietic protoporphyria (EPP). This application was granted Orphan designation. There are no approved treatments for EPP in the United States. The Division of Dermatology and Dental Products (DDDP) consulted the Division of Pediatric and Maternal Health (DPMH) on 2-13-2019, for assistance with pregnancy and lactation labeling.

BACKGROUND

Product Background

Drug Class and Description	Melanocortin 1 receptor (MC1-R) agonist; synthetic tridecapeptide and structural analog of α-melanocortin 1 receptor (MC1-R)
Mechanism of Action	Increases the production of eumelanin by the MC1 receptor, independent of exposure to sunlight or UV light sources; this is accompanied by darkening of the skin
Molecular Weight	1,645.84 Daltons
Half-life	The pharmacokinetics have not been fully characterized; over 90% is released by the 5th day after administration; in most clinical studies plasma levels were undetectable by the 10th day after administration
Dosing Regimen	1 subcutaneous implant every 2 months
Serious Adverse Reactions	Proposed Warnings and Precautions for skin monitoring, particularly in patients with a personal or family history of skin cancers
European Approval Date	12-2014

Erythropoietic Protoporphyria and Pregnancy and Lactation

Erythropoietic protoporphyria (EPP) is a rare autosomal disorder caused by a deficiency of ferrochelatase, the final enzyme in the heme biosynthetic pathway that inserts iron into protoporphyrin to form heme.[1] This deficiency results in the accumulation of protoporphyrin IX (PPIX) in red blood cells, plasma and tissues such as the skin. Severe phototoxicity and pain that is not alleviated by analgesics is the main clinical feature of EPP. Additionally erythema, swelling, and blistering may be present. Currently, management of EPP consists of avoidance of sun exposure.

There are published case series (sample sizes from 32-67 pregnancies) on over 150 pregnancies that have shown that there may be improvement in photosensitivity in approximately half of

[1] Langendonk JG, Balwani M, Anderson KE, et al. Afamelanotide for erythropoietic protoporphyria. NEJM 2015; 373:48-59.

pregnancies affected by EPP.[2,3,4] A published retrospective chart review showed that 32 pregnant women with EPP had similar rates of pregnancy complications (gestational hypertension, pre-eclampsia, gestational diabetes, preterm birth, low birth weight, low Apgars) compared with pregnant women without EPP, based on Swedish population-based data.[2] Additionally, this chart review showed that one third of 32 breastfeeding women with EPP had improvement in photosensitivity.

REVIEW

Pregnancy

Nonclinical Experience

Subcutaneous administration of afamelanotide to Sprague Dawley and Lister Hooded rats during organogenesis at doses 12 times the MRHD, based on a body surface area comparison, resulted in no adverse embryofetal developmental effects. Please refer to the toxicology review by Dr. Jiaqin Yao for further details.

Review of Human Pregnancy Data

Applicant's Literature Review

The applicant did not identify any published data on afamelanotide use in pregnancy.

DPMH Literature Review

This reviewer did not identify any new published data on afamelanotide exposure during pregnancy.

Applicant's Review of Pharmacovigilance Database

There are pregnancy outcome data on 20 pregnancies (including 8 in partners of male patients) that occurred one to several months after exposure to afamelanotide. These pregnancies occurred during the development program or were captured in a postmarketing registry in Europe; no birth defects were reported. The applicant's response to our Information Request regarding clarification of the timing of exposure in pregnancy states the following: "Concerning the gestational timing of exposure, none of the female patients received treatment with afamelanotide following conception."

Reviewer Comment

No birth defects were noted in the pregnancies reported to the applicant's pharmacovigilance database. These pregnancies occurred one to several months after administration of afamelanotide. In view of the fact that plasma levels of afamelanotide were undetectable by the

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[2] Wahlin S, Marschall HU, Fischler B. et al. Maternal and fetal outcome in Swedish women with erythropoietic protoporphyria. Br J Dermatol. 2013 Jun;168(6):1311-5.

[3] Holme SA1, Anstey AV, Finlay AY, et al. Erythropoietic protoporphyria in the U.K.: clinical features and effect on quality of life. Br J Dermatol. 2006 Sep;155(3):574-81.

[4] Went LN, Klasen EC. Genetic aspects of erythropoietic protoporphyria. Ann Hum Genet. 1984 May;48(2):105-17.

10th day after administration in most studies, it is reasonable to conclude that no exposure occurred during pregnancy, unless there are target organ effects that last longer.

Discussion and Conclusion
Nonclinical studies of afamelanotide showed no adverse developmental effects at doses 12 times the MRHD, based on a body surface area comparison. Pregnancy cases reported to the applicant's pharmacovigilance database include 12 cases; however, exposure to afamelanotide did not occur actually during pregnancy. Therefore, there are no human data on afamelanotide exposure in pregnancy to assess the risk of major birth defects, miscarriage, or adverse pregnancy outcomes.

Postmarketing Requirement (PMR)
Although EPP is a rare disease, there are over 150 pregnancies reported in the literature; therefore, there is a need to collect pregnancy safety data as there may be potential exposure to afamelanotide in pregnancy if approved in the United States. DPMH recommends issuance of a PMR to collect pregnancy outcome data in a surveillance program (enhanced pharmacovigilance). If DDDP issues a PMR for a disease registry, or if there is an existing disease registry, pregnancy outcomes could be collected through those mechanisms. Otherwise, pregnancy outcomes could be collected through a pregnancy surveillance program, as described in the recently published Postapproval Pregnancy Safety Studies Draft Guidance for Industry.[5]

Lactation
Nonclinical Experience
It is not known if afamelanotide is present in animal milk. No adverse effects were seen in a pre and post-natal development study in Sprague Dawley rats administered oral doses of afamelanotide up to 12 times the MRHD, based on a body surface area, through lactation.

Review of Human Lactation Data
Applicant's Literature Review
The applicant did not identify any published data on afamelanotide and breastfeeding.

DPMH Literature Review
This reviewer did not identify any published data on afamelanotide and lactation.

Applicant's Review of Pharmacovigilance Database
There were no lactation cases reported to the applicant's pharmacovigilance database.

Discussion and Conclusion
There are no data on the presence of afamelanotide in human or animal milk, the effects on the breastfed infant, or the effect on milk production. Because afamelanotide is a large molecule, it is less likely to transfer into milk. Additionally, because afamelanotide is a tridecapeptide, it is likely to be denatured in a breastfeeding infant's gastrointestinal tract which could limit

[5] https://www.fda.gov/media/124746/download

absorption of the intact molecule. In the absence of serious safety concerns, it is reasonable to include the Pregnancy and Lactation Labeling Rule (PLLR) breastfeeding benefit-risk risk statement in labeling.

Although EPP is a rare disease, there are over 30 breastfeeding women with EPP reported in the literature; therefore, there may be potential exposure to afamelanotide in breastfeeding infants if approved in the United States. DDDP may wish to consider issuance of a postmarketing requirement to collect milk samples in breastfeeding women to assess the amount of afamelanotide in milk and safety in breastfed infants. Please see the recently published Clinical Lactation Studies: Considerations for Study Design Draft Guidance for Industry.[6]

Females and Males of Reproductive Potential

Infertility

Nonclinical Experience

Nonclinical studies indicated no adverse effects on infertility.

Applicant's Literature Review

The applicant did not identify any published data on afamelanotide and infertility.

DPMH Literature Review

This reviewer did not identify any published data on afamelanotide and fertility effects.

Applicant's Review of Pharmacovigilance Database

There were no infertility cases reported to the applicant's pharmacovigilance database.

Discussion and Conclusion

Since there are no data that support an association between afamelanotide and effects on fertility, Subsection 8.3, Females and Males of Reproductive Potential will not be added to afamelanotide labeling.

(b) (4)

[redacted]

[6] https://www.fda.gov/media/124749/download

DPMH LABELING RECOMMENDATIONS
DPMH recommendations are below. **See final labeling for all of the labeling revisions negotiated with the applicant.**

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no data on SCENESSE use in pregnancy to evaluate for any drug associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproduction studies, no adverse developmental effects were observed with afamelanotide administration during the period of organogenesis to pregnant rats at doses up to 12 times the maximum daily human dose *(see Data)*.

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

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).

8.2 Lactation

Risk Summary

There are no data on the presence of afamelanotide in human or animal milk, the effects on the breastfed infant, or the effect on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SCENESSE and any potential adverse effects on the breastfed infant from SCENESSE or from the underlying maternal condition.

