Subject: Scenesse (afamelanotide) Implant	Original Effective Date: Q2 2020
Policy Number: MCP-367	**Revision Date(s):**
P&T Approval Date: Q2 2020	

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP document and provide the directive for all Medicare members.

SUMMARY OF EVIDENCE/POSITION

This policy addresses Scenesse (afamelanotide) Implant for the treatment of erythropoietic protoporphyria (EPP) to increase pain free light exposure in adult patients with a history of phototoxic reactions from EPP when appropriate criteria are met.

The intent of this policy, Scenesse (afamelanotide) Implant, is to ensure appropriate selection of patients for therapy based on product labeling, clinical studies, nationally recognized authoritative references and current peer-reviewed scientific literature. The information outlined in the Molina Clinical Policy includes but is not limited to a review of evidence based information obtained from the following sources Evaluation of New and Existing Technologies (UM 10). This policy is intended to address coverage criteria that are appropriate for the majority of individuals/members with a particular disease, illness, or condition. Each member's unique clinical circumstances may warrant individual consideration, based on review of applicable medical records.

Molina Healthcare reserves the right to update this policy and revise coverage criteria to include or omit any off-label condition(s) as necessary based on medical literature and clinical studies that may become available.

Erythropoietic Protoporphyria (EPP) Balwani 2012; Balwani 2019; Langendonk 2015

- A rare disorder caused by mutations leading to impaired ferrochelatase activity that leads to an accumulation of protoporphryin IX (PPIX) in skin and liver
- Protophyrin IX reacts to visible light (sunlight and some artificial light) and can cause anaphylactoid and phototoxic reactions in people with EPP
- Inheritance pattern is autosomal recessive; thus, clinical manifestations occur only in people with 2 defective FECH alleles, or more commonly, one defective and one low-expressing wild-type allele
- Manifests in infancy or early childhood as severe painful photosensitivity
- Reported prevalence of 1 in 75,000 to 1 in 200,000; the most common porphyria in children and the third most common in adults; equally common in women and men and has been described worldwide
- The long term prognosis appears uniform however the severity of the condition can vary from patient to patient

Clinical features include burning, tingling, and itching within 30 minutes of sun exposure, followed later by erythema and swelling; burning, itching, and intense pain may occur without obvious skin damage, and blisters or bullae are generally absent or sparse.[Balwani 2012]

- Phototoxic reactions cause damage to subdermal capillary walls resulting in erythema of skin, edema and intense burning sensation, which can last weeks until damage heals. Symptoms are exacerbated or prolonged by further exposure to light, heat variation, pressure and air movement. Pain may last for hours to days and does not respond to pain medications.[Balwani 2012; Langendonk 2015]
- When skin is exposed to sun or visible light, the accumulated phototoxic protoporphyrin in superficial vessels is activated by blue-violet light (400 to 410 nm), triggering singlet oxygen free-radical reactions that lead to severe pain.[Langendonk 2015]
- Photosensitivity results from accumulated protoporphyrin in erythroid cells and tissues due to decreased activity of ferrochelatase, the heme biosynthetic enzyme that inserts iron into protoporphyrin to form heme. Protoporphyrin is released from erythroid cells into circulation, gains access to the vascular endothelium and liver, and is excreted through the biliary system. Protoporphyrin in transit in the liver may precipitate, resulting in gallstones and cholestatic hepatitis in about 5% of cases. Hepatic dysfunction may occur in 20% to 30% of patients with EPP; mild anemia and vitamin D deficiency can also occur.[Balwani 2012; Langendonk 2015]
- Sun-induced pain in early childhood often leads to a fear of sunlight and deliberate efforts to avoid sun exposure. The resulting adaptive behaviors impact quality of life.[Langendonk 2015]

Diagnosis. Established by detection of markedly increased free erythrocyte protoporphyrin and/or by the identification of biallelic pathogenic variants in FECH on molecular genetic testing.

