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Afamelanotide for Erythropoietic Protoporphyria

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Abstract

BACKGROUND—Erythropoietic protoporphyria is a severe photodermatosis that is associated with acute phototoxicity. Patients with this condition have excruciating pain and a markedly

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reduced quality of life. We evaluated the safety and efficacy of an α-melanocyte–stimulating hormone analogue, afamelanotide, to decrease pain and improve quality of life.

METHODS—We conducted two multicenter, randomized, double-blind, placebo-controlled trials of subcutaneous implants containing 16 mg of afamelanotide. Patients in the European Union (74 patients) and the United States (94 patients) were randomly assigned, in a 1:1 ratio, to receive a subcutaneous implant containing either afamelanotide or placebo every 60 days (a total of five implants in the European Union study and three in the U.S study). The type and duration of sun exposure, number and severity of phototoxic reactions, and adverse events were recorded over the respective 180-day and 270-day study periods. Quality of life was assessed with the use of validated questionnaires. A subgroup of U.S. patients underwent photoprovocation testing. The primary efficacy end point was the number of hours of direct exposure to sunlight without pain.

RESULTS—In the U.S. study, the duration of pain-free time after 6 months was longer in the afamelanotide group (median, 69.4 hours, vs. 40.8 hours in the placebo group; P = 0.04). In the European Union study, the duration of pain-free time after 9 months was also longer in the afamelanotide group than in the placebo group (median, 6.0 hours vs. 0.8 hours; P = 0.005), and the number of phototoxic reactions was lower in the the afamelanotide group (77 vs. 146, P = 0.04). In both trials, quality of life improved with afamelanotide therapy. Adverse events were mostly mild; serious adverse events were not thought to be related to the study drug.

CONCLUSIONS—Afamelanotide had an acceptable side-effect and adverse-event profile and was associated with an increased duration of sun exposure without pain and improved quality of life in patients with erythropoietic protoporphyria. (Funded by Clinuvel Pharmaceuticals and others; ClinicalTrials.gov numbers, NCT01605136 and NCT00979745.)

Erythropoietic protoporphyria is a rare, autosomal recessive inborn error of metabolism that typically manifests in early childhood as severe painful photosensitivity. The photosensitivity results from accumulated protoporphyrin in erythroid cells and tissues because of the decreased activity of ferrochelatase, the heme biosynthetic enzyme that inserts iron into protoporphyrin to form heme.[1–4] An X-linked form of erythropoietic protoporphyria[5,6] that accounts for 2 to 10% of cases results from a gain of function of erythroid-specific aminolevulinic acid synthase 2.

Pathophysiologically, protoporphyrin is released from erythroid cells into the circulation, gains access to the vascular endothelium and liver, and is excreted through the biliary system. When the skin is exposed to sun or visible light, the accumulated phototoxic protoporphyrin in superficial vessels is activated by blue light (400 to 410 nm), triggering singlet oxygen free-radical reactions that lead to severe neuropathic pain that lasts for hours to days.[1–4,7] The protoporphyrin in transit through the liver may precipitate, resulting in gallstones and cholestatic hepatitis in about 5% of cases; cholestatic hepatitis can progress to liver failure requiring transplantation.[8–10] The disease occurs across races and ethnic groups but is rare among blacks.[11]

Photosensitivity in patients with erythropoietic protoporphyria usually manifests in early childhood; it occurs 1 to 20 minutes after direct exposure to the sun. Patients have severe burning pain, typically on the hands and face, and this pain is often followed by swelling

and redness.[12] The neuropathic pain can be incapacitating and last for several days and does not respond to pain medications, including narcotic analgesics.[2]

Once patients are sensitized to the excruciating pain, they recognize early symptoms, which typically include tingling, burning, and itching, and they immediately avoid further sun exposure.[13,14] The sun-induced pain in childhood leads to an early and ingrained fear of sunlight and deliberate efforts to avoid sun exposure. Patients modify their lives to minimize light exposure, wear protective clothing to prevent phototoxic reactions, or remain indoors. This adaptive behavior has a major effect on their quality of life and markedly affects work opportunities, activities of daily living, and lifestyle choices.[15,16]

Currently, there is no effective treatment for erythropoietic protoporphyria.[14,17] Although several treatments (including beta carotene, *N*-acetyl-L-cysteine, and vitamin C) have been described in the literature, a systematic review of more than 20 studies showed little to no benefit.[18]

Afamelanotide (Scenesse, Clinuvel Pharmaceuticals) is a potent analogue of human α-melanocyte–stimulating hormone (α-MSH).[19–21] It is a tridecapeptide that binds to the melanocortin 1 receptor (MC1R) in dermal cells, including melanocytes, and increases the production of eumelanin in the epidermis without the ultraviolet light–induced cellular damage that occurs when melanin production is stimulated by ultraviolet radiation.[21,22] Melanin, in the form of eumelanin, is photoprotective.[23] It absorbs, scatters, and quenches ultraviolet light, scavenges free radicals, and acts as a neutral density filter that reduces all wavelengths of light equally.[23,24] Moreover, melanogenesis may provide a major antioxidant defense in melanocytes, neutralizing the deleterious effects of free radicals and reactive oxygen species.[24,25]

After a pilot study was conducted in Switzerland,[26,27] phase 2, randomized, placebo-controlled trials were conducted in the European Union[28] and the United States. These studies showed that afamelanotide had an acceptable adverse-event profile and enabled patients with erythropoietic protoporphyria to have more direct exposure to sunlight without pain due to phototoxicity. Here, we describe the results of phase 3 trials of afamelanotide in patients with erythropoietic protoporphyria in the European Union and the United States.