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/s/

LEYLA SAHIN
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TAMARA N JOHNSON
07/11/2019 12:31:51 PM

LYNNE P YAO
07/15/2019 10:27:04 AM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	July 02, 2019
Requesting Office or Division:	Division of Dermatology and Dental Products (DDDP)
Application Type and Number:	NDA 210797
Product Name and Strength:	Scenesse (afamelanotide) implant, 16 mg
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Clinuvel Inc
FDA Received Date:	June 21, 2018
OSE RCM #:	2018-1326
DMEPA Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA

PURPOSE OF REVIEW

This review evaluates the proposed container label, carton labeling, and Prescribing Information (PI) submitted by Clinuvel Inc. on June 21, 2018, for Scenesse (afamelanotide) implant (NDA 210797) to identify areas of vulnerability that may lead to medication errors. The Division of Dermatology and Dental Products (DDDP) requested this review as part of the NDA approval process for Scenesse.

1 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters	C (N/A)
FDA Adverse Event Reporting System (FAERS)*	D (N/A)
Other	E (N/A)
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

2 FINDINGS AND RECOMMENDATIONS

We reviewed the proposed container label, carton labeling, and Prescribing Information (PI). We noted that the Applicant cross referencing an implanter device in the original NDA submission which was not approved for USA market. However, since then, the Applicant submitted other implanter devices to be referenced, which are currently being reviewed by the Center for Devices and Radiological Health (CDRH). We defer to CDRH and the clinical team on the appropriateness of the implanter device. We have no comment about the implanter device at this time.

We note, the net quantity of "1 implant" on the carton labeling and we defer to the Office of Pharmaceutical Quality (OPQ) to determine the correct package type term for this product.

We also note, the container label and carton labeling can be improved to increase the prominence of important information (i.e. product name, strength, etc.), add lot number and expiration date, and to facilitate product identification.

Tables 2 and 3 below include the identified medication error issues with the submitted label and labeling, DMEPA's rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2: Identified Issues and Recommendations for Division of Dermatology and Dental Products (DDDP)

Prescribing Information			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Highlights of Prescribing Information			
1.	Under Dosage and Administration, centres is spelled "centers" and centres".	Inconsistency in spelling could lead to confusion.	For consistency, revise the spelling of the word "centres" to "centers".
Full Prescribing Information			
1.	The National Drug Code (NDC) is denoted by a placeholder (XXXX-XXX-XX) in Section 16, How Supplied/Storage and Handling	Per 21 CFR 201.57(c)(17)(iii), the How supplied section should include "Appropriate information to facilitate identification of the dosage forms, such as shape, color, coating, scoring, imprinting, and National Drug Code number".	We recommend adding the intended (NDC) numbers.
General Comments			
1.	We note the implanter devices are currently being reviewed by the Center for Devices and Radiological Health (CDRH). We defer to CDRH and the clinical team on the appropriateness of the implanter device.		
2.	We note the net quantity of "1 implant" on carton labeling and we defer to the Office of Pharmaceutical Quality (OPQ) to determine the correct package type descriptor for this product. Ensure that the OPQ determined package type term is consistent throughout the label and labeling.		

Table 3: Identified Issues and Recommendations for Clinuvel, Inc (entire table to be conveyed to Applicant)

Container Label			
1.	As currently presented, the National Drug Code (NDC) is denoted by a placeholder (XXXX-XXX-XX).	The NDC is often used to facilitate identification of the product.	We request that you add the intended numbers to the container label.
2.	As currently presented, container label states "BARCODE" directly under the dosage form. Additionally, the word "BARCODE" is placed horizontally.	We are unclear if the barcode is linear and if it contains the NDC number. The linear barcode is an important safety feature necessary to correctly identify the product and to help prevent product selection and administration errors. Additionally, barcodes placed in a horizontal position may not scan due to vial curvature.[a]	Ensure that the barcode is linear as required per 21CFR 201.25(c) and is surrounded by sufficient white space to allow scanners to read the barcode properly in accordance with 21 CFR 201.25(c)(1)(i). Additionally, we recommend that the barcode on the container label be oriented in the vertical position to improve scannability, as barcodes placed in a horizontal position may not scan due to the curvature of the container.
3.	The format for the expiration date is not defined.	The use of abbreviations within the expiration date can result in confusion regarding the actual expiration date leading to deteriorated drug medication errors.	To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the expiration date format you intend to use. We recommend that the human-readable expiration date on the drug package label include a year, month, and non-zero day. We recommend that the expiration date appear in YYYY-MM-DD format if only

[a] Neuenschwander M. et al. Practical guide to bar coding for patient medication safety. Am J Health Syst Pharm. 2003 Apr 15;60(8):768-79.

			numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. We recommend that a hyphen or a space be used to separate the portions of the expiration date. See *Draft Guidance: Product Identifiers Under the Drug Supply Chain Security Act-Questions and Answers*, September 2018 (lines 277-283), for further insight into FDAs current thinking (found at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621044.pdf).
Carton Labeling			
1.	As currently presented the National Drug Code (NDC) is denoted by a placeholder (XXXX-XXX-XX).	The NDC is often used to facilitate identification of the product.	We request that you add the intended numbers to the carton labeling.
2.	The proprietary name, “Scenesse,” the established name, and the product strength are not the most prominent information on the principal display panel	The proprietary name, “Scenesse,” the established name, and the product strength should be easily identifiable and prominently displayed on the label. However,	Present the proprietary name, established name, and product strength in larger font to improve readability in accordance with 21 CFR 201.10 (a), 21 CFR 201.10 (g), and 21 CFR 201.15 (a)(6).

	(PDP) of the carton labeling.	"CLINUVEL" appears more prominent and may interfere with the readability of this important information on the labeling.	Consider decreasing the font size of "CLINUVEL" on the PDP.
3.	Storage information currently reads: "Store at 2-8°C (36-46°F).	The units of measurement following the first numbers in the temperature ranges [e.g., Centigrade symbol (C) following the 2° and Fahrenheit symbol (F) following the 36°] are missing. The use of hyphens can be confused with negative temperatures. Additionally, increasing the prominence of this information may minimize the risk of the storage information being overlooked.	Revise and bold the storage statement to the following: "Must be refrigerated, store at 2°C to 8°C (36°F to 46°F).". We recommend this to increase the prominence of this important information and minimize the risk of the storage information being overlooked.
4.	There is only a placeholder showing location for a 2D code.	The linear barcode is an important safety feature necessary to correctly identify the product and to help prevent product selection and administration errors. Additionally, the presence of multiple barcodes is confusing to the healthcare providers.	We request you add the product's linear barcode containing the NDC to each individual carton as required per 21CFR 201.25(c)(2). Ensure the 2D barcode is away from the linear barcode containing the NDC number and present it in a size that does not compete with, or distract from the presentation of other required or recommended information on the labeling.
5.	We did not identify a placeholder ("LOT" or "EXP") for the lot number and expiration date on the proposed carton labeling.	The lot number statement is required on the carton labeling per 21 CFR 201.10(i)(1) and the product expiration date is also required on the carton labeling per 21 CFR 201.17.	Ensure that the lot number and expiration date are presented in accordance with 21 CFR 201.10(i) and 21 CFR 201.17, and that they are clearly differentiated from one another. Ensure that the

			lot number and expiration date are not located in close proximity to other numbers where the numbers can be mistaken as the lot number or expiration date. We recommend that the human-readable expiration date on the drug package label include a year, month, and non-zero day. We recommend that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. We recommend that a hyphen or a space be used to separate the portions of the expiration date. See *Draft Guidance: Product Identifiers Under the Drug Supply Chain Security Act-Questions and Answers*, September 2018 (lines 277-283), for further insight into FDAs current thinking (found at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621044.pdf).

3 CONCLUSION

Our evaluation of the proposed container label, carton labeling, and Prescribing Information (PI) identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to the applicant so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Scenesse that Clinuvel Inc. submitted on June 21, 2018.

Table 4. Relevant Product Information for Scenesse	
Initial Approval Date	n/a
Active Ingredient	afamelanotide
Indication	[redacted] (b) (4) in adult patients with erythropoietic protoporphyria (EPP)
Route of Administration	subcutaneous
Dosage Form	implant
Strength	16 mg
Dose and Frequency	One implant is administered subcutaneously every 2 months when required for photoprotection
How Supplied	supplied in a single-dose Type I amber glass vial
Storage	sealed with a PTFE coated rubber stopper.
Container Closure	solid white to off-white rod approximately 1.7 cm in length and [redacted] (b) (4) mm in diameter and contains 16 mg of afamelanotide (as afamelanotide acetate) and the biodegradable excipient poly(DL-lactide-co-glycolide).