Management. Typically centers on avoidance of sun/light, i.e. the use of sun protective clothing, window tinting or films for the vehicle or house.[Balwani 2012] Effective therapeutic options for treatment of EPP are lacking and patients avoid light. The consequences of long-term light avoidance on physical and psychological wellbeing is not fully understood, but is linked to anxiety, social isolation and very poor quality of life. Other treatments for EPP are symptomatic and supportive.

- Sunscreens containing physical reflecting agents (e.g., zinc oxide, titanium dioxide) or tanning creams that increase skin pigmentation (e.g., creams containing dihydroxyacetone) may be helpful to some patients.
- Oral beta-carotene, a high potency form of oral beta-carotene, has been used to try to improve affected patients tolerance of sunlight; however, there is no data to support this treatment.
- Vitamin D supplements: Recommended as EPP patients are likely to have low vitamin D levels from avoiding sunlight.

Scenesse (afamelanotide) Implant

- First-in-class therapy for the treatment of with EPP to increase pain‑free light exposure in adult patients with a history of phototoxic reactions from erythropoietic protoporphyria
- Afamelanotide is an α-melanocyte stimulating hormone (α-MSH) analog that functions as a melanocortin-1 receptor (MC1-R) agonist, resulting in increased production of eumelanin in the skin independent of exposure to sunlight or artificial UV light sources.
- Administered via a dissolvable implant inserted subcutaneously above the anterior supra-iliac crest every 2 months

Efficacy

The FDA approval was based on results from two multicenter, randomized trials (CUV039 and CUV029). The efficacy of Scenesse was established in two parallel group clinical trials in which patients 18 years or older with EPP or XLP received either Scenesse implant or a placebo form of the implant subcutaneously every two months. Both trials measured the number of hours the patient was able to spend in direct sunlight with no pain.

⌘ CUV039 trial (United States trial): 93 patients were followed for six months; 48 received Scenesse

- The primary endpoint was the total number of hours over 180 days spent in direct sunlight between 10 a.m. and 6 p.m. on days with no pain.

- Results showed that EPP patients treated with three Scenesse implants in the U.S. spent a median of 70 hours over six months in direct sunlight with no pain, while the placebo group spent 41 hours: duration of pain-free time in direct sunlight (outdoors between 10 am and 6 pm) was longer in the afamelanotide group (median 69.4 versus 40.8 hours); the greater number of hours in the U.S. trial reflects a longer portion of the day in which sunlight tolerance was assessed. (NCT01605136)

⌘ In CUV029 (European trial): 73 patients were followed for nine months); 38 received Scenesse

- The primary endpoint was the total number of hours over 270 days spent outdoors between 10 a.m. and 3 p.m. on days with no pain for which "most of the day" was spent in direct sunlight.
- The analysis did not include sun exposure on days patients reported spending time in a combination of both direct sunlight and shade.
- The median total number of hours over 270 days spent outdoors between 10 a.m. and 3 p.m. on days with no pain for which "most of the day" was spent in direct sunlight was 6.0 hours for patients receiving Scenesse versus 0.75 hours for patients receiving placebo.
- The duration of pain-free time in direct sunlight was longer with afamelanotide versus placebo (median 6.0 versus 0.8 hours) and the number of phototoxic reactions was lower in the afamelanotide group (77 versus 146) (NCT 00979745)

The trials found that afamelanotide substantially reduced photosensitivity and improved sunlight tolerance (Langendonk JG, et al 2015). In both trials, quality of life improved with afamelanotide therapy. Some participants described this treatment as 'life changing' in terms of activities they could engage in during treatment, which previously were not possible.

⌘ The FDA requires the manufacturer to complete the following post-marketing requirements: Conduct a thorough QT clinical study and conduct an observational cohort study assessing long-term safety, particularly related to rates of skin cancer, implant-site reactions, changes in pigmentary expressions, pregnancy outcomes, effects on lactation and breastfeeding infants, and implantation device malfunction or failure.

