

# Erythropoietic protoporphyria in the Netherlands: Clinical features, psychosocial impact and the effect of afamelanotide

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## Abstract

Erythropoietic protoporphyria (EPP) patients experience severe burning pain after light exposure, which results in a markedly reduced quality of life. However, there is limited information on the psychosocial aspects of EPP. To investigate the clinical features and social aspects of living with EPP, before and during afamelanotide treatment in the Netherlands. A single-center prospective longitudinal study of adult patients with EPP attending the Erasmus MC Rotterdam. Patients completed questionnaires, comprising demographic, clinical and social details, including two generic (DS-14 and SF-36) and a disease specific (EPP-QoL) QoL questionnaires. 121 adult EPP patients were included. The educational level of EPP patients seemed higher compared to the Dutch population (36% vs. 30% high-education, 42% vs. 37% middle-education). At baseline 5% of the EPP patients were unemployed, none were unemployed during afamelanotide treatment. Full- and part-time employment rate increased from 59.5% to 69.9% on afamelanotide treatment ( $p > 0.05$ ). EPP-QoL improved from 44% to 75% on afamelanotide treatment ( $p < 0.001$ ). Type-D personality was present in 27.4% of patients; their social inhibition scores improved significantly on afamelanotide treatment ( $p = 0.019$ ). EPP patients scored low on the social functioning domain (SF-36) compared to the Dutch population ( $74.4 \pm 27.3$  vs.  $84.0 \pm 22.4$ ; respectively), and improved during afamelanotide treatment ( $84.3 \pm 20.9$ ,  $p = 0.001$ ). EPP has a significant negative impact on social aspects, with less employment despite a higher education level. Afamelanotide treatment improves quality of life, social functioning and possibly employment rate. It is important to recognize the impact of EPP on social life, although, more research is needed.

## KEYWORDS

inborn errors of metabolism, photosensitivity, porphyrias, psychosocial functioning, rare diseases

## 1 | INTRODUCTION

Erythropoietic protoporphyria (EPP; OMIM 177000) is characterized by painful photosensitivity, starting from early childhood and lasting throughout life, which severely impairs quality of life.<sup>1</sup> Excessive

light exposure triggers symptoms of intense pain, erythema, edema, and in severe cases petechiae and crusts.<sup>2</sup> The symptoms can last for days and the severe pain responds poorly to pain medication.

Erythropoietic protoporphyria, a rare inherited disorder of heme biosynthesis, is caused by autosomal recessive mutations in the *FECH*

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gene (in the majority of cases), which result in decreased activity of the ferrochelatase enzyme. Around 96% of EPP patients are compound heterozygote for a pathogenic variant (loss of function mutations) and a second low-expression pathogenic variant (c.315-48T>C; also known as IVS3-48T>C, which is an hypomorphic mutation that is prevalent in several populations), the combination results in decreased ferrochelatase activity.<sup>3</sup> This leads to protoporphyrin IX (PPIX) accumulation in erythroid cells and other tissues.<sup>4</sup> PPIX in erythrocytes and the skin absorb blue light, inducing reactive oxygen species, leading to endothelial and dermal damage.<sup>5</sup> Severe liver damage is possible with a risk of acute cholestatic hepatitis in 1–5% of the patients.<sup>6</sup> The prevalence of EPP differs between populations, and is estimated to be 1:75 000 in the Netherlands.<sup>7</sup> A recent study suggests that the prevalence of EPP is underestimated due to underdiagnoses and diagnostic delay.<sup>8</sup>

From a young age patients develop light avoiding behavior due to the early onset and severity of the pain after sunlight exposure. They learn to recognize early symptoms, often referred to as prodromes,<sup>9</sup> as a warning signal to immediately go out of direct light. This is likely to result in impairment of social activities and career perspectives.

