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

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Summary

Background In erythropoietic protoporphyria (EPP), an inherited disease of porphyrin-biosynthesis, the accumulation of protoporphyrin in the skin causes severely painful phototoxic reactions. Symptom prevention was impossible until recently when afamelanotide became available. Afamelanotide-induced skin pigmentation has statistically significantly improved light-tolerance, although the clinical significance of the statistical effect was unknown.

Objectives To assess clinical effectiveness by recording compliance and safety during prolonged use.

Methods We report longitudinal observations of 115 ambulatory patients with EPP, who were treated with a total of 1023 afamelanotide implants over a period of up to 8 years at two porphyria centres; one in Rome, Italy, and the other in Zurich, Switzerland.

Results Since the treatment first became available in 2006, the number of patients treated with 16 mg afamelanotide implants rose continuously until June 2014, when 66% of all patients with EPP known to the porphyria centres were treated. Only three patients considered afamelanotide did not meet their expectations for symptom improvement; 23% discontinued the treatment for other, mostly compelling, reasons such as pregnancy or financial restrictions. The quality of life (QoL) scores, measured by an EPP-specific questionnaire, were 31 ± 24% of maximum prior to afamelanotide treatment, rose to 74% after starting afamelanotide and remained at this level during the entire observation period. Only minor adverse events attributable to afamelanotide, predominantly nausea, were recorded.

Conclusion Based on the improved QoL scores, high compliance and low discontinuation rates, we conclude that afamelanotide exhibits good clinical effectiveness and good safety in EPP under long-term routine conditions.

What's already known about this topic?

- Afamelanotide implants have been studied in two phase II and three phase III studies with significant improvement of outcomes: sun sensitivity and EPP-related pain. However, in absolute values the effects have been small.
- The afamelanotide-induced tanning causes unblinding, so that a positive bias cannot be excluded.

What does this study add?

- This long-term observational study shows that 97% of patients considered afamelanotide to be effective in ameliorating EPP symptoms and 93% adhered to treatment for a prolonged time, if there were no compelling reasons to discontinue, which indicates good clinical effectiveness.
- This study supports a good safety profile for afamelanotide, as even in long-term usage, only minor adverse effects were observed.

Erythropoietic protoporphyria (EPP) is an inherited disease of porphyrin biosynthesis, in which the accumulation of protoporphyrin IX is the causative factor for phototoxic reactions in light-exposed skin.[1–4] These reactions may be elicited by as little as a few minutes of sun-exposure.[5] Initially, patients suffer from burning pain. If irradiation is prolonged, oedema, petechia, skin fissures, erosions, crusting and bullae may develop,[6] but pain is the most prominent and most incapacitating symptom. It may last for more than a week and only strong analgesics such as opioids relieve it in part. The experience of such excruciating pain causes a distinct sun- and light-avoidance behaviour. However, daily circumstances and social pressure may prevent the patient from avoiding the harmful light. During childhood and adolescence, patients progressively adapt to their disease, although this adaption means that they are excluded from social and occupational activities.[7] Consequently, patients with EPP are more frequently unemployed than the general population.[8]

In Italy and Switzerland we attempted to prevent phototoxic skin reactions with sunscreens containing titanium dioxide,[9] high-dose betacarotene,[10] cysteine[11] or local antioxidants.[12] The patients themselves experimented with locally applied self-tanning compounds. However, within a short time period, patients consistently reported a failure of all attempts and stopped these treatments. Cholestyramine, which has been considered to improve EPP-related liver disease by interrupting the enterohepatic recirculation of protoporphyrin,[13] did not improve uncomplicated EPP.[14] A meta-analysis dated from 2009 excluded any scientifically proven effective therapy for EPP.[15]

Afamelanotide (Scenesse®), an α-melanocyte-stimulating hormone (αMSH) analogue, induces skin-tanning and exerts an anti-inflammatory effect on the skin.[16–18] Recently, its ability to prevent phototoxic episodes in patients with EPP was shown in several studies (Table S1; see Supporting Information).[17,19–21] Improved tolerance to artificial light, prolongation of spontaneous sunlight exposure, decrease in pain intensity and improved quality of life were measured in the actively treated participants. When we started treating patients with afamelanotide during the first open-label clinical trial,[19] patients reported an impressive reduction of their sun sensitivity and improvement of their life quality. After the trials, the participants could choose the compassionate use (CU) programme and the majority of them used this option. In 2009, the Italian authorities enabled the unrestricted application to all patients with EPP based on specific legislation and this decision allowed afamelanotide treatment of patients with EPP in Switzerland according to Swiss regulations (expanded access programme, EA). As patients received the treatment only at central porphyria centres, i.e. in Rome for Italy and in Zurich for Switzerland, they had to make substantial sacrifices of time, travel and healthcare costs in order to receive this treatment.