Summary: Afamelanotide is approved to increase pain-free light exposure in adults with a history of phototoxic reactions from EPP. In small, placebo-controlled trials, afamelanotide was associated with increased duration of sun exposure without pain, less severe phototoxic reactions, faster phototoxic reaction recovery time, and improved quality of life. An estimated 2-5% patients experience liver failure, however for the majority of patients with EPP life expectancy is normal. Hepatic complications of EPP are unlikely to be influenced by afamelanotide therapy.

FDA Indications

⌘ **Erythropoietic protoporphyria** To increase pain free light exposure in adult patients with a history of phototoxic reactions from erythropoietic protoporphyria

Available as: Subcutaneous implant containing 16 mg of afamelanotide; implant is a bioresorbable sterile rod measuring approximately 1.7 cm in length and 1.45 mm in diameter. Supplied in a sealed glass vial packaged individually in a cardboard box; not supplied with an implantation device.

Approved by the FDA: October 8, 2019
Orphan Drug Designation in 2008 from the FDA; Fast Track Status in May 2017; Priority Review in January 2019. Approved in adults in Europe in December 2014.

Boxed Warning/REMS program: None at this time

Pharmacologic Category: Alpha-Melanocyte Stimulating Hormone Analog, Synthetic; Melanocortin 1 Receptor (MC1-R) Agonist

COVERAGE CRITERIA FOR INITIAL AUTHORIZATION

Scenesse (afamelanotide) Implant may be authorized for members who meet **ALL** of the following criteria **[ALL]**

1. Prescriber specialty [ONE]

- ❒ Prescribed and administered by a dermatologist or a specialist in the treatment of porphyria who has completed training for Scenesse administration

2. Diagnosis/Indication [ALL]

Documentation of ALL of the following criteria are required. May include chart notes from the member's medical records, relevant labs and/or tests, and other relevant clinical information supporting the diagnosis:

- ❒ Definitive diagnosis of Erythropoietic Protoporphyria (EPP) or X-linked protoporphyria (known as XLP or XLEPP) confirmed by genetic testing. Gene sequencing shows an FECH, CLPX, or ALAS2 mutation
  - *Genetic testing for FECH mutations is available from the Porphyria Center at Mount Sinai Medical Center (212-659-6780 or 866-322-7968) and Mayo Medical Laboratories. The Mount Sinai center also offers testing for ALAS2 and CLPX mutations. Reference: Mittal S, UpToDate 2020. Note: The genetic testing contact information above was updated on April 2020. If links are not functioning, please notify.*
- ❒ Biochemical finding of a marked increase erythropoietic protoporphyria (EPP) (e.g. elevated free protoporphyrin in peripheral erythrocytes) confirmed by ONE of the following tests: [ONE] ·
  - ❍ Elevated **total** erythrocyte protoporphyrin (i.e. 300 to 8,000 mcg/dL)
    - *Normal ranges up to 80 mcg/dL*[Mittal S]
  - ❍ Elevated Erythrocyte fractionation shows ≥ 50% metal-free vs. zinc protoporphyrin
    - *In EPP, metal-free protoporphyrin generally represents >85 percent of total porphyrins. In XLP, metal-free protoporphyrin generally represents 50 to 85 percent of total porphyrins*
- ❒ Evidence of EPP/XLP-associated acute non-blistering cutaneous reactions (e.g., pain, stinging, redness, swelling, blanching) following exposure to sun

3. Age/Gender/Other restrictions [ALL]

- ❑ 18 years of age or older
  - *The safety and effectiveness of afamelanotide acetate have not been established in pediatric patients*

4. **Step/Conservative Therapy/Other condition Requirements [ALL]**
Documentation of ALL of the following criteria are required. May include chart notes from the member's medical records, relevant labs and/or tests, and other relevant clinical information:

- ❒ Sun avoidance and use of sunscreen, protective clothing, and pain medication have proven inadequate in controlling EPP-associated painful skin reactions
- ❒ Member will continue to maintain sun and light protection measures during treatment to prevent phototoxic reactions
- ❒ Member does not have any malignant or premalignant skin lesions (e.g., melanoma, dysplastic nevus syndrome, Bowen's disease, basal cell or squamous cell carcinomas, etc.) as evidenced by a baseline full body skin examination for pre-existing skin lesions
- ❒ Prescriber will submit documentation of full-body skin examination twice annually to monitor preexisting and new skin pigmentary lesions.