METHODS

STUDY DESIGN AND OVERSIGHT

Multicenter, randomized, double-blind, placebo-controlled trials were performed in the European Union and the United States. The former study was conducted at eight European centers for porphyria treatment, all of which were members of the European Porphyria Network.[29] This study was concluded before the U.S. trial began. The U.S. trial was conducted at seven U.S. porphyria centers.

Although the two trials followed similar protocols, changes to the U.S. trial were made on the basis of the results of the European Union trial. For example, the inclusion period was limited to 2 months, which enabled the trial to be performed mainly during the summer

months, and the trial period was changed to 6 months, instead of the 9-month study period in the European Union trial. In addition, more specific diary data on direct exposure to sunlight were collected. Patients were randomly assigned to afamelanotide or placebo for 6 months in the U.S. trial and for 9 months in the European Union trial.

The study was designed and sponsored by Clinuvel Pharmaceuticals, with input from investigators in the European Union and the United States. The last two authors had a primary role in reviewing and approving the protocol and ensuring the completeness and accuracy of the reported data and the analysis and adherence to the study protocol, which is available with the full text of this article at NEJM.org. The sponsor supplied the medication and monitored the trial. Data were collected by the investigators at each site and were forwarded to the sponsor. The sponsor was responsible for ensuring the accuracy and completeness of the recorded data. The authors received the locked database to check the accuracy of the data and analyses. Drafts of the manuscript were written by the first two authors with the assistance of the last two authors. No one who is not an author contributed to the manuscript.

PATIENTS

The eligibility criteria were the same in the two trials. Patients were eligible for participation if they were at least 18 years of age, had biochemically confirmed erythropoietic protoporphyria, and did not have clinically significant hepatic or other organ dysfunction, skin cancer, or premalignant lesions or other photodermatoses. Patients with a history of drug or alcohol abuse and pregnant women were not eligible for the trial. Men and premenopausal women were instructed to use adequate contraceptive measures during the entire trial and for 3 months thereafter.

A computer-generated randomization list for each site was used to assign patients to a study group. The studies were conducted in accordance with Good Clinical Practice guidelines and with approval of the medical ethics committee at each site. Written informed consent was obtained from all patients.

DRUG ADMINISTRATION

Patients were randomly assigned, in a 1:1 ratio, to receive either an implant formulation of afamelanotide, administered subcutaneously at a dose of 16 mg,[30] or a placebo implant formulation. Study investigators, research staff, and patients were unaware of the study-drug assignments.

Placebo implants were identical to the afamelanotide implants, but they contained only poly(D,L-lactide-co-glycolide). In both trials, an implant was inserted on days 0, 60, and 120; in the European Union trial, an implant was also inserted on days 180 and 240. Pretreatment with local anesthetic was optional. Under sterile conditions, the implant was introduced into the subcutaneous fat above the iliac crest with a 14-gauge catheter needle and then pushed into the fat tissue with a 16-gauge stylet.

ASSESSMENTS AND END POINTS

Safety and adverse events occurring during the study period were assessed at every visit for the duration of both trials. The primary end point was the duration of direct exposure to sunlight without pain between 10 a.m. and 3 p.m. (in the European Union trial) or between 10 a.m. and 6 p.m. (in the U.S. trial). The intensity and duration of pain and exposure to sunlight and shade were recorded daily by the patients in a diary. Time spent outdoors was recorded in 15-minute intervals. In the European Union trial, the duration of time spent every day in sunlight, shade, or outdoors in alternating sun and shade was documented. In the U.S. trial, this information was recorded in 15-minute intervals only as “direct sunlight” or “shade.”

Pain was scored on an 11-point Likert pain-intensity scale (with scores ranging from 0 to 10, and higher scores indicating greater severity of symptoms). Phototoxic reactions and their durations were defined as pain with a Likert score of 4 or higher occurring in light-exposed skin for one or more consecutive days.

Quality of life was assessed with the use of the Erythropoietic Protoporphyria Quality-of-Life (EPP-QOL) questionnaire (scores range from 0 to 100, with higher scores indicating a better quality of life) and the Dermatology Life Quality Index (scores range from 0 to 30, with lower scores indicating improved quality of life) (see the Supplementary Appendix, available at NEJM.org). Photoprovocation testing was performed in 21 U.S. patients (details are provided in the Supplementary Appendix).

Patients returned to the European Union sites on day 270 or to the U.S. sites on day 360 for complete safety assessments. These assessments included evaluation of epidermal pigment reversibility.