While the placebo-controlled studies showed statistically significant improvements in study endpoints (Table S1; see Supporting Information), the question arose as to whether these effects were also of clinical significance. Moreover, the skewed distribution pattern of the results can be interpreted as showing that only a subgroup of patients benefited from afamelanotide treatment. An alternative interpretation is that the typical sun-avoidance behaviour acquired by the patients since their early childhood prevented their exposure to the sun even during active treatment, so that the measureable absolute effects on the phototoxic pain intensity and on the time exposed to sun – although significant – were minor. Both interpretations are in stark contrast to the major positive effects reported by the patients themselves.

Trials in rare diseases are often difficult to perform.[22] This is especially true in photosensitivity disorders such as EPP[23] and solar urticaria,[24] where the lack of a validated outcome measurement is one of the big obstacles. Studies of orphan medicines frequently do not completely fulfil the rigid requirements of classical study design as pointed out by Buckley, a former member of the Committee for Orphan Medicinal Products of the European Medicines Agency.[25] In his review on orphan drug marketing authorization by the European Medicines Agency, Buckley reported that data from open comparative studies, uncontrolled studies or CU were taken into account in many approval processes of such drugs.

In this retrospective study, we report patient compliance in the afamelanotide CU and EA programmes, the causes of discontinuation, the longitudinal effect of afamelanotide treatment on quality of life, skin melanin density (MD) and the number of adverse events between 2006 and 2014. These data document safety and patient-reported effects during long-term usage, which resembles routine clinical practice more than clinical trial conditions.

Patient groups and methods of assessments

Afamelanotide (Scenesse®), a controlled release 16 mg implant, is administered subcutaneously every second month. Current contraindications include pregnancy, lactation and age below 18 years, personal history of melanoma or dysplastic naevus syndrome, current Bowen's disease, basal or squamous cell carcinoma, or other malignant or premalignant skin lesion.

The diagnosis of EPP was based on severe phototoxic skin reactions since childhood and on a significantly, i.e. at least fivefold, elevated protoporphyrin in the erythrocytes.

The observation period lasted from the first phase II trial in 2006 until 14 June 2014. In the first phase II trial (CUV010) 2006, five Swiss patients participated. In the first multicentre phase III trial (CUV017) 2007–2009, 17 Swiss patients, including four phase II participants and 22 Italian patients participated. The CU programme, starting immediately after the trials and restricted to trial participants, was replaced in 2009 in Italy and in 2012 in Switzerland by the EA programme that was open to all patients with EPP but restricted to the two porphyria centres in Rome and Zurich in order to prevent abuse of the drug. Implants per patient per year were counted, whereby time zero was set as the time a patient received the first implant.

In Italy, all healthcare costs were covered by social insurance. In Switzerland, patients had to pay between 1000 and

3300 Swiss francs annually, dependent on their specific insurance. In both countries, the patients had to cover the travel costs to the treating centres.

In both countries, prior to the first dose, a whole body dermatological examination excluded precancerous skin lesions. This dermatological screening was repeated every second year. Females of childbearing potential were tested for pregnancy before each implant administration. Laboratory safety tests consisted of a blood count, serum glutamic oxaloacetic transaminase, creatinine, lactate dehydrogenase, urine test and protoporphyrin in the erythrocytes and were performed at least every half year. At the same time points, the patients were asked to fill in an EPP-specific quality of life (QoL) questionnaire. In Switzerland only, MD was measured at six anatomical sites (forehead, cheek, inner upper arm, medial forearm, abdomen, buttock) and the mean of these measurements was calculated.[26] The difference between the mean before the first dose (baseline) and subsequent measurements was calculated.

The EPP-specific QoL questionnaire used in Zürich (Appendix 1) was based on the original set of 18 questions developed by clinical experts in association with Clinuvel Pharmaceuticals Ltd. In Rome, the questionnaire was modified by removing the three questions (No. 5, 11 and 14) and the three unnumbered Likert-type QoL questions to make it compatible with other trials. During subsequent psychometric validation by Oxford Outcomes (Oxford, U.K.), a further three questions were removed (No. 3, 12 and 16). The scores were corrected for missing values by multiplying the sum of the answers by the factor: total possible answers/number of answers. In 138 Swiss questionnaires, all 18 questions were answered; in 16 questionnaires, 17 questions were answered; in four questionnaires, 16 questions were answered and in three questionnaires, fewer than 16 questions were answered. All 460 Italian questionnaires were complete.

Each time before receiving a new implant, patients' adverse events experienced since the previous implantation and any other health problems were documented according to MedDRA[27] and recorded on a 5-point scale, whether or not the recorded adverse events were related to afamelanotide. Implants were administered consistently with the procedures followed in the clinical trials.

All data were collected primarily for clinical purposes to document effectiveness and safety for individual patients. Therefore, outcome endpoints were not defined in advance. The collected data are now published upon the request of the European health authorities.