  NOTE: Subsequent authorizations require full skin examination. Clinical documentation must be submitted for initial request and for continuation of treatment requests.

5. ***Contraindications/Exclusions/Discontinuations to Scenesse (afamelanotide) therapy**
**There are no contraindications listed in the manufacturer's labeling. No drug interaction studies have been conducted with afamelanotide*
Authorization will <u>not</u> be granted if ANY of the following conditions apply [ANY]
   - ❒ Non-FDA approved indications
   - ❒ Hypersensitivity to afamelanotide or its inactive ingredient (i.e., poly [DL-lactide-co-glycolide] bioresorbable copolymer)

   <u>Exclusions</u>
   Member does NOT have any of the following conditions: [ANY]
   - ❒ EPP with significant hepatic involvement
     - *Hepatic dysfunction may occur in 20% to 30% of patients with EPP. Pivotal trials do not include patients clinically significant hepatic or other organ dysfunction*
   - ❒ Current Bowen's disease, basal cell carcinoma, squamous cell carcinoma, or other malignant or premalignant skin lesions
   - ❒ Any other photodermatosis such as polymorphic light eruption, actinic prurigo, discoid lupus erythematosus, chronic actinic dermatitis or solar urticaria

6. **Labs/Reports/Documentation required [ALL]**
All documentation for determination of medical necessity must be submitted for review. Prescriber to submit documentation as indicated in the criteria above, including but not limited to chart notes, applicable lab values and/or tests, adverse outcomes, treatment failures, or any other additional clinical information or clinical notes from the member's medical records supporting the diagnosis. Letters of support and/or explanation are often useful, but are not sufficient documentation unless ALL specific information required by this MCP are included.

   NOTE: Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.

REAUTHORIZATION /CONTINUATION OF THERAPY

Scenesse (afamelanotide) Implant may be authorized for continuation of therapy if meet **ALL** of the following criteria are met: **[ALL]**

1. Initial Coverage Criteria [ALL]

- ❑ Member currently meets ALL initial coverage criteria

2. Compliance

- ❑ Continuous adherence to therapy as verified by member's claim history (review member's prescription claims history for compliance). Any indicator of compliance or adherence issues should be discussed with discussed among treating physician, member, and Medical Director for a treatment plan or discontinuation of treatment.

3. Labs/Reports/Documentation required [ALL]

- ❒ Scenesse (afamelanotide) Implant therapy may be re-authorized when stabilization of disease, or absence of disease progression is **DOCUMENTED** by at least ONE (1) of the following: **[ONE]**
  - ❍ Decreased severity and number of phototoxic reactions
  - ❍ An increase in pain free time during light exposure
  - ❍ Improvement in acute non-blistering cutaneous reactions (e.g., pain, stinging, redness, swelling, blanching) following exposure to sun
  - ❍ Improvement on a pain-intensity Likert scale or QOL questionnaire
- ❒ Member has received a full skin examination by the Prescriber/Dermatologist within the last six months to monitor pre-existing and new skin pigmentary lesions. Documentation required.

  NOTE: Clinical documentation must be submitted with every continuation of treatment request.