STATISTICAL ANALYSIS

In both trials, statistical analysis was performed by CPR Pharma Services. The analysis was performed on an intention-to-treat basis with the use of SAS software, version 9.3. Differences between the study-drug groups were assessed with the use of the Kruskal–Wallis test for primary outcomes, chi-square tests for proportions, and a Wilcoxon rank-sum test for changes in quality of life. Additional detailed information regarding data collection and statistics is provided in the Supplementary Appendix.

RESULTS

PATIENT CHARACTERISTICS

A total of 168 patients were enrolled in the two trials (74 patients in the European Union trial and 94 patients in the U.S. trial). After 1 patient discontinued the study before receiving a study drug, 86 patients received implants containing afamelanotide and 81 patients received implants containing placebo. Baseline characteristics, the reasons for early withdrawal from the study and the number of patients who withdrew from the study early, and adverse events were similar in the study groups in both trials (Table 1). The European

Union trial was conducted from January 2010 through May 2011, and the U.S. trial was conducted from May 2012 through July 2013.

EFFICACY

There were differences between the two trials with respect to the end points, the number of study-drug doses administered, the duration of the trial, the recruitment periods, and the data collected from the diaries. However, in both trials, the primary end point — the length of time during which patients were pain-free in direct sunlight — was significantly longer among patients who received afamelanotide than among patients who received placebo. After 6 months in the U.S. trial, the pain-free time in direct sunlight was 70% longer among patients who received afamelanotide than among patients who received placebo (median, 69.4 hours vs. 40.8 hours; P = 0.04); the duration of pain-free time was also significantly longer among patients who received afamelanotide than among those who received placebo after 9 months in the European Union trial (median, 6.0 hours vs. 0.8 hours; P = 0.005) (Table 2).

The total number of phototoxic reactions after 9 months was reduced among patients in the European Union trial (77 vs. 146, P = 0.04), although no significant changes were seen after 6 months in the U.S. trial (46 and 43 reactions, respectively; P = 0.60). In both studies, placebo recipients tended to have more pain relative to the time spent in direct sunlight, and they had more days with moderate-to-severe pain (Table 3).

To provide an objective measure of light tolerance, photoprovocation under standardized conditions was performed in 21 U.S. patients. As compared with patients who received placebo, patients who received a second afamelanotide implant had a significantly higher tolerance to light on the dorsum of the hand and the lower back. At day 90 (30 days after dose 2), the median change from the baseline minimum symptom dose in J per square centimeter on the hand was 208.3 in the afamelanotide group versus 56.2 in the placebo group (P = 0.01); on the lower back, the median change was 227.5 versus −2.4 (P<0.001). At day 120 (60 days after dose 2 and before dose 3), the median change from the baseline minimum symptom dose was 162.1 versus 30.0 (P = 0.045) on the hand and 82.5 versus 12.1 (P = 0.03) on the lower back (Table S3 in the Supplementary Appendix).

Quality of life, as measured with the use of the Dermatology Life Quality Index in both studies, did not change over time in either study-drug group. However, in both studies, the EPP-QOL questionnaire (Table S1 in the Supplementary Appendix) revealed marked improvements in the afamelanotide group (Table 4). In the European Union trial, the mean absolute scores at day 120 were 78.8 in the afamelanotide group, versus 63.6 in the placebo group (P = 0.005); at day 270, these scores were 79.7 and 67.2, respectively (P = 0.06). In the U.S. trial, the mean change in the score at day 60 relative to the baseline score was 44.0 in the afamelanotide group, versus 23.4 in the placebo group (P<0.001); at day 120, the mean change was 49.8 versus 30.4 (P<0.001), and at day 180, the mean change was 51.1 versus 36.8 (P = 0.02).

SAFETY

There were no deaths during the study. The four serious adverse events in the afamelanotide groups (subcapital humerus fracture, herniated disk, abdominal pain, and benign compound nevus) and the two serious adverse events in the placebo groups (pulmonary embolus and melanoma) were considered by the principal investigator to be unrelated to the study drug (Table 1). Adverse events that occurred during the study period were generally mild to moderate in severity; in both trials, the most common adverse events were headache, nausea, nasopharyngitis, and back pain (Table 5). There were no clinically relevant between-group differences in the incidence or severity of adverse events, except for mild hyperpigmentation at the implant site in one third of the patients who received afamelanotide and moles that darkened in a few patients who received this drug.

DISCUSSION

Our phase 3, multicenter, randomized, double-blind, placebo-controlled trials in the European Union and the United States were designed to evaluate the safety and effectiveness of afamelanotide in treating photosensitivity in patients with erythropoietic protoporphyria. The European Union trial, which was completed before the initiation of the U.S. trial, provided increased understanding of the patients' ingrained sun avoidance; this understanding led to various modifications in data collection and study end points in the U.S. trial (see the Supplementary Appendix). The five-dose, 9-month European Union trial and the three-dose, 6-month U.S. trial provided complementary results. The main results, which were concordant and consistent across the two trials, indicated that afamelanotide was safe and effective.