Statistics

Mean, median, SD and interquartile ranges (IQR) were calculated by Excel 2007. The t-test with unequal variance was applied to data with symmetric distributions but unequal variance. The nonparametric Mann–Whitney and Kruskal–Wallis tests were applied to asymmetric distributed data (http://vassarstats.net). The Mann–Whitney test was used to compare two groups, the Kruskal–Wallis to compare more than two groups and ANCOVA to compare two groups with an additional concomitant variable.

Results

Treatment compliance and dropouts

Of a total of 173 patients with EPP (120 Italian and 53 Swiss), known to the Rome and Zurich centres prior to the CU programme, 115 (66%) were treated with afamelanotide, 72 (60%) in Italy and 42 (79%) in Switzerland and one in both countries, until 14 June 2014. The number of treated patients continuously increased during the observation period (Fig. 1a). Of all patients treated with afamelanotide during the trials, two of the five participants in the first phase II trial and 21 of the 35 participants in the first phase III trial (not counting the patients from phase II) are currently being treated (Table 1). When the introduction of the EA programme eliminated the restrictions of the CU programme, the number of treated patients rose steeply. On 14 June 2014, the porphyria centres counted 85 patients who had received at least one dose within the preceding 12 months. This corresponds to 74% of all patients ever treated with afamelanotide.

The total number of implants per patient against treatment duration is displayed in Figure 2a. The maximum number was 39 implants in 7 years corresponding to 5·6 implants per year and a total dose of 624 mg. In addition, Figure 2a illustrates the variation in the number of implants per patient per year. Thus, in the group of patients treated for 7 years, the number of implants ranged between 9 and 39 implants per patient. The number of implants administered per patient and year differed between the two centres (Fig. 2b). It was 4·4 ± 1·6 (median 5; IQR 3–6) in the Swiss and 2·6 ± 1·6 (median 2; IQR 2–4) in the Italian patients ($P < 0·001$). The number of implants per patient per year within one centre did not depend on the length of treatment (data not shown).

Of the 73 ever-treated Italian patients, 18 discontinued treatment and four CUV017 trial participants did not participate in the CU or EA programme (Table 2). Only two (3%) patients indicated that the treatment effect did not meet their expectations. One patient died from heart failure and the rest of the patients mentioned different reasons for discontinuation as listed, financial restrictions being most frequent. Of the 43 Swiss patients, nine discontinued. The intention to become pregnant was most frequent and only one patient (2%) indicated lack of effect. All patients who did not respond stopped their treatment after the first dose. Half of those who discontinued the treatment did so within the first year of treatment and 90% within the first 3 years (Fig. 1b).

Quality of life questionnaires

QoL questionnaires were investigated separately for the two countries, respecting their different versions. All answers from the original as well as from the revised versions were analysed.