4. Discontinuation of Treatment

Member should be assessed for discontinuation of therapy if **ANY** of the following are applicable: **[ANY]**

- ❑ Member has not experienced unacceptable toxicity, significant non-anaphylactic reaction(s), or anaphylaxis from Scenesse (afamelanotide) Implant therapy. Examples of unacceptable toxicity include the following: severe skin darkening, etc.
  - *The most common adverse effects observed in clinical trials included implant-site reaction, nausea, oropharyngeal pain, cough, fatigue, dizziness, skin hyperpigmentation, somnolence, melanocyte nevus, respiratory tract infection, nonacute porphyria, and skin irritation*

5. *Contraindications/Exclusions to Scenesse (afamelanotide) therapy

**There are no contraindications listed in the manufacturer's labeling. No drug interaction studies have been conducted with afamelanotide*

Authorization will not be granted if ANY of the following conditions apply [ANY]

- ❒ Non-FDA approved indications
- ❒ Hypersensitivity to afamelanotide or its inactive ingredient (i.e., poly [DL-lactide-co-glycolide] bioresorbable copolymer)

  Exclusions

  Member does NOT have any of the following conditions: [ANY]
- ❒ EPP with significant hepatic involvement
  - Hepatic dysfunction may occur in 20% to 30% of patients with EPP. Pivotal trials do not include patients clinically significant hepatic or other organ dysfunction
- ❒ Current Bowen's disease, basal cell carcinoma, squamous cell carcinoma, or other malignant or premalignant skin lesions
- ❒ Any other photodermatosis such as polymorphic light eruption, actinic prurigo, discoid lupus erythematosus, chronic actinic dermatitis or solar urticaria

6. Labs/Reports/Documentation required [ALL]

All documentation for determination of medical necessity must be submitted for review. Prescriber to submit documentation as indicated in the criteria above, including but not limited to chart notes, applicable lab values and/or tests, adverse outcomes, treatment failures, or any other additional clinical information or clinical notes from the member's medical records supporting the diagnosis. Letters of support and/or explanation are often useful, but are not sufficient documentation unless ALL specific information required by this MCP are included.

NOTE: Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.

ADMINISTRATION, QUANTITY LIMITATIONS, AND AUTHORIZATION PERIOD

Consult the manufacturer's labeling for more detailed information on dosage and administration of this drug, cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and monitoring.

1. Recommended Dosage [ONE]

- ❒ Erythropoietic protoporphyria: A single implant (16 mg) inserted every 2 months by a health care professional
  - *The afamelanotide implant should be inserted using an SFM Implantation Cannula or other implantation devices that have been determined by the manufacturer to be suitable for implantation of Scenesse. Refer to Scenesse Prescribing Information for specific implantation instructions. Contact Clinuvel Inc. for other implantation devices that have been determined by the manufacturer to be suitable for implantation of Scenesse*

- ❒ Prescriber must agree that the member will be monitored by a health care provider for at least 30 minutes after the implant administration

2. Authorization Limit [ALL]

- ❑ Quantity limit: [ALL]
  - ❍ One implant every 2 months
  - ❍ Maximum: THREE (3) implants per year for seasonal coverage *(most likely during spring and summer)*
    - Three implants per year are recommended, depending on the length of protection required. The recommended maximum number of implants is four per year.[NICE, EMA]
  - ❍ For requests beyond 3 implants a year: Medical justification is required. Prescriber submit all relevant supporting documentation for clinical staff review.
    - The recommended maximum number of implants is FOUR (4) per year. [NICE, EMA]

- ❒ Duration of initial authorization: **6 months**

- ❒ Continuation of treatment: Re-authorization for continuation of treatment is required every **6 months** to determine continued need based on member meeting 'Continuation of Therapy' criteria

3. Route of Administration [ALL]

- ❑ Administration by a health care professional who is proficient in the subcutaneous implantation procedure and has completed the training program provided by the manufacturer (Clinuvel)
- ❑ May be authorized in a **physician office setting** only. Routine administration in a hospital or outpatient setting will not be authorized
- ❑ Refer to MHI Policy & Procedure (P&P): Specialty Medication Administration Site of Care Policy: MHI Pharm 11
- ❑ If member meets all criteria and approval for therapy is granted, medication will be dispensed by a specialty pharmacy vendor at the discretion of Molina Healthcare.
  - The manufacturer, Clinuvel, may distribute Scenesse (afamelanotide) directly to hospitals and clinics where the implants can be inserted.

COVERAGE EXCLUSIONS

This policy only addresses the indication of Scenesse (afamelanotide) when appropriate criteria are met.