The results of both trials showed significant improvement with afamelanotide as compared with placebo with respect to the primary end point ($P = 0.005$ in the European Union trial and $P = 0.04$ in the U.S. trial). Phototoxic reactions were significantly less severe ($P = 0.04$) and recovery time was significantly faster ($P = 0.04$) among patients who received afamelanotide in the longer European Union study. The shortened recovery time from phototoxic reactions is a benefit, since these painful reactions can last up to several days and lead to absence from school or work and lost productivity. The benefits with afamelanotide with respect to secondary end points in the U.S. trial were also significant (Table 2). The photoprovocation study provided additional support for the results with respect to the primary end point by showing objective improvement in light tolerance (Table S3 in the Supplementary Appendix).

The EPP-QOL questionnaire, which was designed specifically for patients with this disorder, showed significant differences between the afamelanotide and placebo groups and favored afamelanotide in both trials for all questions. These findings further support the favorable effect of afamelanotide on the patients' daily lives (Table 4).

Limitations of these studies included the finding that both among patients who received afamelanotide and among patients who received placebo, those in whom increased pigmentation did not develop did not challenge themselves and continued to avoid sun exposure for fear of an incapacitating prolonged painful reaction, as evidenced by their

mean total hours in direct sunlight. Even patients who did challenge themselves did so in a limited manner, which probably decreased the magnitude of the treatment benefit. In addition, the increased skin pigmentation in participants who received afamelanotide partially unblinded the trial. Of note, in both trials, a few patients who received placebo were convinced that they received active drug and reportedly increased their sun exposure.

The differences between the European Union patients and the U.S. patients with respect to pain-free sunlight exposure at baseline and during the trial may be due in part to the higher latitudes of the European centers (range, 48 to 60°N) as compared with the U.S. centers (range, 29 to 42°N). Moreover, the end points measured time spent in direct sunlight and did not measure the probably much larger increase in the hours during which patients who received afamelanotide were in the shade or outside on cloudy days, since the drug may have led to greater outdoor protection and may have had a larger effect on the daily lives of patients with erythropoietic protoporphyria than the effect that we observed. There was no evidence that afamelanotide impeded bile flow or other hepatic functions.

Liver disease ranging from pigmented gallstones to cholestasis, cirrhosis, and liver failure develops in a small percentage of patients with erythropoietic protoporphyria. These complications are unlikely to be influenced by afamelanotide, since the liver disease is related to high protoporphyrin levels that do not change with afamelanotide treatment (Table S2 in the Supplementary Appendix).

A possible misconception is that α-MSH or an analogue might stimulate the development of melanoma. However, the primary risk factor for melanoma is ultraviolet B (UVB) irradiation, which can induce DNA damage and lead to acquisition of pro-proliferative and anti-senescence mutations.[31] α-MSH drives increased eumelanin production, inhibits production of pro-inflammatory cytokines,[32,33] and reduces the expression of vascular-cell adhesion molecule 1 and E-selectin.[32] MC1R signaling in response to α-MSH binding also stimulates DNA repair.[34] Eumelanin provides protection against melanoma by reducing UVB penetration of the skin and scavenging oxygen radicals generated as a result of exposure to UVB irradiation.[35] Moreover, since the MC1R receptor is not expressed in melanocyte stem cells in the hair follicle,[36] such stem cells would not be activated by α-MSH.

In the absence of specific strategies to increase mutant ferrochelatase activity or to deplete the accumulated phototoxic erythroid protoporphyrin, afamelanotide provided a safe and effective treatment of symptoms in patients with erythropoietic protoporphyria. Afamelanotide has been approved on a compassionate-use basis for patients with confirmed erythropoietic protoporphyria in Italy and Switzerland for more than 8 years. The high rate of adherence to the use of this drug and the low rate of side effects indicated extended benefit from the drug over 8 years.[37] Moreover, these patients, who also were monitored by means of the EPP-QOL questionnaire, had a significantly increased quality of life (expressed as the percentage of the maximum 100% quality) over that at baseline (74% vs. 31%) that was sustained over time. On the basis of the results of our clinical trials, the European Medicines Agency and the European Commission recently approved the use of afamelanotide in patients with confirmed erythropoietic protoporphyria.