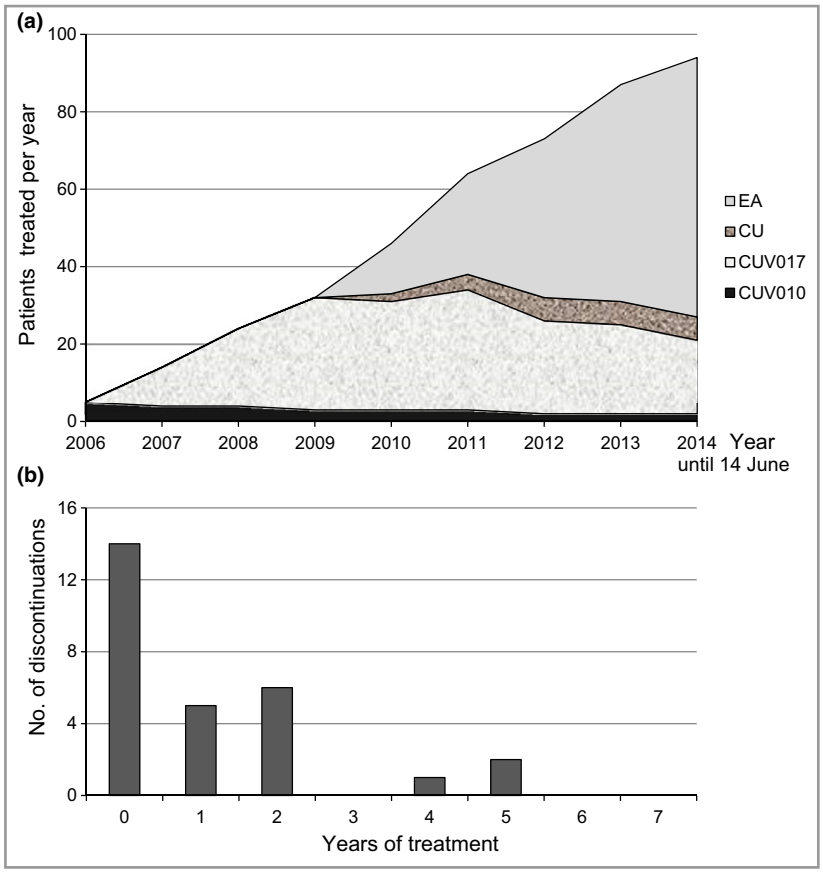

Fig 1. Treatment compliance and discontinuation. (a) The number of patients treated since afamelanotide was first used to treat patients with EPP and the treatment duration of these patients until 14 June 2014. Patients receiving their first afamelanotide dose during the phase II trial CUV010 are shown in black, those during the phase III trial CUV017 are indicated by light grey and those during the compassionate use programme (CU) in dark grey. CU was limited to trial participants including those not eligible for the CUV017 trial. Since 2009 in Italy and since 2012 in Switzerland treatment was accessible to all patients with EPP in these countries, which greatly increased the number of treated patients. The latter expanded access scheme (EA) is plotted in mid-grey. (b) Discontinuation rate vs. treatment duration. Discontinuation was rare after the first year.

Table 1 Long-term compliance since initialization of the first afamelanotide application to patients with EPP in Switzerland and Italy

Treatment initializing event	Year	Centre	Number of patients	Continuously treated[b] No. (%)
CUV010	2006	Swiss	5	2 (40)
CUV017	2007/8	Swiss	13	7 (54)
	2008	Italy	22	15 (68)
CU	Since 2008	Swiss	6	6 (100)
	Since 2009	Italy	0	0
EA	Since 2012	Swiss	19	17 (89)
	Since 2009	Italy	51	39 (76)
Total	Since 2006	Swiss	43[a]	32 (74)
	Since 2008	Italy	73[a]	54 (74)

[a]One patient was treated in both countries and is counted twice here. [b]Until 14 June 2014.

The scores were assessed as mean QoL ± SD. In Switzerland, 161 questionnaires were completed (Fig. 3a). Nineteen were filled in before the first implantation and the longest time span between first dose and completion of the questionnaire was 2541 days. Before the first implantation of afamelanotide, the mean QoL score was 32 ± 22% (Oxford Outcome revised questionnaire 31 ± 24%) of maximum. In the first 6 months of treatment with afamelanotide, it rose to 74 ± 17% (74 ± 17%) and remained between 69% and 91% (66% and 84%) of maximum during the whole observation period of 6 years.

In the Swiss version of the questionnaire, the patients rated their QoL on a Likert-type scale,[28] where 0 meant the lowest possible and 10 the highest possible life quality. The retrospective mean life quality as a child or adolescent, and the current life quality in untreated and treated adult patients with EPP was estimated to be 2·6 ± 2·2, 3·0 ± 2·1, 4·0 ± 2·9 and 8·0 ± 1·9, respectively, the difference between untreated and treated adults being highly significant ($P < 0·001$).

In Italy, 460 questionnaires were available between the second month and the fifth year of treatment (Fig. 3b), as no questionnaires were given to the patients before the first dose. The mean QoL remained stable at between 73% and 80% (revised questionnaire 74% and 80%) of maximum with a slight increase in year 5, to 85% (83%). The mean of the QoL

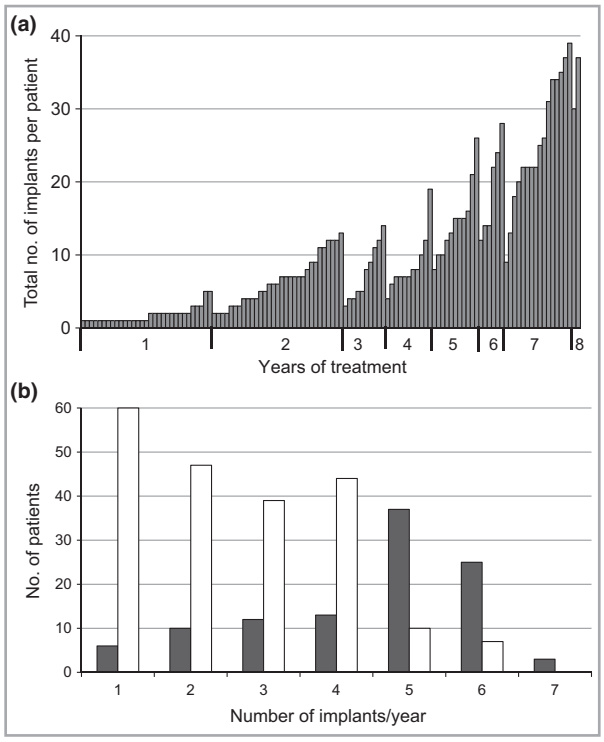

Fig 2. Number of implants per patient. (a) The total number of implants per patient (ordinate) vs. treatment duration (abscissa). Each bar in the diagram represents a single patient. The patients treated for the longest time received between 20 and 39 implants; the patients with an intermediate treatment duration received between 10 and 20 implants. (b) The number of implants per patient per year (abscissa) is displayed vs. the number of patients (ordinate) using the data from the 207 Italian (open bars) and 107 Swiss (black bars) patient treatment years. The mean number of implants per year is 2·6 ± 1·6 in the Italian and 4·4 ± 1·6 in the Swiss patients ($P < 0·001$).