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On October 26, 2018, we searched for previous DMEPA reviews relevant to this current review using the terms, ‘afamelanotide’. Our search did not identify any relevant previous reviews.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Scenesse labels and labeling submitted by Clinuvel Inc. on June 21, 2018.

- Container label received on June 21, 2018
- Carton labeling received on June 21, 2018
- Prescribing Information (Image not shown) received on June 21, 2018

F.2 Label and Labeling Images

Container Label

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Carton Labeling

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/

MADHURI R PATEL
07/02/2019 04:14:38 PM

SEVAN H KOLEJIAN
07/02/2019 04:42:31 PM

Clinical Inspection Summary

Date	17 April 2019
From	Cheryl Grandinetti, Pharm.D. Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Cristina Attinello, RPM Melissa Reyes, M.D., Clinical Reviewer Snezana Trajkovic, M.D., Ph.D. Clinical Team Leader Division of Dermatology and Dental Products
NDA #	210797
Applicant	Clinuvel Pharmaceuticals Limited
Drug	Scenesse (afamelanotide 16 mg implant)
NME	Yes
Proposed Indication	Treatment of patients with erythropoietic protoporphyria
Consultation Request Date	3 December 2018
Summary Goal Date	8 May 2019
Action Goal Date	8 June 2019
PDUFA Date	8 July 2019

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Bonkovsky, Bloomer, and Parker were inspected in support of this NDA. Despite several protocol violations (all of the same type) by Dr. Parker as well as some data discrepancies due to transcription errors that occurred at the clinical sites of Drs. Bonkovsky and Bloomer, the study (Protocol CUV039) appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

The final compliance classification of the inspections of Drs. Bonkovsky and Bloomer was No Action Indicated (NAI). The final classification of the inspection of Dr. Parker was Voluntary Action Indicated (VAI).

II. BACKGROUND

This application was submitted to support the use of subcutaneous bioresorbable afamelanotide (Scenesse) implants for treatment of patients with erythropoietic protoporphyria (EPP). Inspections were requested of the following pivotal study in support this application:

> **Protocol CUV039**, "A Phase III, Multicenter, Double-Blind, Randomized, Placebo-Controlled Study to Confirm the Safety and Efficacy of Subcutaneous

Bioresorbable Afamelanotide Implants in Patients with Erythropoietic Protoporphyria (EPP)"

Subjects: 97 subjects were screened; 94 subjects were randomized

Sites: 7 sites in the United States (US Reference Centers for Porphyria)

Study Initiation and Completion Dates: 23 May 2012 (date first subject in) to 31 July 2013 (date last subject out)

This was a double-blind, randomized, placebo-controlled, parallel-group study to evaluate the efficacy, safety, and tolerability afamelanotide compared to placebo in patients with EPP. The primary objective was to determine whether afamelanotide can enable EPP patients to expose themselves to sunlight without incurring pain and phototoxic reactions.

To determine eligibility for study inclusion, subjects underwent a screening evaluation up to 14 days prior to enrollment and randomization. Subjects who met eligibility criteria were randomized to one of the following groups:

- Group A: Afamelanotide 16 mg implants, administered on Days 0, 60, and 120
- Group B: Placebo implants, administered on Days 0, 60, and 120

A computer-generated randomization list for each study site was issued to unblinded study personnel (e.g., unblinded site pharmacist) and this site-specific list was used to assign each subject to a treatment arm. Subjects who satisfied the inclusion/exclusion criteria were allocated patient randomization numbers sequentially and chronologically, based on the timing of their attendance at the clinic for the first study implant.

Subjects received up to 3 doses and were treated for a 6-month period. Subjects were instructed to record the number and severity of phototoxic reactions, the type and duration of sun exposure, treatment-emergent adverse events, and the use of concomitant medications in study diaries between Days 0 and 180.

Three months after completion of the efficacy assessment, patients returned to the study site for a full safety assessment, including an evaluation of the reversibility of pigmentation of the epidermis. At this time an additional questionnaire was administered, and an inventory of activities taken.

The *primary efficacy endpoint* was the number of hours that subjects exposed themselves to direct sunlight between 10:00-18:00 hours on days when no pain was experienced (Likert pain score of 0). The subject recorded reactions to light and time spent outdoors in subject diaries that were issued to them on visit 1 (Day 0).

Rationale for Site Selection

The clinical sites were chosen primarily based on numbers of enrolled subjects, high number of protocol deviations, and prior inspectional history.

III. RESULTS (by site):

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

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

1. Herbert Bonkovsky, M.D.

At this site, 13 subjects were screened, all of whom were enrolled. An additional subject (b) (6) who was consented by Dr. Parker at the University of Utah (Site #7) was transferred to this study site. One subject withdrew, and of the original 13 subjects consented by this site, 12 subjects completed the study. Subject (b) (6) (the transferred subject) also completed the study.

Records reviewed included, but were not limited to, the study protocol and amendments, Institutional Review Board (IRB) submissions and approvals, subject selection criteria, informed consent, source data, case report forms, source records for the primary efficacy endpoint, financial disclosure, drug accountability, adverse event reporting, protocol deviations, and monitor logs and follow-up letters. An audit of the study records for the original 13 subjects enrolled by this site was conducted.

There was no evidence of under-reporting of adverse events. Paper source data (i.e., subject's diary data used to evaluate the primary efficacy endpoint) were reviewed and verified against the data listings provided by the sponsor for all 13 subjects enrolled by this site. Of note, the subjects returned the completed diaries to site personnel. The site personnel would review the diary information and only the daily pain scores reported by the subject were transcribed to the paper case report form (CRFs). Thus, the study monitor collected the diaries and provided them to the sponsor, where the remaining information (e.g., time in the shade and time in the sun) from the diaries were entered into the sponsor's database by sponsor personnel. The original diaries were then returned to the study site.

The table below notes the discrepancies for time in the shade and time in the sun observed during inspection between the source diaries and the data listings provided by the sponsor. Also observed during inspection and noted below were discrepancies for laboratory data transcribed by site personnel from the source records to the paper CRFs and then entered by the sponsor into the sponsor's database.

Subject ID	Visit, Date	Diary Data/ Lab Parameter	Source Data Value	CRF value	Data Listing Submitted to FDA
(b) (6)	Visit 3, (b) (6)	Transferrin	242 mg/dL	276 mg/dL	276 mg/dL
	Visit 4, (b) (6)	Transferrin	254 mg/dL	245 mg/dL	245 mg/dL
	(b) (6)	Time in the shade	2.50 hours	N/A	2.75 hours
	Visit 2, (b) (6)	Glucose	83 mg/dL	87 mg/dL	87 mg/dL

(b) (6)	(b) (6)	Time in the shade	0.50 hours	N/A	0.25 hours
	Visit 3, (b) (6)	Creatinine kinase	181 U/L	181 U/L	101 U/L
	(b) (6)	Time in the sun	0.00 hours	N/A	0.75 hours
	(b) (6)	Time in the shade	0.75 hours	N/A	0.00 hours

Reviewer's comment: Discrepancies related to laboratory parameters noted in the above table are negligible and therefore likely do not have an impact on the safety results of afamelanotide. The data discrepancies that involve the reported number of hours in the shade likely do not have an impact on the efficacy results of the study as the number of hours in the shade was not used to assess the primary efficacy endpoint. The discrepancy related to time in the sun for subject (b) (6) involved the assessment of the primary efficacy endpoint. We recommend that the above diary data for time in the sun for Subject (b) (6) be corrected as shown in the above table.

Of note, the data discrepancies for time in the shade and time in the sun are likely due to transcription errors made by the sponsor, as it was the sponsor who transcribed the subjects' diary entries for time in the shade and time in sun into the sponsor's database. The data discrepancies for the laboratory data are likely due to transcription errors made by site personnel. Although no Form FDA 483 was issued, these transcription errors were discussed with Dr. Bonkovsky during the close-out meeting of the inspection.

In addition, the inspector verified that an unblinded pharmacist at the site maintained the paper randomization schedule and dispensed the study drug. During inspection, one discrepancy was noted in the data listings provided by the sponsor and the randomization log maintained at the site. Subject (b) (6) was randomized to and received afamelanotide, but the sponsor's data listings indicated that Subject (b) (6) received placebo. Subject (b) (6) was randomized to and received placebo, but the sponsor's data listings indicated that Subject (b) (6) received afamelanotide. Drug accountability records were reviewed, and no randomization or dispensing error occurred at the site.