All other uses of Scenesse (afamelanotide) that are not an FDA-approved indication or not included in the 'Coverage Criteria' section of this policy are considered experimental/investigational or not a covered benefit of this policy. This subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

Refer to the Off-label Use Policy if requested diagnosis is NOT specifically listed in the Coverage Criteria section of this policy.

BACKGROUND/SUMMARY

Phase III Confirmatory Studies in Erythropoietic Protoporphyria
The efficacy of SCENESSE was evaluated in 2 randomized, multicenter, prospective, vehicle controlled clinical trials two trials (Study CUV039 and Study CUV029). The trials were designed to assess exposure to direct sunlight on days with no phototoxic pain. The two trials differed in the number of days of follow-up, the time windows within a day in which time spent outdoors was recorded, and how the amount of time spent in direct sunlight on each day was characterized. The subjects enrolled in these trials were primarily Caucasian (98%), the mean age was 40

CUV039 trial (NCT 01605136)
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) (Langendonk JG, et al, 2015)

Subjects: 93 patients (18 years and older) with biochemically confirmed EPP and without clinically significant hepatic or other organ dysfunction, or skin cancer, premalignant skin lesions, or other photodermatoses. Eligibility criteria was the same as for the CUV029 trial. Mean patient age was 40.4 years in the afamelanotide group and 39.1 years in the placebo group; 98% and 96% of patients in the afamelanotide and placebo groups, respectively, were white.

Intervention: Patients were randomized 1:1 to afamelanotide 16 mg (n=48) or vehicle-containing placebo (n=45) implanted subcutaneously every 2 months for 6 months. Patients received 3 implants (i.e., on days 0, 60, and 120). Pretreatment with a local anesthetic was optional. The study was completed and all implants received by 96% of patients in the afamelanotide group and 93% of the placebo group.

Results
Primary End Point(s)
- Number of hours spent in direct sunlight between 10 am and 6 pm without pain over the 6-month period: Median number of hours per patient was 69.4 (range, 0 to 651 hours) with afamelanotide and 40.8 (range, 0 to 224 hours) with placebo (*P*=0.04); mean number of hours per patient was 115.6 with afamelanotide and 60.6 with placebo.

Secondary End Point(s)
- Number of days patients spent time in some direct sunlight without pain: Median per patient was 85.5 days (range, 0 to 167 days) with afamelanotide and 54 days (range, 0 to 124 days) with placebo (*P*=0.005); mean per patient was 80.5 days with afamelanotide and 51.7 days with placebo.
- Number of hours spent in direct sunlight between 10 am and 6 pm on days with no pain or mild pain: Median per patient was 80 hours (range, 0.5 to 825 hours) with afamelanotide and 51 hours (range, 1.25 to 251 hours) with placebo (*P*=0.05); mean per patient was 141.1 hours with afamelanotide and 74.6 hours with placebo.

- Number of hours spent in direct sunlight between 10 am and 3 pm without pain: Median per patient was 39.6 hours (range, 0 to 419 hours) with afamelanotide and 31.8 hours (range, 0 to 199 hours) with placebo (*P*=0.09); mean per patient was 71.2 hours with afamelanotide and 41.6 hours with placebo.
- Total number of phototoxic reactions did not differ between groups (46 and 43 in the afamelanotide and placebo groups, respectively; *P*=0.6).
- Number of phototoxic reactions: Median per patient was 1 (range, 0 to 15) with afamelanotide and 1 (range, 0 to 35) with placebo (*P*=0.6); mean per patient was 2 with afamelanotide and 3.3 with placebo.
- Duration of phototoxic reactions: Median was 1 day (range, 0 to 34 days) with afamelanotide and 1 day (range, 0 to 98 days) with placebo (*P*=0.5); mean was 3.2 days with afamelanotide and 6.6 days with placebo.
- Sum of Likert score for severity of phototoxic reactions during the study: Median per patient was 4 (range, 0 to 196) with afamelanotide and 6 (range, 0 to 507) with placebo (*P*=0.44); mean per patient was 16.3 with afamelanotide and 34.1 with placebo. Likert pain scores favored afamelanotide, with no pain reported for a greater percentage of days in the afamelanotide group (89% vs 85%; *P*<0.001).