Table 2 Causes for discontinuations during compassionate use and expanded access schemes

Cause	Italy	Switzerland
Compelling reasons		
Financial restrictions	7	2
Residency moved out	3[a]	1[b]
(Planned) pregnancy	1	4
Death	1	
Ineffectiveness		
Drug not (sufficiently) effective	2	1
Not compelling reasons		
Lack of time/personal reason	2	1
Weight gain	1	
Dietary supplements	1	
Total	18	9

[a]Including one patient who moved to Switzerland where she is now treated. [b]Patient now treated in Austria.

scores during treatment was similar between the two countries, although variation in Switzerland was larger. The revised questionnaire compared well with the original ones.

Patients who discontinued the treatment reported a slightly lower, but not statistically different mean QoL score (70·3 ± 16·3%) compared with those on continuous treatment (76·4 ± 10·3%; $P = 0·17$).

EPP is a seasonal disease with the symptoms being much stronger during the seasons with high light intensity, i.e. spring and summer. We therefore analysed whether the QoL scores during afamelanotide treatment varied depending on the season (Fig. 4). More questionnaires were available during the summer months than during winter, as patients requested more implants at this time of the year. The mean QoL value in winter (December to February) was slightly higher (about 84%) than during summer (June to August) when it dropped to 75% in July, the difference between the months being slightly significant ($P = 0·037$). Median values were similar to means and ranged from 72·2 IQR 66·7–88·9 (June and July) to 91·7 IQR 81·9–93·1 (December). The QoL scores determined before first treatment dose were limited to the season of high sunlight irradiation intensity, i.e. between March and September. Except for a single measurement, all data points of untreated patients were below the mean QoL score of the treated ones, the difference between untreated and treated patients being highly significant ($P < 0·001$, ANCOVA including the month as a variable, the influence of which being statistically controlled).

Melanin density

As indicated above, MD data were standardized to baseline (Fig. S1; see Supporting Information). MD rose by about 0·4 units during months 1 and 2 and by about 0·7 units during months 3 and 4. Between the fifth month and the sixth year, MD remained stable between 0·7 and 1·0 units. Some of the patients interrupted treatment during the winter, which decreased their MD value, whereas others increased their sun exposure, which contributed to a rise. Both influences, together with the natural variation in Fitzpatrick skin type, explain the large between-patient variations.

Safety controls

Table S2 (see Supporting Information) lists safety data from the EA programme of both countries, including adverse events related and unrelated to afamelanotide. In total, 680 events were reported, 401 related and 279 not related to afamelanotide. The most frequent events were gastrointestinal disorders (n = 212) and among them nausea (n = 156, 146 times related, 10 times unrelated) was the most frequent. The next most numerous adverse events concerned nervous system disorders (n = 164) with headache as the most frequent (n = 125; 81 times related, 44 times unrelated) and general disorders and administration site conditions (n = 107) with fatigue being reported most frequently (n = 59; 33 times related and 26 times unrelated). Two patients noted a new melanocytic naevus, appearing 2·5 and 5 years after the first dose of afamelanotide, respectively. One of them was removed and showed no signs of malignancy.