Reviewer's comment: FDA identified and raised this issue initially at a pre-NDA meeting on 22 November 2016. The sponsor provided a written response to the randomization issue explaining that the error occurred due to a transcription error by the study monitor and, as also noted by the inspector during inspection, not due to an error that occurred at the site. Subject (b) (6) correctly received afamelanotide and Subject (b) (6) received placebo.

2. Joseph Bloomer, M.D.

At this site, 12 subjects were screened, all of whom were enrolled, one subject was lost to follow-up, and 11 subjects completed the study. Records reviewed included, but were not limited to, the study protocol and amendments, IRB submissions and approvals, subject

selection criteria, informed consent, source data, case report forms, source records for the primary efficacy endpoint, financial disclosure, drug accountability, adverse event reporting, protocol deviations, and monitor logs and follow-up letters. An audit of the study records for all 12 enrolled subjects was conducted.

There was no evidence of under-reporting of adverse events. The inspector verified that the unblinded pharmacist at the site maintained the paper randomization schedule and dispensed the study drug. No discrepancies or errors were noted in the randomization and drug accountability records. In addition, the subject's source diary data and EPP Quality of Life (QOL) Questionnaire were reviewed and verified against the data listings provided by the sponsor for all 12 subjects enrolled. Minor discrepancies were noted as indicated in the table below.

Subject Number	Date	Subject Source Diary and EPP QOL Questionnaire	Sponsor's Data Listing
(b) (6)	(b) (6)	0.75 hours in the shade	0.25 hours in the shade
	Visit 5	EPP QOL Question 11- Score 0	EPP QOL Question 11 – Score 1
	Visit 2	EPP QOL Question 11- Score 0	EPP QOL Question 11 – Score 1
	Visit 5	EPP QOL Question 10- Score 1	EPP QOL Question 10 – Score 0

Reviewer's comment: The data discrepancies noted above likely do not have an impact on the efficacy or safety results of the study. They involved the reported number of hours in the shade and questions on the EPP QOL Questionnaire, which are both not related to the primary efficacy endpoint. Of note, the data discrepancy for time in the shade is likely due to a transcription error made by the sponsor, as it was the sponsor who transcribed the subjects' diary entries for time in the shade and time in sun into the sponsor's database. The data discrepancies for the EPP QOL Questionnaire are likely due to transcription errors by site personnel. These transcription errors were discussed with Dr. McGuire, a sub-investigator of the study. Dr. McGuire acknowledged the data discrepancies and committed to improvements in the future.

3. Charles Parker, M.D.

At this site, 13 subjects were screened and 12 were enrolled, all of whom completed the study. Of note, Subject (b) (6) was transferred to Dr. Bonkovsky's site after Visit 1, while Subject # (b) (6) was transferred to Dr. Parker's site at Visit 4. Presumably the subjects transferred due to subjects relocating to different states (i.e., North Carolina and Utah, respectively) Records reviewed included, but were not limited to, the study protocol and amendments, IRB submissions and approvals, subject selection criteria, informed consent, source data, case report forms, source records for the primary efficacy endpoint, financial disclosure, drug accountability, adverse event reporting, protocol deviations, and monitor

logs and follow-up letters. An audit of the study records for the original 12 subjects who were enrolled at this site was conducted.

There was no evidence of under-reporting of adverse events. The subjects' source diary data were reviewed and verified against the data listings provided by the sponsor for all 12 subjects enrolled. No discrepancies were noted. The unblinded pharmacist at the site maintained the paper randomization schedule and dispensed the study drug. During inspection, randomization and drug accountability records were reviewed, and no discrepancies were noted. Dr. Parker confirmed that the blind for the treatment assignment was maintained throughout the trial. However, Dr. Parker noted that most subjects knew what they were receiving based solely upon the pigmentation of their skin over time; subjects randomized to afamelanotide developed a tan-like coloration to their dermal layers.

A Form FDA 483, Inspection Observations, was issued at the end of the inspection for failure to adhere to the protocol. Specifically, 6 of the 11 subjects (55%) enrolled at the site were not evaluated against all screening criteria before being randomized and receiving study drug. Missing screening criteria and tests included information and data on concomitant medications, contraceptive use, Fitzpatrick Skin Type, beta-carotene use, and ophthalmic examinations and retinal screenings. All missing screening criteria for these 6 subjects were obtained at the latest within 3 weeks after randomization, and all 6 subjects were subsequently deemed to have met the eligibility criteria.

Reviewer's comment: Dr. Parker acknowledged the enrollment of these subjects before all screening criteria were obtained and documented, and he adequately responded to the inspection findings in a letter dated January 30, 2019. As mentioned above, all 6 subjects were subsequently deemed to have met the eligibility criteria, so this protocol violation likely did not have an effect on the efficacy or safety results of the study.

{See appended electronic signature page}
Cheryl Grandinetti, Pharm.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D. Team Leader,
Good Clinical Practice Assessment Branch
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cc:
Central Doc. Rm. NDA 210797
DDDP/Project Manager/Cristina Attinello
DDDP/Medical Officer/Melissa Reyes
DDDP/Clinical Team Leader/Snezana Trajkovic
OSI/DCCE/Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Phillip Kronstein
OSI/DCCE/GCP Reviewer/Cheryl Grandinetti
OSI/ GCP Program Analysts/Yolanda Patague
OSI/Database Project Manager/Dana Walters

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/

CHERYL A GRANDINETTI
04/17/2019 12:37:34 PM

PHILLIP D KRONSTEIN
04/17/2019 02:02:28 PM

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: February 15, 2019

From: CDER DCRP QT Interdisciplinary Review Team

Through: Christine Garnett, Pharm.D.
Clinical Analyst
Division of Cardiovascular and Renal Products /CDER

To: Cristina Petrucelli Attinello, RPM
DDDP

Subject: QT-IRT Consult to NDA 210797 (SDN 007/014)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 1/2/2019 regarding the sponsor's request to not conduct a dedicated QT study. The QT-IRT reviewed the following materials:

- Sponsor's QT Waiver Request (Submission 0006);
- Sponsor's summary of clinical pharmacology (Submission 0005);
- Study CUV039 clinical trial report (Submission 0005);
- Proposed label (Submission 0005);
- Highlights of clinical pharmacology and cardiac safety (Submission 0019); and
- Sponsor's response to Information Request dated 02/11/2019 (Submission 0024).

1 QT-IRT Review of the QT Study Waiver Request

The sponsor'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 sponsor did not provide any information related to the *in vitro* characterization of afamelanotide effect on cardiac ion channels.

2 Internal Comments to the Division

1) Afamelanotide is a new molecular entity and a QT study to characterize the effect of afamelanotide on cardiac repolarization is recommended as per ICH E14 and ICH E14 Q & A (R3) guidelines. The QT study can be conducted with an alternative formulation, if needed.

2) Given the low systemic absorption of afamelanotide [*i.e.*, the maximum plasma concentration after implantation is 4 ng/mL (~2 nM) at around 36 hours postdose], the Division could consider a high safety margin from a good quality *in vitro* ion channel assay as having low likelihood of direct ion channel effects. The recommended voltage protocols are provided (http://cipaproject.org/wpcontent/uploads/sites/24/2018/06/CiPA-protocol-061318.pdf; use hERG current protocol to assess IC50 only). The sponsor should submit safety ECGs collected at times during exposure to afamelanotide (within 48 h of implantation) in clinical trials to evaluate off-target cardiac effects.

3) The sponsor has not proposed QT-related language in product label. We recommend that the sponsor conduct QT assessment according to the recommendations provided above to support labeling discussion at a later stage of the review cycle.

3 BACKGROUND

3.1 Product Information

Afamelanotide, a 13-amino acid peptide, is a new molecular entity developed for (b) (4) adult patients with erythropoietic protoporphyria (EPP). It is a structural analogue of the endogenous compound α-melanocyte stimulating hormone (α-MSH) and a first-in-class melanocortin 1 receptor agonist. It mimics the pharmacological activity of α-MSH by binding to MC1R and activating the synthesis of eumelanin. The intended commercial product is SCENESSE® (afamelanotide) implant, 16 mg. The proposed dosing regimen is one implant administered subcutaneously every 2 months. The overall duration of treatment is at the specialist physician's discretion.

No treatment is currently approved for EPP in the United States. SCENESSE® was granted Marketing Authorization in the European Union in late 2014.