End Point(s)

- Quality of life (measured by DLQI) did not change in either study group; however, higher EPP-QOL scores were observed with afamelanotide than with placebo at day 60 (44 vs 23.4; *P*<0.001), day 120 (49.8 vs 30.4; *P*<0.001), and day 180 (51.1 vs 36.8; *P*=0.02).
- Photoprovocation was performed in 21 patients; patients who received a second afamelanotide implant had a higher tolerance to light on the dorsum of the hand and lower back than placebo-treated patients. At day 90 (30 days after dose 2), median change from baseline in minimum symptom dose (calculated using time to the patient's first prodromal symptom [eg, burning, tingling] and irradiation output) on the hand was 208.3 J/cm^2 with afamelanotide and 56.2 J/cm^2 with placebo (*P*=0.01); on the lower back, median change was 227.5 J/cm^2 with afamelanotide and −2.4 J/cm^2 with placebo (*P*<0.001). At day 120 (60 days after dose 2, and before dose 3), median change on the lower hand was 162.1 and 30 J/cm^2 with afamelanotide and placebo, respectively (*P*=0.045); on the lower back, median change was 82.5 and 12.1 J/cm^2, respectively (*P*=0.03).

Summary: This confirmatory phase 3 study, initiated after conclusion of the European trial (CUV029), was conducted in the United States from May 2012 through July 2013. The European study was conducted over a 9-month period; the US trial was conducted over 6 months and was designed so most of the study took place during the summer months, with patients recruited from 7 porphyria centers in the United States.

Limitations: Those in whom increased pigmentation did not develop reportedly did not challenge themselves with sun exposure for fear of developing a reaction, as evidenced by their mean total hours in direct sunlight. Increased pigmentation in the afamelanotide recipients partially unblinded the trial.

CUV029 trial (NCT 00979745)

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)

Phase 3, randomized, double-blind, placebo-controlled, multicenter study (Langendonk JG, et al, 2015)

Subjects: 74 patients (18 years and older) with biochemically confirmed EPP and without clinically significant hepatic or other organ dysfunction, or skin cancer, premalignant skin lesions, or other photodermatoses. Mean patient age was approximately 38 years; 100% and 97% of patients in the afamelanotide and placebo groups, respectively, were white.

Intervention: Patients were randomized 1:1 to afamelanotide 16 mg (n=38) or vehicle-containing placebo (n=36) implanted subcutaneously every 2 months for 9 months. Patients received 5 implants (i.e., on days 0, 60, 120, 180,

and 240). Pretreatment with a local anesthetic was optional. The study was completed and all scheduled implants received by 89% of patients in the afamelanotide group and 94% of the placebo group.

Results

Primary End Point(s)

- Number of hours spent in direct sunlight between 10 am and 3 pm without pain over the 9-month period: Median number of hours per patient was 6 (range, 0 to 193 hours) with afamelanotide and 0.8 (range, 0 to 35 hours) with placebo (*P*=0.005); mean number of hours per patient was 20.4 with afamelanotide and 5.6 with placebo. This analysis evaluated exposure on days for which "most of the day" was spent in direct sunlight and did not include sun exposure on days for which subjects reported spending time in a combination of both direct sunlight and shade.