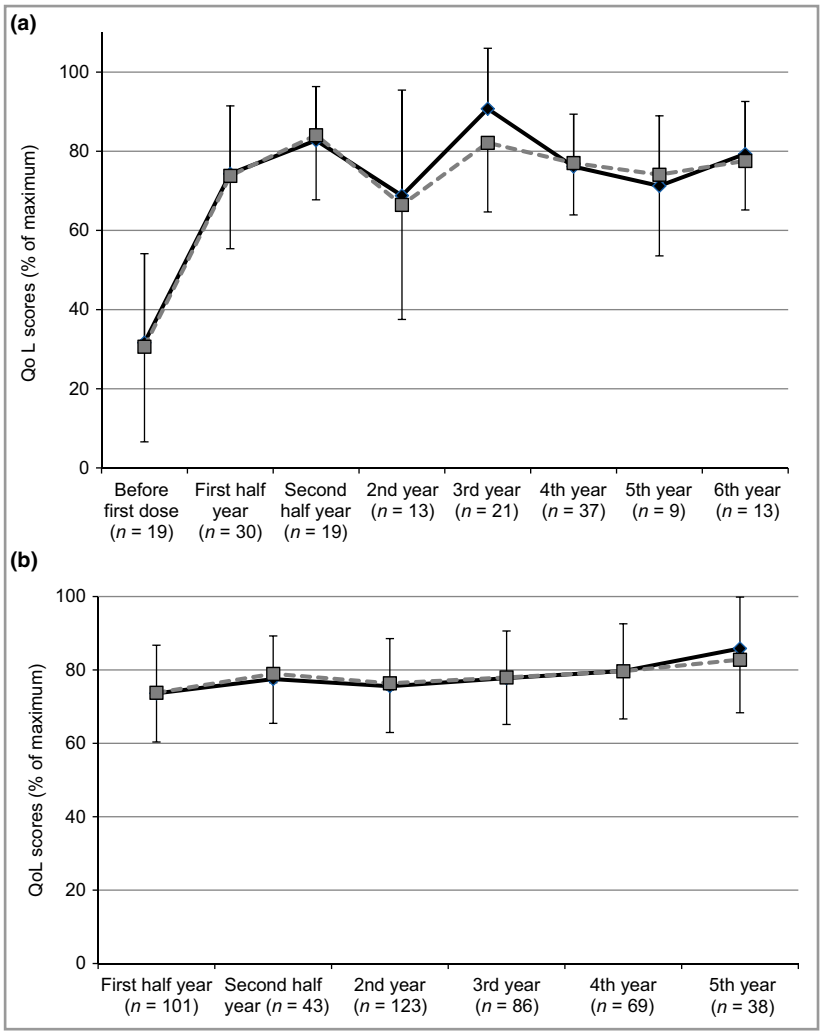

Fig 3. Quality of life (QoL) scores vs. treatment duration. The treatment period is indicated on the abscissa and the QoL scores on the ordinate. Based on the time between first dose and the date of the answer, the questionnaire results were grouped into different classes. Assuming a strong initial variability, we separated the data from the first year into two half-year periods and later into 1-year periods. All data are expressed as percentage of maximal QoL scores, thereby mean and SD are plotted. Data from the original questionnaires (black marks, black lines and SD indicated in the positive direction) and the revised questionnaire (grey marks, grey broken line, SD in the negative direction) are displayed. (a) Swiss patient group; (b) Italian patient group; n, number of questionnaires analysed per time span.

In total, five children were born to study patients; four of them were children from females, who had all interrupted the afamelanotide treatment before getting pregnant. One was a child of a male patient. All offspring were reported to be healthy.

Discussion

This observational study, lasting from 2006 to 2014, included 115 patients, 72 of whom were treated in Italy and 42 in Switzerland and one in both countries. Observational studies are mainly useful for safety considerations and not for efficacy determination. However, in rare diseases, where validated endpoints are lacking and the number of patients is limited, observational studies may contribute to an estimate of clinical effectiveness[25] and may enable decisions to be made as to whether statistical effectiveness corresponds or does not correspond to clinical significance. This may especially apply to a treatment aimed to alleviate subjective symptoms, as is the case for EPP. In our opinion, this observational study supports effectiveness of afamelanotide in EPP based on the following reasons:

(i) The discontinuation rates were low despite the long duration of treatment and the considerable sacrifice of time and costs that had to be carried by the patients.
(ii) Only three of the 115 patients indicated that afamelanotide did not improve their condition. Most others who left did so for compelling reasons, such as intended pregnancy or intolerable financial burden.
(iii) The QoL scores being only 32% of maximum before initiation of afamelanotide treatment rose strongly after initiation of treatment to 74% and remained stable at this level during the whole 6 years of observation. The similarity between the Swiss and Italian QoL scores of the treated patients confirms that the gain in score following afamelanotide treatment is reproducible. If a placebo effect contributed significantly to the initial improvement, we would expect some fading during this long observation period, although we have to admit that it is unknown how long a placebo effect can last. Nonetheless, our clinical experience with drugs such as cysteine and beta-carotene underlines that EPP-patients report treatment failures within a few weeks. Furthermore, EPP-patients discontinue a treatment that does not benefit them, as did three study

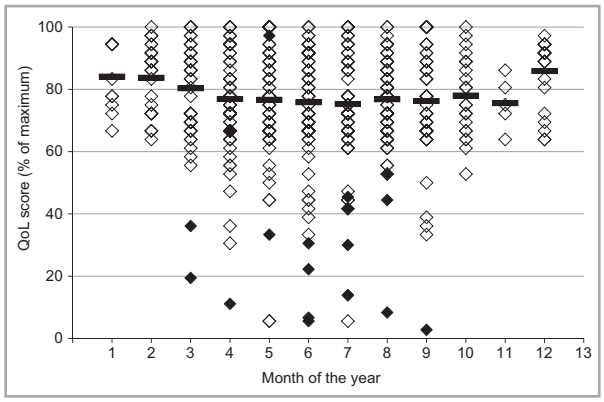

Fig 4. Quality of life scores (revised version) according to season. On the abscissa the month from 1 January to 12 December and on the ordinate the QoL scores in % of maximum are shown. Open diamonds show data from treated patients, thereby the more intense borderlines of the diamonds representing two or more overlaid data points. Closed diamonds show QoL scores of untreated patients. Black lines show monthly mean QoL scores of treated patients.

patients who considered afamelanotide to be ineffective. No patient ever mentioned that the afamelanotide-induced tanning was a treatment aim *per se*.

(iv) During the sunshine-rich and -intense summer season the QoL scores of treated patients only slightly decreased compared with winter time; thereby, the mean QoL scores were clearly higher in treated patients than in untreated ones. We therefore conclude that afamelanotide treatment strongly improved QoL in these patients, likely due to mitigated light intolerance.