3.2 Sponsor's position related to the question

The sponsor claims that pharmacology, preclinical, clinical and post-marketing data do not provide any indication that afamelanotide 16 mg would exert any effect on human cardiac function and output:

- The melanocortin-1 receptor is not expressed in cardiac myocytes, myo-, endoor epicardium, atria, or valves. The probability of drug interaction with cardiovascular function had been deemed small or absent to date.

- In a 90 day dog study (Study no. 507361), ECG tracings were taken from all animals on one occasion during the pre-trial period and then on Day 1 and during Week 13 of the study. There was no treatment effect on P-R, QRS and Q-T waves and cardiac output or heart rate.
- In a 10 month chronic toxicity study in dogs (Study 1822-001), ECG was monitored predose and 1 day post implant administration on Days 90, 180, and 270. There were no effects on ECG or on systolic, diastolic or mean arterial blood pressure.
- Over the course of 21 years, normotensive healthy human volunteers have been exposed to daily subcutaneous injections of aqueous solution afamelanotide 0.16 mg/kg equivalent to 11.2 mg dosing per day in an adult of 70 kilogram.
- ECG assessments were evaluated in studies EP006, CUV006, CUV007, CUV009, CUV011, CUV015, and CUV038. In these studies afamelanotide did not alter cardiac function.
- In the pivotal US study CUV039, a 12-lead ECG was performed at each clinical visit until the end of the study for all patients enrolled in the CUV039 study in response to a FDA request (ID# 3150691). There are no data to suggest that afamelanotide has had an impact on QT interval or prolongation. ECG measurements in this study were taken at Days 60, 120, 180 or at Early Termination Visit, if applicable, and on Day 360 safety follow-up visit.
- In the compassionate use, special access and post-marketing authorization program more than 400 EPP patients are being followed up and no cardiovascular signal has been detected, and the use of the drug is thus far reported as uneventful.
- The applicant has used an individualized approach to afamelanotide as an investigational drug. Long term safety data indicate that cardiac anomalies were not reported in 76 patients who received more than 13 SCENESSE® implants. Of the 530 patients who had received up to 12 SCENESSE® implants, palpitations and tachycardia, both mild in nature, were reported by 1 patient each.

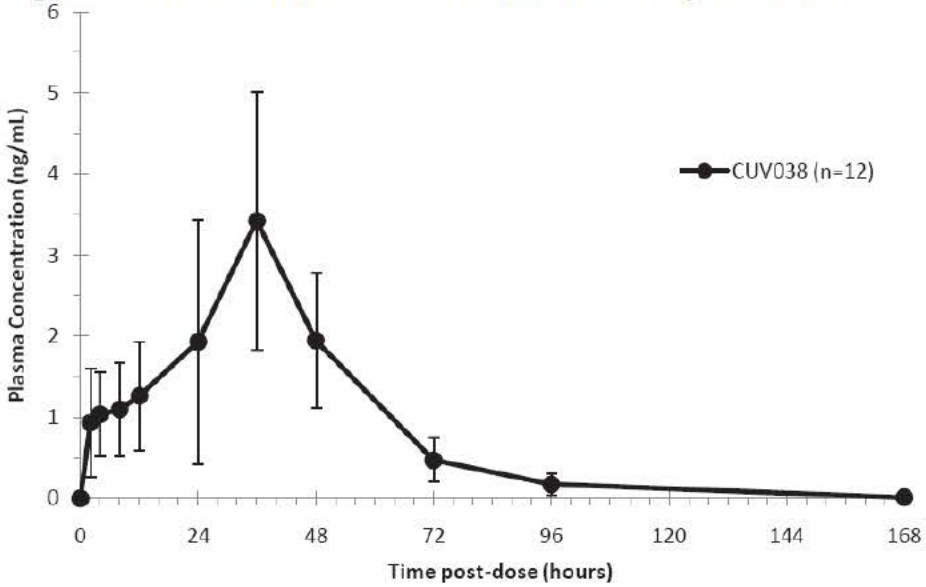
Reviewer's comment: *The sponsor only has safety ECG data from clinical trials. Available nonclinical and clinical data are not adequate for the characterization of drug effect on QT interval.*

1) *Based on study report and study protocol, safety ECGs were collected every 60 days in study CUV039 (a placebo-controlled study). 48 subjects received at least one afamelanotide dose.*

   QT-IRT did not review the ECG monitoring plan in CUV039. On 07/02/2012, the FDA asked the sponsor to collect 12-lead ECGs at every visit until the potential of the drug to cause QT prolongation is addressed (correspondence under IND 103131). The request, however, did not specify the timing of the ECG relative to dosing at each study visit.

   According to CUV039 study protocol, ECG data were collected pre-dose in each clinical visit. There would be no drug available in systemic circulation at the time of ECG sampling. ECG data were collected within a few hours post-dose in ten instances and on a different day in another instance. These ECG data are not sufficient for characterizing drug effect on QTc interval.

Figure 1. Mean plasma concentration of afamelanotide for Study CUV038



Source: Figure 2.7.2-1 in sponsor's summary of clinical pharmacology

Table 1. Summary of mean plasma PK parameters for 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
$AUC_{0\text{-96h}}$	133.1	38.7	130.4	84.9	225.4	128.5

Source: Table 2.7.2-5 in sponsor's summary of clinical pharmacology

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) *Sponsor did not provide any information related to the in vitro characterization of afamelanotide effect on cardiac ion channels.*

4) *We defer to the Division regarding the interpretation of toxicology study data. Based on sponsor's description, ECG monitoring schedule in the 90-day and 10-month dog studies were too sparse to characterize the time course of drug effect on QT intervals in animals.*

5) *Sponsor did not provide details about dose/exposure or ECG acquisition in studies involving subcutaneous injections. It is not known if any of those studies may serve the purpose of QTc assessment.*

6) *There is no information about ECG acquisition from compassionate use or sponsor's individual INDs.*

3.3 Nonclinical Cardiac Safety

Although no stand-alone safety pharmacology studies have been conducted as described in the ICH S7A – S7B guidelines, an evaluation of the effects of afamelanotide on the cardiovascular system (including ECG and effects on the QT interval) was incorporated into the single and repeat-dose toxicology studies conducted throughout development. Blood pressure and ECG measurements formed part of the repeat-dose studies in dogs. No adverse effects were noted in any of these investigations.

3.4 Clinical Cardiac Safety

During clinical trials (n=28), 554 subjects/patients have received controlled-release implants containing afamelanotide. Of these, 231 were EPP patients. Clinical studies CUV006, CUV007, CUV009, CUV028, CUV038 and CUV039 studies included EKG assessment plus vital signs (including heart rate and blood pressure). The only cardiac disorders that were reported as possibly related to treatment and which were reported by more than one subject/patient and more frequently than in placebo recipients are palpitations (n=3) and tachycardia (n=1).

In response to the FDA's request to include safety ECGs in the pivotal trial CUV039, the protocol was amended to collect 12-lead ECG recordings on Days 60, 120 and 180, or at EOT/Early Termination. The sponsor summarized the ECG findings as "Normal" or "Abnormal" as shown below in Table 14.3.16. Listing 16.2.26 provides a description of ECG findings. Prolonged QT interval was noted for Subject (b) (6) but the QT/QTc value was not provided in the listing.

Table 2. Summary of Electrocardiogram Assessments - Safety Population

	Active (N=48)			Placebo (N=45)		
Assessment	Visit 2 Day 60	Visit 3 Day 120	Visit 4 Day 180	Visit 2 Day 60	Visit 3 Day 120	Visit 4 Day 180
Normal	16 (33%)	29 (60%)	24 (50%)	18 (40%)	21 (47%)	27 (60%)
Abnormal	15 (31%)	17 (35%)	22 (46%)	10 (22%)	21 (47%)	15 (33%)

Source: Table 14.3.15 in Study CUV039 clinical study report.