In summary, afamelanotide had an acceptable side-effect profile and improved tolerance to sunlight in patients with erythropoietic protoporphyria. Afamelanotide-induced eumelanin synthesis provided photoprotection that enabled patients to have more exposure to visible light and decreased the consequences of phototoxicity. Patients who received afamelanotide had significantly improved quality of life.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Anderson, KE.; Sassa, S.; Bishop, DF.; Desnick, RJ. Disorders of heme biosynthesis: X-linked sideroblastic anemia and the porphyrias. In: Valle, D.; Beaudet, AL.; Vogelstein, B., et al., editors. The online metabolic and molecular bases of inherited disease. McGraw-Hill; New York: 2006. p. 95-105.
2. Todd DJ. Erythropoietic protoporphyria. Br J Dermatol. 1994; 131:751–66. [PubMed: 7857832]
3. Bonkovsky HL, Guo JT, Hou W, Li T, Narang T, Thapar M. Porphyrin and heme metabolism and the porphyrias. Compr Physiol. 2013; 3:365–401. [PubMed: 23720291]
4. Balwani, M.; Bloomer, J.; Desnick, R. Erythropoietic protoporphyria, autosomal recessive. In: Pagon, RA.; Adam, MP.; Ardinger, HH., et al., editors. GeneReviews. University of Washington; Seattle: 2014.
5. Whatley SD, Ducamp S, Gouya L, et al. C-terminal deletions in the ALAS2 gene lead to gain of function and cause X-linked dominant protoporphyria without anemia or iron overload. Am J Hum Genet. 2008; 83:408–14. [PubMed: 18760763]
6. Balwani M, Doheny D, Bishop DF, et al. Loss-of-function ferrochelatase and gain-of-function erythroid-specific 5-aminolevulinate synthase mutations causing erythropoietic protoporphyria and X-linked protoporphyria in North American patients reveal novel mutations and a high prevalence of X-linked protoporphyria. Mol Med. 2013; 19:26–35. [PubMed: 23364466]
7. Porter RM, Anstey A. Evidence and conjecture about mechanisms of cutaneous disease in photodermatology. Exp Dermatol. 2014; 23:543–6. [PubMed: 24910168]
8. Bloomer JR. The liver in protoporphyria. Hepatology. 1988; 8:402–7. [PubMed: 3281889]
9. McGuire BM, Bonkovsky HL, Carithers RL Jr, et al. Liver transplantation for erythropoietic protoporphyria liver disease. Liver Transpl. 2005; 11:1590–6. [PubMed: 16315313]

10. Anstey AV, Hift RJ. Liver disease in erythropoietic protoporphyria: insights and implications for management. Gut. 2007; 56:1009–18. [PubMed: 17360790]
11. Gouya L, Martin-Schmitt C, Robreau AM, et al. Contribution of a common single-nucleotide polymorphism to the genetic predisposition for erythropoietic protoporphyria. Am J Hum Genet. 2006; 78:2–14. [PubMed: 16385445]
12. Lecha M, Puy H, Deybach JC. Erythropoietic protoporphyria. Orphanet J Rare Dis. 2009; 4:19. [PubMed: 19744342]
13. Lecha M. Erythropoietic protoporphyria. Photodermatol Photoimmunol Photomed. 2003; 19:142–6. [PubMed: 12914599]
14. Thunell S, Harper P. Porphyrins, porphyrin metabolism, porphyrias. III. Diagnosis, care and monitoring in porphyria cutanea tarda — suggestions for a handling programme. Scand J Clin Lab Invest. 2000; 60:561–79. [PubMed: 11202050]
15. Holme SA, Anstey AV, Finlay AY, Elder GH, Badminton MN. Erythropoietic protoporphyria in the U.K.: clinical features and effect on quality of life. Br J Dermatol. 2006; 155:574–81. [PubMed: 16911284]
16. Wahlin S, Floderus Y, Stål P, Harper P. Erythropoietic protoporphyria in Sweden: demographic, clinical, biochemical and genetic characteristics. J Intern Med. 2011; 269:278–88. [PubMed: 20412370]
17. Murphy GM. Diagnosis and management of the erythropoietic porphyrias. Dermatol Ther. 2003; 16:57–64. [PubMed: 12919128]
18. Minder EI, Schneider-Yin X, Steurer J, Bachmann LM. A systematic review of treatment options for dermal photosensitivity in erythropoietic protoporphyria. Cell Mol Biol (Noisy-le-grand). 2009; 55:84–97. [PubMed: 19268006]
19. Castrucci AM, Hadley ME, Sawyer TK, Hruby VJ. Enzymological studies of melanotropins. Comp Biochem Physiol B. 1984; 78:519–24. [PubMed: 6332706]
20. Sawyer TK, Sanfilippo PJ, Hruby VJ, et al. 4-Norleucine, 7-D-phenylalanine-alpha-melanocyte-stimulating hormone: a highly potent alpha-melanotropin with ultralong biological activity. Proc Natl Acad Sci U S A. 1980; 77:5754–8. [PubMed: 6777774]
21. Fabrikant J, Touloei K, Brown SM. A review and update on melanocyte stimulating hormone therapy: afamelanotide. J Drugs Dermatol. 2013; 12:775–9. [PubMed: 23884489]
22. Pathak, MA. Functions of melanin and protection by melanin. In: Zeise, L.; Chedekel, MR.; Fitzpatrick, TB., editors. Melanin: its role in human photoprotection. Valdenmar; Overland Park, KS: 1995. p. 125-34.
23. Kaidbey KH, Agin PP, Sayre RM, Kligman AM. Photoprotection by melanin — a comparison of black and Caucasian skin. J Am Acad Dermatol. 1979; 1:249–60. [PubMed: 512075]
24. Bustamante J, Bredeston L, Malanga G, Mordoh J. Role of melanin as a scavenger of active oxygen species. Pigment Cell Res. 1993; 6:348–53. [PubMed: 8302773]
25. Kollias N, Sayre RM, Zeise L, Chedekel MR. Photoprotection by melanin. J Photochem Photobiol B. 1991; 9:135–60. [PubMed: 1907647]
26. Harms JH, Lautenschlager S, Minder CE, Minder EI. Mitigating photosensitivity of erythropoietic protoporphyria patients by an agonistic analog of alpha-melanocyte stimulating hormone. Photochem Photobiol. 2009; 85:1434–9. [PubMed: 19656325]
27. Harms J, Lautenschlager S, Minder CE, Minder EI. An alpha-melanocyte-stimulating hormone analogue in erythropoietic protoporphyria. N Engl J Med. 2009; 360:306–7. [PubMed: 19144952]
28. Minder EI, Schneider-Yin X. Afamelanotide (CUV1647) in dermal phototoxicity of erythropoietic protoporphyria. Expert Rev Clin Pharmacol. 2015; 8:43–53. [PubMed: 25470471]
29. Tollånes MC, Aarsand AK, Villanger JH, et al. Establishing a network of specialist porphyria centres — effects on diagnostic activities and services. Orphanet J Rare Dis. 2012; 7:93. [PubMed: 23227998]
30. Haylett AK, Nie Z, Brownrigg M, Taylor R, Rhodes LE. Systemic photoprotection in solar urticaria with α-melanocyte-stimulating hormone analogue [Nle4-D-Phe7]-α-MSH. Br J Dermatol. 2011; 164:407–14. [PubMed: 20969564]
31. Bennett DC. How to make a melanoma: what do we know of the primary clonal events? Pigment Cell Melanoma Res. 2008; 21:27–38. [PubMed: 18353141]