Secondary End Point(s)

- Number of phototoxic reactions: Median per patient was 1 (range, 0 to 11) with afamelanotide and 2 (range, 0 to 20) with placebo (*P*=0.04); mean per patient was 2 with afamelanotide and 4.1 with placebo.
- Total number of phototoxic reactions during the study was lower in the afamelanotide group (77 vs 146; *P*=0.04).
- Duration of the longest phototoxic reaction: Median per patient was 1 day (range, 0 to 7 days) with afamelanotide and 2 days (range, 0 to 37 days) with placebo (*P*=0.08); mean per patient was 1.5 days with afamelanotide and 3.8 days with placebo.
- Duration of phototoxicity: Median per patient was 1 day (range, 0 to 23 days) with afamelanotide and 3 days (range, 0 to 90 days) with placebo (*P*=0.04); mean per patient was 3.7 days with afamelanotide and 10 days with placebo.
- Sum of the Likert score for severity of phototoxic reactions during the study: Median per patient was 5 (range, 0 to 113) with afamelanotide and 17.5 (range, 0 to 490) with placebo (*P*=0.02); mean per patient was 18 with afamelanotide and 52.9 with placebo. Likert pain scores favored afamelanotide, with no pain reported for a greater percentage of days in the afamelanotide group (92% vs 88%; *P*<0.001).
- Number of patients with a severe phototoxic reaction during the study was 25 (66%) in the afamelanotide group and 28 (78%) in the placebo group (*P*=0.25).

End Point(s)

- Quality of life (measured using the Dermatology Life Quality Index [DLQI]) did not change in either study group; however, higher Erythropoietic Protoporphyria Quality-of-Life (EPP-QOL) scores (higher scores indicating better quality of life) were observed with afamelanotide than with placebo at day 120 (78.8 vs 63.6; *P*=0.005), day 180 (84.6 vs 73.5; *P*=0.03), day 240 (84.8 vs 73.1; *P*=0.01), and day 270 (79.7 vs 67.2; *P*=0.06).

Long-term observational study of afamelanotide in 115 patients with erythropoietic protoporphyria

A retrospective study of 115 individuals with EPP who received afamelanotide at one of two porphyria centers for up to six years, 74 percent found the therapy to be effective (Biolcati 2015). Of the remaining individuals, 23 percent had to discontinue therapy for pregnancy or financial reasons, and 3 percent found the therapy to be ineffective. The mean quality of life scores for the group rose from 32 to 74 percent during the first six months of therapy and remained high (69 to 91 percent) for the duration of the study. Melanin density also increased but was challenging to interpret due to reduced therapy during the winter and increased sun exposure with effective therapy in some patients. The most frequent reasons for drug discontinuation were financial restrictions and pregnancy. This study population represented two-thirds of all individuals with EPP at these centers.

Limitations: Those in whom increased pigmentation did not develop reportedly did not challenge themselves with sun exposure for fear of developing a reaction, as evidenced by their mean total hours in direct sunlight. Increased pigmentation in the afamelanotide recipients partially unblinded the trial.

DEFINITIONS

Porphyrias are a group of inherited disorders with enzymatic deficiency in the blood synthesis pathway (also called porphyrin pathway). They are broadly classified as erythropoietic porphyrias based on the site of the overproduction and main accumulation of porphyrin. They manifest with either skin problems, neurological complications or gastro-intestinal problems (occasionally all).

CODING INFORMATION: The codes listed in this clinical policy are for informational purposes only. The listing of a service or device code in this policy does not imply that the service described by this code is a covered or non-covered. Coverage is determined by the benefit document. This list of codes may not be all inclusive and inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

CPT	Description

HCPCS	Description
C9399	Unclassified drugs or biologicals (hospital outpatient use)
J3490	Unclassified drugs

Billing Units: When billing for Scenesse using the NOC (Not Otherwise Classified) codes C9399 or J3490, the units billed should be represented as each (EA).

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Policy History	Approval
Policy Developed Peer Review: AMR Peer Review Network. 4/12/2020. Practicing Physician. Board certified in Dermatology	P&T Q2 2020

**All content, clinical evidence, coverage criteria, practice guidelines, appendices and reference sections reviewed and revised with the most recent medical literature and available evidence for both 'Annual Reviews' and 'Policy Revisions.' Annual Reviews without notable changes to coverage criteria or position may not require Peer Review. Policy Revisions include notable content updates or revisions that which may have affected criteria or requires review by a practicing specialist, Peer Reviewer.*

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