Reviewer's comment: *A descriptive summary of the ECG intervals could not be located in the CSR for CUV039.*

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

4 Appendices

4.1 IRT's Highlight of Clinical Pharmacology and Cardiac Safety

Therapeutic dose and exposure	The proposed therapeutic dose is one controlled-release implant (16 mg) administered every 2 months (60 days) when required for pandermal photoprotection. Implants release the 16 mg dose over a period of 7 to 10 days maximum, (median 7 days). Mean Cmax from the CUV038 study was 3.65 ± 1.27 ng/mL (mean ± SD). AUC0-inf was 138.9 ± 42.6 hr*ng/mL (mean ± SD). No difference between the first and subsequent doses is expected.	
Maximum tolerated dose	Maximum tolerated dose was not formally studied. However, in the EP002 study in which the aqueous solution presentation of afamelanotide was used, the highest withdrawal rate occurred. Nausea was given as the most common reason for discontinuation. It should be noted that the pharmacokinetics following the aqueous solution and the controlled-release implant are quite different. The Cmax levels in the order of 100 ng/mL were observed with the use of the aqueous solution dosage form following a dose of 0.16 mg/kg. Following the experiences from EP001 and EP002 (which used the aqueous solution formulation), the current dose formulation was developed. It exposes patients to a significantly lower quantity of drug per day than during the use of the aqueous solution of 0.16 mg/kg (16 mg of drug is released over 7 to 10 days, equivalent to 1.6-2.3 mg of drug per day (assuming linear release).	
Principal adverse events	Headache and nausea occur very commonly the first 24 hours following the implant administration. Transient decreased appetite, dizziness, somnolence, flushing, hot flush, pigmentation disorder (darkening of pre-existent lesions and hyperpigmentation), asthenia, fatigue and implant site pain have been reported since marketing authorization in the Europe Union. There have not been any adverse events which caused cessation or discontinuation of drug dosing the past 9 years or during the marketing authorization in the Europe Union. There were no dose limiting adverse events, although transient nausea was reported as the reason that several subjects withdrew from the EP002 study in 2003 which subjects received 0.16 mg/kg of the now discontinued aqueous solution presentation daily by subcutaneous injection.	
Maximum dose tested	Single Dose	Implant: 40 mg (earlier formulation; EP004)
	Multiple Dose	Implant: 20 mg (12 administration, every 2 months; CUV011) Aqueous solution: 0.16 mg/kg (10 daily doses per month for three consecutive months; EP002)
Exposures Achieved at Maximum Tested Dose	Single Dose	Cmax from the CUV038 study was 3.65 ± 1.27 ng/mL (mean ± SD). $AUC_{0\text{-inf}}$ was 138.9 ± 42.6 hr*ng/mL (mean ± SD). Note: the 16 mg implant has been the most studied of all formulations developed.
	Multiple Dose	Not applicable. No difference between the first and subsequent doses is expected because the afamelanotide content of an implant is released and cleared from the systemic circulation within 7 to 10 days while the dosing interval is 60 days.
Range of linear PK	Unknown. SCENESSE® is available in one strength only, as a 16 mg implant administered once every 60 days.	
Accumulation at steady state	Not applicable.	
Metabolites	Four "metabolites" identified in an in vitro study in which afamelanotide was incubated in human plasma. The "metabolites" (breakdown products) identified were: Ser-Tyr-Ser-Nle-Glu-**His-DPhe-Arg-Trp**-Gly; Glu-**His-DPhe-Arg-Trp**-Gly-Lys-Pro-	

	Val; **His-DPhe-Arg-Trp**-Gly-Lys-Pro-Val; and Glu-**His-DPhe-Arg-Trp**-Gly. Each retains the four amino acid sequence (bold text) considered necessary as the pharmacophore for the activation of melanogenesis. The activities of these smaller peptides have not been elucidated.	
Absorption	Bioavailability	Formal bioavailability studies have not been conducted.
	Tmax	• Controlled-release 16 mg implant: 36.0 hours (24.1- 49.6 hours) • Aqueous solution presentation: 0.55 ± 0.15 hours (mean ± SD) • Metabolites not studied
Distribution	Vd/F or Vd	Aqueous solution presentation: 1,199.9 ± 348.3 mL/kg (Dose 1) and 1,273.1 ± 307.3 mL/kg (Dose 10); mean ± SD from EP001 study
	% bound	Not studied.
Elimination	Route	• Renal clearance is the major route for excretion with some evidence of being obtained for biliary excretion as well. • An in vitro study suggests that hydrolysis of the peptide occurs and, in a study using labelled drug, the species excreted in the urine could not be conclusively identified, but did not appear to be the intact peptide. • No other routes of elimination.
	Terminal t½	• Aqueous solution presentation: 0.48 ± 0.16 hours (Dose 1) and 0.51 ± 0.13 hours (Dose 10); mean ± SD from EP001 study. • Metabolites not studied
	CL/F or CL	Aqueous solution presentation: 1644.4 ± 531.6 mL/hr/kg (Dose 1) and 1643.2 ± 342.8 mL/hr/kg (Dose 10); mean ± SD from EP001 study
Intrinsic Factors	Age	Pharmacokinetic studies enrolled only adult subjects. Changes in pharmacokinetics with age have not yet been studied.
	Other	No data available on sex, race, or hepatic/renal impairment
Extrinsic Factors	Drug interactions	No specific interaction studies have been performed. Afamelanotide is metabolized by peptide hydrolysis and not via oxidative metabolism by the cytochrome P450 enzymes. As an oligopeptide with a short half-life, afamelanotide is expected to be rapidly hydrolyzed into shorter peptide fragments and into its individual amino acids. Thus, it is not expected to be an inducer or inhibitor of P450 enzymes and should have no impact on drugs metabolized by P450 enzymes. It is not expected to bind to blood proteins due to its short half-life. From a PD perspective, no other agonists or antagonists of the melanocortin-1 receptor are concomitantly administered with afamelanotide.
	Food Effects	Impact on food intake has not been studied.
Expected High Clinical Exposure Scenario	The drug will be administered by trained physicians in expert porphyria treatment centers. No deviations from the recommended dosing regimen of 16 mg every 2 months are therefore expected nor have been seen under Real World Experience in the European Union. The Sponsor intends to follow the same dose regimen and conditions of use in the United States.	

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Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Templates
Version: 2018-01-24

Date:	October 8, 2019
Reviewer:	Michelle R. Iannacone, PhD, MPH Division of Epidemiology I
Team Leader:	Patricia L. Bright, PhD, MSPH Division of Epidemiology I
Deputy Division Director:	Sukhminder K. Sandhu, PhD, MPH, MS Division of Epidemiology I
Subject:	Active Risk Identification and Assessment (ARIA) Sufficiency: Memo: Theoretical malignancy risk following afamelanotide treatment in patients with erythropoietic protoporphyria
Drug Name:	Afamelanotide (Scenesse), subcutaneous implant
Application Type/Number:	NDA 210797
Applicant/sponsor:	Clinuvel, Inc.
OSE RCM #:	2018-1325

EXECUTIVE SUMMARY *(place "X" in appropriate boxes)*

Memo type		
-Initial		
-Interim		
-Final	X	
Source of safety concern		
-Peri-approval	X	
-Post-approval		
Is ARIA sufficient to help characterize the safety concern?	Malignancy	Device related outcomes
-Yes		
-No	X	X
If "No", please identify the area(s) of concern.		
-Surveillance or Study Population	X	X
-Exposure		
-Outcome(s) of Interest	X	X
-Covariate(s) of Interest	X	
-Surveillance Design/Analytic Tools		

A. General ARIA Sufficiency Template

1. BACKGROUND INFORMATION

1.1. Medical Product

This Memo considers ARIA sufficiency for the post-market safety study of afamelanotide (SCENESSE) implant use in patients with erythropoietic protoporphyria (EPP). The following description of the drug product and the population being studied is from the NDA 210797 Multi-disciplinary Review and Evaluation[a] and the prescribing information (PI)[b].

EPP is a rare, lifelong disorder caused by an enzyme deficiency of ferrochelatase conferred through gene mutation. The disorder affects the heme pathway leading to the accumulation of photoactive protoporphyrin IX in red blood cells, plasma, and tissues, such as the skin. Protoporphyrin IX in the skin reacts with light generating a phototoxic reaction (the main clinical feature of EPP). Patients with EPP experience intense pain upon sunlight exposure. Management is guided by strict photoprotection (e.g., clothing, sunscreen, sun avoidance) that significantly impacts the quality of life. The worldwide incidence of EPP is reported to range between 1:75,000 to 1:200,000.

Currently, there is no FDA-approved treatment of EPP. Oral beta carotene and phototherapy are often relied upon for their photoprotective effects. Drugs approved for the treatment of pain are typically not effective in treating pain due to phototoxic reaction of EPP. Afamelanotide implant, 16 mg, is a subcutaneous implant indicated to increase pain-free light exposure in adult patients with a history of phototoxic reactions from EPP. The active ingredient is afamelanotide, an α-melanocyte stimulating hormone (MSH) agonist that stimulates melanogenesis, specifically eumelanin in the epidermis. The proposed mechanism of action for afamelanotide leading to an increased pain-free light exposure time in patients with EPP is reduced protoporphyrin IX excitation due to increased absorption of sunlight by the increased epidermal eumelanin.