32. Luger TA, Brzoska T, Scholzen TE, et al. The role of alpha-MSH as a modulator of cutaneous inflammation. Ann N Y Acad Sci. 2000; 917:232–8. [PubMed: 11268349]

33. Brzoska T, Luger TA, Maaser C, Abels C, Böhm M. Alpha-melanocyte-stimulating hormone and related tripeptides: biochemistry, antiinflammatory and protective effects in vitro and in vivo, and future perspectives for the treatment of immune-mediated inflammatory diseases. Endocr Rev. 2008; 29:581–602. [PubMed: 18612139]

34. Hauser JE, Kadekaro AL, Kavanagh RJ, et al. Melanin content and MC1R function independently affect UVR-induced DNA damage in cultured human melanocytes. Pigment Cell Res. 2006; 19:303–14. [PubMed: 16827749]

35. Hill HZ. The function of melanin or six blind people examine an elephant. Bioessays. 1992; 14:49–56. [PubMed: 1546980]

36. Osawa M, Egawa G, Mak SS, et al. Molecular characterization of melanocyte stem cells in their niche. Development. 2005; 132:5589–99. [PubMed: 16314490]

37. Biolcati G, Marchesini E, Sorge F, Barbieri L, Schneider-Yin X, Minder EI. Long-term observational study of afamelanotide in 115 patients with erythropoietic protoporphyria. Br J Dermatol. 2015; 172:1601–12. [PubMed: 25494545]

Table 1

Baseline Characteristics, Reasons for Early Withdrawal from the Study, and Adverse Events.*

Variable	European Union Trial		U.S. Trial	
	Afamelanotide (N = 38)	Placebo (N = 36)	Afamelanotide (N = 48)	Placebo (N = 45)
Age — yr	38.3±13.0	38.6±11.6	40.4±12	39.1±16.2
Body-mass index†	24.0±3.0	26.5±5.2	26±4.8	26.7±5.4
White race — no. (%)‡	38 (100)	35 (97)	47 (98)	43 (96)
Fitzpatrick skin type — %				
I (never tans, always burns)	16	33	27	22
II (tans less than average [with difficulty], mostly burns)	47	42	42	33
III (tans at average level, sometimes has mild burn)	34	25	25	36
IV (rarely burns, tans more than average [with ease])	3	0	6	9
Early discontinuation — no. of patients§	4	2	3	4
Protocol violation	1	0	0	0
Suspected pregnancy	1	0	0	0
Withdrawal of consent	2	1	2	0
Lost to follow-up	0	0	0	2
Sponsor decision	0	0	0	1
Physician decision	0	1	1	1
Adverse events				
Adverse events that occurred during the study period — no.	189	166	272	216
Patients with any adverse event that occurred during the study period — no. (%)	34 (89)	32 (89)	45 (94)	39 (87)
Severity of adverse events that occurred during the study period — no. (%)				
Mild	19 (50)	17 (47)	17 (35)	14 (31)
Moderate	12 (32)	14 (39)	25 (52)	23 (51)
Severe	3 (8)	1 (3)	3 (6)	2 (4)
Most frequent adverse events that occurred during the study period — no. (%)				
Nausea	7 (18)	6 (17)	9 (19)	8 (18)
Headache	13 (34)	14 (39)	19 (40)	13 (29)
Nasopharyngitis	8 (21)	8 (22)	6 (12)	10 (22)
Serious adverse events — no.¶	1	0	3	2
Patients who completed the study and received all implants — no. (%)‖	34 (89)	34 (94)	46 (96)	42 (93)

*Plus-minus values are means ±SD. There were no significant differences between the groups.

†Body-mass index is the weight in kilograms divided by the square of the height in meters.