(v) Moreover, many subjective arguments also support the effectiveness of afamelanotide in EPP. Patients provided us with many anecdotes about the improvement they gained and we will mention just a few related to employment and familial duties:

- Two young adults who had interrupted their education because their EPP symptoms became unbearable were able to resume their studies;
- A 30-year-old patient who was offered a 1-month mission in Jakarta, was excited to be able to accept it, which represented not only his freedom to choose but also a financial opportunity;
- Another patient changed to a more rewarding position the demands of which he could only meet with treatment;
- A teacher does sports with her pupils out of doors;
- Several business men can do their business travels without phototoxic pain and can meet their clients out of doors if required;
- A young trade agent, compelled to drive long distances for his work was no longer afraid to get stuck in the traffic or to have to change a punctured tyre while driving on the highway, on a sunny day;
- A professional educator in the psychiatric community now participates in summer camps with her patients;
- Parents with EPP now permit their young children to play outside on a sunny day, as they are able to supervise them there; they walk to school with them and help them to cross busy streets;
- The most frequent sentence patients formulated to sum up the positive effects of afamelanotide was: 'This drug gave me a new life.'

Our data do not support the idea that there are specific subgroups of patients who are either especially responsive or unresponsive to the afamelanotide treatment, except for the 3% who indicated lack of improvement. There is a significant discrepancy between the apparent major improvements due to afamelanotide, shown in our clinical observations, and the small effect in the range of minutes of prolonged spontaneous sunlight exposure, as measured in the afamelanotide trials. This divergence might be explained by the high degree of complexity of the disease, such as highly variable individual factors including variable protoporphyrin levels (range 5–70 μM), skin types (Fitzpatrick skin type I–IV), individual pain susceptibility and external factors, such as difficult to compare subtle changes in weather conditions and seasonal effects. Moreover, we lack a suitable tool to precisely measure factors, such as the intensity of the harmful wavelengths of visible light and the air dryness at the affected body sites. Patients attest that an improved light tolerance of even a few minutes reduces the obstacles to living a normal life and therefore positively influences their QoL.

The results from the retrospective QoL questions using the Likert scale indicate that children affected by EPP suffer most. In adolescence and more in adulthood, the QoL increases from 2·6 to 4, likely due to the fact that patients adjusted their daily activities and routine to the limitations imposed by the disease.[7] However, the QoL score of 4 out of 10 indicates a still strongly decreased quality of life in adults with EPP. This value closely normalized to 8 out of 10 under afamelanotide treatment.

Swiss patients received significantly more implants per year than Italian patients. At the moment, we can only speculate about the reasons. One explanation is that the Swiss weather in winter is frequently characterized by snow and sunshine, a combination that is critical for patients with EPP, whereas in Italy sunlight intensity is low during the winter. Secondly, the distances from patients' homes to the porphyria centre are smaller in Switzerland than in Italy, so fewer logistic and financial reasons prevented the Swiss patients from getting their treatment.

MD under treatment remained stable at between 0·7 and 1·0 MD units above the baseline value during the whole treatment period. This plateau after the initial rise refutes the notion that afamelanotide has the potential to cause hyperpigmentation during prolonged treatment.

Afamelanotide caused only mild adverse effects. Taking into consideration that the study comprises 314 patient years, the appearance of the two new naevi was not considered as unusual, as 10·3% of naevi develop during life.[29] The few published reports on induction of either atypical naevi or

melanoma by illegal internet-distributed products containing αMSH analogues usually document a time span of a few weeks between the first dose of the illegal product and the detection of serious disease.[30–33] The rapid manifestation indicates that the serious condition likely was present before the application of the illegal product and was unmasked by the pigmentation-enhancing effect of the αMSH analogue. This is consistent with the risk profile of users of illegal products for tanning purposes, since these individuals are more likely than the general population to expose themselves to harmful doses of intense ultraviolet radiation by frequent and prolonged sun exposure or the use of tanning salons.[34] Moreover, such illegal products may contain other melanotropic agents or unidentified harmful components. The listing of skin premalignancies or malignancies as contraindications is a precautionary measure only, as up to now afamelanotide has not been reported to cause such conditions. Recent review articles on molecular signalling pathways in melanoma development no longer indicate that the αMSH/melanocortin-1 receptor (MC1R) intracellular signalling pathway has melanoma-inducing or promoting activities.[35,36] In contrast, low activity MC1R variants are associated with increased risk of sporadic melanoma[37–40] which indicates that decreased and not increased MC1R signalling is associated with melanoma development. Moreover, melanocyte stem cells and therefore most likely also melanoma stem cells, the latter being crucial for melanoma promotion, do not express MC1R and therefore do not react to αMSH analogues.[41,42]

In conclusion, our clinical experience based on treatment with 1023 implants of afamelanotide in 115 patients with EPP over up to 8 years comprising 314 patient-years indicates that this therapy can be considered safe and efficacious.