Afamelanotide is a new molecular entity and is not currently marketed in the United States. The proposed dose is 16 mg and is administration by subcutaneous implantation every two months by a healthcare provider who has completed the applicant's training program (a risk evaluation and mitigation strategy (REMS) is not being issued). Afamelanotide, under the registered name SCENESSE®, is currently distributed in Europe (approved by European Medical Association (EMA) in December 2014; commercial marketing began in June 2016). Upon approval the EMA required post-authorization safety studies (see Section 1.2), including skin cancer as an outcome. No skin cancers had been

[a] NDA 210797 Multi-disciplinary Review and Evaluation. DARRTS Reference ID: 4503111.
[b] Scenesse Prescribing Information – Pre-Approval Draft – retrieved on October 3, 2019 from GlobalSubmit Review, SDN 64, 10/03/2019.

identified in the Periodic Safety Update Report #6 with a database lock on December 22, 2017.[c]

1.2. Describe the Safety Concern

This memo considers two primary safety concerns of interest:

1. Skin cancer (melanomas and non-melanomas)
2. Administration/injection/implant site reactions

The NDA Multi-disciplinary Review describes in detail the clinical development program and safety profile for afamelanotide implant in adults with EPP.[a]

In brief, the sponsor conducted three multicenter, randomized, double blinded clinical trials, collectively enrolling 244 patients with EPP in the United States. Table 1 below presents the most common adverse reactions associated with afamelanotide implant treatment as observed in the development program trials.[a]

Table 1: Proportion of Subjects with Adverse Reactions Occurring in More Than 2% of Subjects

Adverse Reaction	SCENESSE n (%) N = 125	Vehicle n (%) N = 119
Implant site reaction[1]	25 (20%)	12 (10%)
Nausea	24 (19%)	17 (14%)
Oropharyngeal pain	9 (7%)	6 (5%)
Cough	8 (6%)	4 (3%)
Fatigue	7 (6%)	3 (3%)
Skin hyperpigmentation[2]	5 (4%)	0 (0%)
Melanocytic nevus	5 (4%)	2 (2%)
Respiratory tract infection	5 (4%)	3 (3%)
Porphyria non-acute	2 (2%)	0 (0%)
Skin irritation	2 (2%)	0 (0%)

[1]Implant site reaction includes: implant site bruising, discoloration, erythema, hemorrhage, hypertrophy, irritation, nodule, pain, pruritus, swelling; injection site bruising, erythema, and administration site reaction.
[2]Skin hyperpigmentation includes skin hyperpigmentation, pigmentation lip (subject also had skin hyperpigmentation), and pigmentation disorder.

Data from the European postmarket authorization safety studies (PASS) identified 12% of patients (32/270) with reported treatment emergent adverse events associated with pigment expression changes (implant site discoloration, pigmentation disorder, pigmentation lip, melanocytic nevus, birth mark, hair color changes, nail pigmentation, skin

[c] Clinuvel Inc. Scenesse® Afamelanotide 16 mg Implant. Common Technical Document Summaries. Retrieved on October 3, 2019 from GlobalSubmit Review, SDN 6, 06/21/2018.

hyperpigmentation, post inflammatory pigmentation change, skin depigmentation, skin discoloration).

1. Skin cancer safety concern:
Afamelanotide stimulates melanogenesis potentially making it difficult to identify early signs of skin related malignancies. Combined with the long latency of skin cancer development and the chronic, life-long use of afamelanotide treatment in EPP, postmarketing data are needed to evaluate the long-term serious risk of malignancies in this patient population.

2. Administration/injection/implant site reactions safety concern:
Implant site reactions were reported during the clinical development program (Table 1). The device used in the clinical development program for subcutaneous implantation is not approved for the intended use in the United States. The applicant has identified a suitable implantation device for use with afamelanotide that is approved for use in the United States.[b] Scenesse Prescribing Information[b] will include specific details on the device and how it should be used for the implantation of Scenesse. However, this device has not been used in clinical practice specifically for the implantation of Scenesse, and therefore, no safety data for this identified device for use with Scenesse is available in the U.S. population of interest.

For both safety concerns described, prescription labeling, and routine pharmacovigilance, in conjunction with the PMR are adequate to manage the risks of the product. A risk evaluation and mitigation strategy (REMS) is not being issued.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

1.4. Statement of Purpose
This memo reflects the discussions between the Division of Epidemiology I (DEPI-I), the Division of Dermatology and Dental Products (DDDP), and CDER's Sentinel Team, on whether to issue a PMR for an observational study to collect additional data on the long-term safety of afamelanotide implant. Collectively, a determination was made to issue a PMR to better understand the safety concerns related to skin cancer risk and administration/injection/implant site reactions. The purpose of this memo is to describe the consideration of whether ARIA is sufficient to meet the regulatory goals of the aforementioned safety concerns.

The regulatory goals of this ARIA evaluation are signal detection of skin cancer and characterization of administration/injection/implant site reactions. The regulatory need is for a longitudinal study that captures detailed clinical information on exposed patients only because there is no active comparator to establish a risk estimate for skin cancer. The anticipated regulatory impact is to further characterize the safety concerns of interest to inform labeling decisions. Specific to skin cancer risk, the events are rare and typically have long-term latency periods, therefore, the sufficiency determination primarily rests upon the need to obtain as complete capture as possible of the EPP population and the availability of long-term follow-up, as well as the availability of relevant covariates to better describe the risk of skin cancer that might not be captured or coded in the course of routine medical care. Specific to the implantation device, information collected should characterize and assess the incidence of any administration/injection/implant site-related reactions in patients receiving afamelanotide.

1.5. Effect Size of Interest or Estimated Sample Size Desired

2. SURVEILLANCE OR DESIRED STUDY POPULATION

2.1 Population

The study population will include patients in the United States treated with an afamelanotide implant.

2.2 Is ARIA sufficient to assess the intended population?

No. According to the Applicant[c] there are 225 EPP patients known to be registered with the American Porphyria Foundation and the scientific literature reports up to 1:75,000 patients in the United States. The tolerance to light or the amount of sunlight exposure can vary widely among EPP patients and is a contributing factor (among others) that will influence use of afamelanotide implant. Although, patients with EPP could be identified using ARIA with ICD-10 code of E80.0, hereditary EPP is a rare disorder with a small number of anticipated users. A product exposure registry might allow the sponsor to capture a greater proportion of users than those insured through the Data Partners contributing to the Sentinel Distributed Database.

The Sponsor is anticipating that in the first two years, the postmarket exposure registry study will enroll 200 patients (the Agency is requesting eight years of follow-up post first afamelanotide implant). DDDP and DEPI-I find the Sponsor's proposed sample size reasonable given the rarity of EPP in the United States. However, the registry sample size will be contingent upon uptake of afamelanotide implant in the postmarket setting and registry participation rates.

3 EXPOSURES

3.1 Treatment Exposure

The exposure of interest is use of afamelanotide implant, which is surgically implanted in

an outpatient surgery setting every two months. The implant is absorbable and therefore does not require removal.

3.2 Comparator Exposure

Not applicable. The study population is limited to afamelanotide implant exposed patients because there is no comparator drug available.

3.3 Is ARIA sufficient to identify the exposure of interest?

Afamelanotide subcutaneous implant, 16 mg, is prescribed and administered every two months by a healthcare provider who has completed the applicant's training program.

ARIA would likely be sufficient to capture exposure to afamelanotide through a potential combination of a claim for a dispensing of afamelanotide and a procedure code in outpatient, healthcare provider/supervised administration, or subcutaneous implantation.

Through a potential combination of a claim for a dispensing of afamelanotide and a procedure code for a subcutaneous implantation of a device, such as afamelanotide implant, by a healthcare provider, it is likely that ARIA would be sufficient to identify the exposure of interest.