‡Race was self-reported.

[§] In the U.S. trial, one patient in the placebo group who had an eye pigmentation abnormality was excluded before receiving the first implant, and two other patients discontinued the study early owing to medical reasons that were unrelated to the study drug. In the European Union trial, a physician decided to withdraw one patient from the study because of worsening of preexisting severe headaches.

[¶] Serious adverse events in the afamelanotide groups were subcapital humerus fracture with uncomplicated repair, herniated disk, abdominal pain, and benign compound nevus. Serious adverse events in the placebo groups were pulmonary embolus and melanoma. All serious adverse events were deemed by the investigators not to be related to study drugs.

[//] Patients in the European Union study received five implants, and those in the U.S. study received three implants.

Table 2

Primary and Secondary End Points.*

End Point	Afamelanotide	Placebo	P Value
European Union trial			
No. of patients	38	36	
Primary end point: no. of hours in direct sunlight between 10 a.m. and 3 p.m. without pain			0.005
Median per patient (range)	6.0 (0–193)	0.8 (0–35)	
Mean per patient	20.4±40.5	5.6±9.3	
Secondary end points			
Phototoxic reactions — no.†			0.04
Median per patient (range)	1.0 (0–11)	2.0 (0–20)	
Mean per patient	2.0±2.8	4.1±5.1	
Phototoxic reactions during study — no.	77	146	0.04
Duration of longest phototoxic reaction — days			0.08
Median per patient (range)	1.0 (0–7)	2.0 (0–37)	
Mean per patient	1.5±1.8	3.8±7.4	
Duration of phototoxicity — days			0.04
Median per patient (range)	1.0 (0–23)	3.0 (0–90)	
Mean per patient	3.7±5.6	10.0±18.3	
Sum of Likert score for severity of phototoxic reactions during study			0.02
Median per patient (range)	5.0 (0–113)	17.5 (0–490)	
Mean per patient	18.0±27.9	52.9±98.2	
Patients with severe phototoxic reactions — no. (%)	25 (66)	28 (78)	0.25
U.S. trial			
No. of patients	46	43	
Primary end point: no. of hours in direct sunlight between 10 a.m. and 6 p.m. without pain			0.04
Median per patient (range)	69.4 (0–651)	40.8 (0–224)	
Mean per patient	115.6±140.6	60.6±60.6	
Secondary end points			
No. of days in some direct sunlight without pain			0.005
Median per patient (range)	85.5 (0–167)	54.0 (0–124)	
Mean per patient	80.5±48.9	510.7±37.3	
No. of hours in direct sunlight between 10 a.m. and 6 p.m. on days with no pain or mild pain			0.05
Median per patient (range)	80.0 (0.5–825)	51.0 (1.25–251)	
Mean per patient	141.1±165.1	74.6±67.5	
No. of days with some sunlight between 10 a.m. and 6 p.m. on days with no pain or mild pain			0.004
Median per patient (range)	97.0 (2–185)	61.0 (3–145)	
Mean per patient	93.9±51.0	64.0±40.6	
No. of hours in direct sunlight between 10 a.m. and 3 p.m. without pain			0.09
Median per patient (range)	39.6 (0–419)	31.8 (0–199)	
Mean	71.2±89.2	41.6±45.3	

End Point	Afamelanotide	Placebo	P Value
Phototoxic reactions — no.†			0.60
Median per patient (range)	1.0 (0–15)	1.0 (0–35)	
Mean per patient	2.0±3.3	3.3±6.8	
Duration of phototoxic reactions — days			0.50
Median (range)	1.0 (0–34)	1.0 (0–98)	
Mean	3.2±6.0	6.6±16.8	
Sum of Likert score for severity of phototoxic reactions during study			0.44
Median per patient (range)	4.0 (0–196)	6.0 (0–507)	
Mean per patient	16.3±33.2	34.1±86.7	

* Plus-minus values are means ±SD. P values for the differences between the afamelanotide and placebo groups were calculated with the use of the Kruskal-Wallis test.

† A phototoxic reaction was defined as a Likert score of 4 or higher. Scores on the Likert scale range from 0 to 10, with 0 indicating no pain and higher scores indicating greater severity of symptoms. Scores between 1 and 3 indicate mild pain.

Table 3

Severity of Pain, According to Likert Score.*

Variable	European Union Trial		U.S. Trial	
	Afamelanotide	Placebo	Afamelanotide	Placebo
Days recorded in diary — no.	9742	9601	8055	7368
Pain level — no. of days (% of recorded days)				
No pain, Likert score of 0	8914 (92)†	8463 (88)	7156 (89)†	6245 (85)
Mild pain, Likert score of 1–3	687 (7)	777 (8)	753 (9)	840 (11)
Moderate pain, Likert score of 4–6	124 (1)	298 (3)	127 (2)	239 (3)
Severe pain, Likert score of 7–10	17 (<1)	63 (<1)	19 (<1)	44 (<1)

* The difference in the distribution of pain scores between study-drug groups was analyzed by means of the chi-square test.

† P<0.001 for the comparison with placebo.