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Appendix 1

QoL Questionnaire Swiss Version in English (Clinuvel©)

1 Over the last 2 months, how much has EPP interfered with your going shopping or looking after your home (indoors and outdoors) or garden on a sunny day?

Very much	▫ 0
A lot	▫ 1
A little	▫ 2
Not at all	▫ 3

2 Over the last 2 months, how much has EPP influenced the choice of the clothes you wear on a sunny day?

Very much	▫ 0
A lot	▫ 1
A little	▫ 2
Not at all	▫ 3

3 Over the last 2 months, how often have you *not* worn protective clothing on a sunny day?[a]

Very often	▫ 3
Often	▫ 2
Not often	▫ 1
Not at all	▫ 0

4 Over the last 2 months, how much has EPP affected any *social* or *leisure* activities on a sunny day?

Very much	▫ 0
A lot	▫ 1
A little	▫ 2
Not at all	▫ 3

5 Over the last 2 months, how much has EPP affected your ability to take part in outdoor *sport* on a sunny day?[a,b]

Very much	▫ 0
A lot	▫ 1
A little	▫ 2
Not at all	▫ 3

6 Over the last 2 months, how much has EPP influenced your need to plan before leaving your house?

Very much	▫ 0
A lot	▫ 1
A little	▫ 2
Not at all	▫ 3

7 Over the last 2 months, how much has EPP limited your amount of outdoor activities?

Very much	▫ 0
A lot	▫ 1
A little	▫ 2
Not at all	▫ 3

8 Over the last 2 months, how much has EPP prevented you from attending outdoor social activities with family and friends?

Very much	▫ 0
A lot	▫ 1
A little	▫ 2
Not at all	▫ 3

9 Over the last 2 months, has EPP limited your ability to undertake activities in a spontaneous manner?

Very much	▫ 0
A lot	▫ 1
A little	▫ 2
Not at all	▫ 3

10 Over the last 2 months, how has your well-being been affected by EPP? I have been:

Much better	▫ 3
Better	▫ 2
Same	▫ 1
Worse	▫ 0

11 Over the last 2 months, how much have you been able to engage in outdoor activities that you could not do before because of EPP? [a,b]

Very much	▫ 3
A lot	▫ 2
A little	▫ 1
Not at all	▫ 0

12 Over the last 2 months, how much have EPP symptoms influenced your capacity to go to work or school?[a]

Very much	▫ 0
A lot	▫ 1
A little	▫ 2
Not at all	▫ 3

13 Over the last 2 months, how often did you experience typical EPP skin complaints?

More than usual	▫ 0
Same as usual	▫ 1
Less than usual	▫ 2
Much less than usual	▫ 3

14 Over the last 2 months, how much have EPP symptoms prevented you from participating in outdoor activities with your family (children, partner)? [a,b]

Very much	▫ 0
A lot	▫ 1
A little	▫ 2
Not at all	▫ 3

15 Over the last 2 months, how much has EPP influenced your method of transportation or seating preference during transportation?

Very much	▫ 0
A lot	▫ 1
A little	▫ 2
Not at all	▫ 3

16 Over the last 2 months, how often did you feel the need to seek out shade?[b]

More than usual	▫ 0
Same as usual	▫ 1
Less than usual	▫ 2
Much less than usual	▫ 3

17 Over the last 2 months, how often did you feel you were at risk of developing EPP symptoms?

Very often	▫ 0
Often	▫ 1
A little	▫ 2
Not at all	▫ 3

18 Over the last 2 months, how much has your quality of life improved?

Very much	▫ 3
A lot	▫ 2
A little	▫ 1
Not at all	▫ 0

Taking your EPP into account, mark the box which best describes the quality of life, whereby 0 means the worst possible and 10 the best possible life quality[a,b]

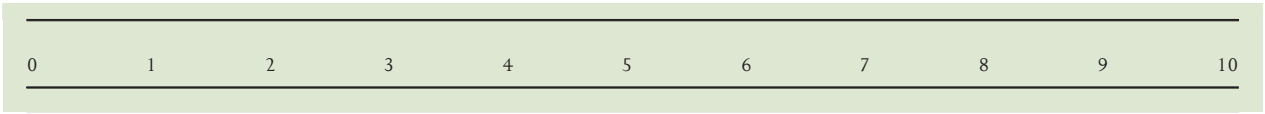
a) during your childhood

0	1	2	3	4	5	6	7	8	9	10

b) during your adolescence

0	1	2	3	4	5	6	7	8	9	10

c) now



[a]Question eliminated by Oxford Outcomes validation.
[b]Question eliminated in the Italian version.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:
Fig S1. Melanin density during afamelanotide treatment.
Table S1. Results from afamelanotide trials in EPP[1].
Table S2. Pooled Safety Data for Italy and Switzerland (including Italian Compassionate Use, Swiss Compassionate Use, Italian 648/96 Scheme and Swiss Expanded Access).