4 OUTCOME

4.1 Outcomes of Interest

The primary outcomes of interest are:

1. Skin malignancy
2. Administration/injection/implant site reactions.

4.2 Is ARIA sufficient to assess the outcome of interest?

1. Skin cancer safety concern:

No. While FDA is concerned about the safety of all skin malignancy, the Agency has a particular concern with the use of afamelanotide and an increased risk of melanoma. To distinguish between undetected (i.e. undiagnosed), existing skin cancers and newly developed skin cancers (i.e. post initiation of afamelanotide), information from full body dermatological examinations, clinical notes, and pathology reports is required for active surveillance, making ARIA insufficient to assess the outcome of interest. Further, there is insufficient long-term follow-up data in the Sentinel system to capture melanoma. As described in Figure 1 below, roughly 14% of Sentinel members would have at least five years of follow-up, even less for the minimum eight years of follow-up as is required for the PMR observational study issued for afamelanotide implant (see Section 7).

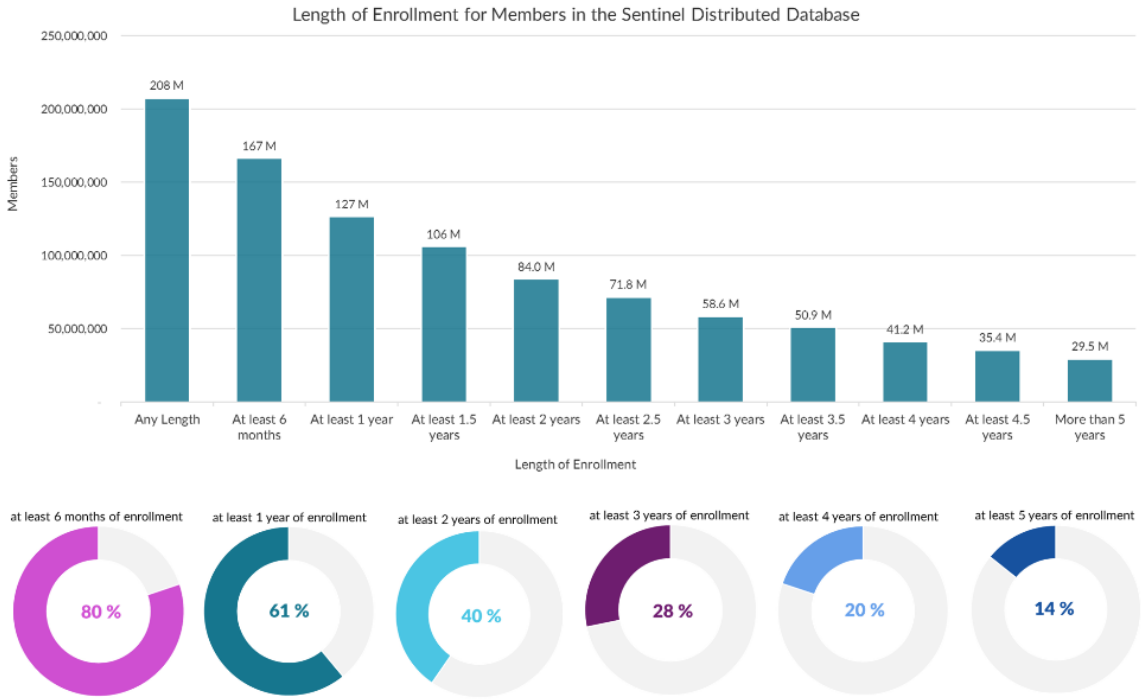

Figure 1. Proportion of Patients with Follow-up Time in the Sentinel Distributed Database from 16 individual data partners.[d]

2. Administration/injection/implant site reactions:

No. The outcomes of interest range in severity and include: implant site bruising, discoloration, erythema, hemorrhage, hypertrophy, irritation, nodule, pain, pruritus, swelling; injection site bruising, erythema, and administration site reaction.

ARIA is not sufficient to assess these outcomes of interest because they include events that are not generally or consistently coded in claims.

According to the ICD-10 CM Coding Guidelines[e], there are three primary methods to code for device complications, as described in the Table 2 below.

Table 2: ICD-10-CM Guidelines for Coding Adverse Events Related to Device Complications

Outcome of Interest	ICD-10 Coding

[d] Source: Snapshot of Database Statistics provided by Sentinel Initiative. Accessed from https://www.sentinelinitiative.org/sentinel/data/snapshot-database-statistics on October 1, 2019.

[e] ICD-10-CM Official Guidelines for Coding and Reporting. FY 2019. Accessed from https://www.cms.gov/Medicare/Coding/ICD10/Downloads/2019-ICD10-Coding-Guidelines-.pdf on October 3, 2019.

1. Pain due to medical devices	"Pain associated with devices, implants or grafts left in a surgical site (for example painful hip prosthesis) is assigned to the appropriate code(s) found in Chapter 19, Injury, poisoning, and certain other consequences of external causes. Specific codes for pain due to medical devices are found in the T code section of the ICD-10-CM. Use additional code(s) from category G89 to identify acute or chronic pain due to presence of the device, implant or graft (G89.18 or G89.28)." (ICD-10 CM Coding Guidelines)
2. Specific device complications	The T80-T88 "Complications of surgical and medical care, not elsewhere classified" contains device and implant complications organized by organ system (cardiac devices, genitourinary devices, orthopedic devices, etc.). These codes can capture breakdown, embolism, erosion, fibrosis, hemorrhage and thrombosis complications very specifically. However, none exist for a subcutaneous implant such as Scenesse. It is difficult to predict how ICD-10 will evolve to adapt to a growing field of subdermal and intradermal drugs and devices. However, it is informative to examine similar drugs such as Nexplanon and Probuphine, both of which have specific HCPCS insertion codes (J7307 Etonogestrel implant system, including implant and supplies; J0570 Buprenorphine implant, 74.2 mg), but do not yet specify device complication codes[f]. In contrast, cardiac, genitourinary and orthopedic devices have detailed device complication codes. T85 "complications of other internal prosthetic devices, implants and grafts" have very specific codes for device breakdown, displacement, and leakage by organ system (ocular, nervous system, breast, etc.) but do not currently have one for device implanted in the skin. Absent a code structure for dermal products, products like Scenesse would have to use T85.8 which can specifically identify device complications such as infection, embolism, hemorrhage, stenosis, pain and thrombosis, but only link them to devices in general.
3. Breakdown and malfunction of medical devices	Sections Y70 – Y82 includes ICD-10 CM codes for "medical devices associated with adverse incidents in diagnostic and therapeutic use" and is intended to capture breakdown and malfunction of medical devices during or after use. However, this section does not capture subdermal devices.

[f] Billing procedures for Aetna Inc.™ and Merck & Co., Incl.®, accessed from http://www.aetna.com/cpb/medical/data/900_999/0910.html , and https://www.merckconnect.com/nexplanon/coverage/billing-codes/ on October 3, 2019.

	Sections Y83 – Y84 includes complications following the use of medical devices without breakdown or malfunction of the device. However, this section does not capture subdermal devices.

5 COVARIATES

5.1 Covariates of Interest

Information on the number and severity of phototoxic reactions experienced, the amount of sunlight exposure hours, and sun protection measures employed will be important for evaluating characteristics of the risk profile for skin cancer events. These data were captured successfully in the clinical trials and existing EU registries have already demonstrated the ability to capture these data elements.

5.2 Is ARIA sufficient to assess the covariates of interest?

No. The information required by dermatologic information as described above and information on sun protection behaviors is not routinely collected in claims-based data.

6 SURVEILLANCE DESIGN / ANALYTIC TOOLS

6.1 Surveillance or Study Design

The study design would be a longitudinal, prospective study for up to 8 years of follow-up, requiring predefined visits and active surveillance.

6.2 Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?

No. Information from full body dermatological exams, clinical notes, and pathology reports are required to assess the outcome of interest, therefore making ARIA not sufficient in respect to study design.

7 NEXT STEPS

On May 15, 2019, DEPI-I, DDDP, and CDER's Sentinel Team deemed ARIA insufficient to capture the necessary information to evaluate the long-term safety of afamelanotide implant in the U.S. population. The reasons for insufficiency include:

- the inability to get substantial capture of the patient population as the incidence of EPP is very low
- the inability to obtain long-term follow-up necessary for the long latency of melanoma development
- the inability of claims-based data to capture information important to inform safety on melanoma outcomes (e.g. number and severity of phototoxic reactions, duration of sunlight exposure, sun protection measures) and administration/injection/implant site reactions (e.g. implant site bruising,

hemorrhage, swelling, erythema).

Therefore, a determination was made by DDDP and DEPI-I to issue a PMR to better understand the safety for afamelanotide implant in the U.S. population. The PMR will capture information on long-term safety related to skin cancer and administration/injection/implant site reactions.

The final PMR language is as follows:

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.*

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