Table 4

EPP-QOL Questionnaire Scores.*

Trial and Questionnaire Score	Afamelanotide		Placebo		P Value
	Score	No. of Patients	Score	No. of Patients	
European Union trial					
Baseline score at day 0, before dose 1	39.0±25.8	37	35.3±23.7	34	0.39
Score at day 60, before dose 2	68.0±19.1	37	60.1±22.0	35	0.09
Score at day 120, before dose 3	78.8±16.2	37	63.6±23.9	35	0.005
Score at day 180, before dose 4	84.6±12.6	35	73.5±24.3	35	0.03
Score at day 240, before dose 5	84.8±10.7	34	73.1±24.1	34	0.01
Score at day 270, final visit	79.7±16.1	32	67.2±25.7	34	0.06
U.S. trial					
Baseline score at day 0, before dose 1	26.6±19.9	47	26.2±19.4	43	
Change at day 60, before dose 2	44.0±25.8	47	23.4±24.6	43	<0.001
Change at day 120, before dose 3	49.8±26.4	46	30.4±25.4	42	<0.001
Change at day 180	51.1±29.1	46	36.8±25.7	43	0.02
Scores at day 360, 240 days after last dose	38.4±27.0	44	45.4±29.6	40	

* Plus–minus values are means ±SD. Scores on the Erythropoietic Protoporphyria Quality-of-Life (EPP-QOL) questionnaire range from 0 to 100, with higher scores indicating a better quality of life. In the European Union trial, P values for the comparison of afamelanotide with placebo were determined by means of the paired Wilcoxon rank-sum test; in the U.S. trial, P values are determined by means of the Kruskal–Wallis test. Additional details about the EPP-QOL questionnaire are provided in Table S1 in the Supplementary Appendix.

Table 5

Most Frequently Reported Adverse Events That Occurred during the Study Period.*

Event	European Union Trial		U.S. Trial	
	Afamelanotide (N = 38)	Placebo (N = 36)	Afamelanotide (N = 48)	Placebo (N = 45)
Total no. of events	189	166	272	216
Ear and labyrinth disorder: ear pain — no. (%)	1 (3)	2 (6)	2 (4)	0
Gastrointestinal disorder — no. (%)				
Abdominal discomfort	0	1 (3)	1 (2)	2 (4)
Abdominal pain	4 (11)	1 (3)	1 (2)	3 (7)
Upper abdominal pain	1 (3)	1 (3)	1 (2)	3 (7)
Diarrhea	3 (8)	4 (11)	2 (4)	3 (7)
Dyspepsia	0	1 (3)	3 (6)	3 (7)
Nausea	7 (18)	6 (17)	9 (19)	8 (18)
Toothache	0	0	3 (6)	3 (7)
Vomiting	1 (3)	2 (6)	1 (2)	0
General disorder and administration-site condition — no. (%)				
Fatigue	1 (3)	2 (6)	3 (6)	0
Implant-site discoloration	4 (11)	0	9 (19)	0
Pain	0	0	4 (8)	4 (9)
Infection and infestation — no. (%)				
Viral gastroenteritis	1 (3)	2 (6)	0	3 (7)
Influenza	6 (16)	3 (8)	2 (4)	7 (16)
Nasopharyngitis	8 (21)	8 (22)	6 (12)	10 (22)
Sinusitis	0	2 (6)	3 (6)	3 (7)
Upper respiratory tract infection	3 (8)	1 (3)	1 (2)	0
Abnormal laboratory result — no. (%)				
Blood in urine	2 (5)	2 (6)	0	0
Increase in γ-glutamyltransferase level	0	3 (8)	0	0
Musculoskeletal and connective-tissue disorder — no. (%)				
Arthralgia	0	2 (6)	5 (10)	2 (4)
Back pain	2 (5)	4 (11)	6 (12)	6 (13)
Musculoskeletal pain	0	1 (3)	3 (6)	1 (2)
Myalgia	1 (3)	2 (6)	3 (6)	1 (2)
Pain in extremity	1 (3)	2 (6)	2 (4)	2 (4)
Nervous system disorder — no. (%)				
Dizziness	0	0	1 (2)	2 (4)
Headache	13 (34)	14 (39)	19 (40)	13 (29)
Migraine	1 (3)	3 (8)	3 (6)	3 (7)
Sinus headache	0	0	1 (2)	2 (4)
Respiratory, thoracic, and mediastinal disorder — no. (%)				
Cough	5 (13)	2 (6)	1 (2)	1 (2)
Oropharyngeal pain	6 (16)	2 (6)	2 (4)	2 (4)

Event	European Union Trial		U.S. Trial	
	Afamelanotide (N = 38)	Placebo (N = 36)	Afamelanotide (N = 48)	Placebo (N = 45)
Skin and subcutaneous tissue disorder — no. (%)				
Eczema	2 (5)	1 (3)	0	1 (2)
Melanocytic nevus	0	0	2 (4)	1 (2)
Pigmentation disorder	3 (8)	0	1 (2)	0
Pruritus	2 (5)	1 (3)	2 (4)	2 (4)

* Events listed were reported by three or more patients in either of the studies.