Since 2016 adult EPP patients may be treated with afamelanotide, a potent  $\alpha$ -melanocyte-stimulating hormone ( $\alpha$ -MSH) synthetic analog, which increases the production of eumelanin by agonistically binding to the melanocortin-1 receptor (MC1R).<sup>10</sup> Several studies investigated the effect of afamelanotide in EPP patients, and demonstrated statistically significant improvements in pain-free time spent in direct sun light,<sup>11</sup> associations with increased duration of sun exposure and less severe phototoxic reactions,<sup>12</sup> and improved quality of life.<sup>11–13</sup> However, there is limited information on the psychosocial aspects of EPP, both untreated and on treatment with afamelanotide. In previous studies the EPP-QoL questionnaire was used to assess quality of life in EPP patients. Although, the domain regarding wellbeing has been dropped out of the questionnaire based on an analysis that explores aspects of the performance of the measure based on available data from the trials.<sup>14</sup> A common questionnaire used as an instrument to determine the general health related quality of life is the SF-36, which has shown good clinical validity, internal consistency, and reliability in many conditions.<sup>15,16</sup>

We investigated the clinical features and social aspects of living with EPP, before and during afamelanotide treatment. With the aid of questionnaires we recorded the education level, employment rate and investigated the outcome of the SF-36 questionnaire and the prevalence of type-D, or distressed, personality. Type-D personality is associated with depressive symptoms, anxiety, and chronic stress,<sup>17,18</sup> and therefore this could be relevant to how EPP patients cope with their disease.<sup>2</sup> We hypothesize that EPP patients have a higher prevalence of type-D personality and that EPP has a substantial negative impact on social aspects of life, with improves by treatment with afamelanotide.

## 2 | METHODS

In this single-center prospective longitudinal study, all adult EPP patients attending the outpatient clinic of the Porphyrin Expert

Center Rotterdam at the Erasmus MC were eligible for inclusion. All included patients had a confirmed diagnosis of EPP, based on clinical phototoxic symptoms with protoporphyrin IX levels in erythrocytes >4 times the upper limit of normal and two pathogenic mutations in the *FECH* gene or a gain-of-function mutation in the *ALAS2* gene. Since 2016, afamelanotide (SCENESSE, Clinuvel Pharmaceuticals Ltd.) treatment was part of standard care, and was given as a subcutaneous controlled release 16mg implant, with a maximum of four implants per year.<sup>12</sup> This study adheres to the principals of the Declaration of Helsinki. All patients gave written informed consent for the use of their data for analysis and publication prior to the study. The study was approved by the Medical Ethics Review Board of the Erasmus Medical Center Rotterdam.

### 2.1 | Data collection and questionnaires

Data collection occurred during routine visits at the outpatient clinic according to local standard healthcare practice. Blood samples for PPIX levels were collected during outpatient clinic visits. A baseline questionnaire was completed before treatment with afamelanotide, and a follow-up questionnaire was completed in 2019. The questionnaire covered several topics including medical history, clinical features including diagnosis and symptoms, and social information like marital status, family composition, education level, employment status, vacation type, questions about lifestyle, VAS scale for perceived health (scale from 0 to 100) and family history. We distinguished three educational categories: low (pre-vocational secondary education, elementary-school or none), medium (senior-general secondary education, pre-university education and secondary vocational education), and high (higher professional education and university education). We used CBS Statline,<sup>19</sup> which provides publicly available data on the national level of education in the Netherlands, to provide reference data. The disposable income of patients (income after deduction of income taxes) was estimated based on their 4-digit postal code, also derived from the CBS Statline database.

Quality of life was investigated with the disease specific EPP-QoL questionnaire<sup>11,13,14</sup> and the generic SF-36 questionnaire. Results of the EPP-QoL are expressed as percentage of maximum score, with 100% being the best and 0% the worst possible QoL. The SF-36 questionnaire has eight domains and two overarching component summaries, the physical component summary (PCS), and mental component summary (MCS) scores. For each domain, a score ranging from 0 to 100 was assessed with a higher score indicating better health.<sup>20</sup> SF-36 scores of EPP patients were compared to scores from a national sample (age cohort 16–40 years) of the Dutch population ( $n = 1742$ ) collected in 1998.<sup>21</sup> To investigate presence of type-D personality the DS14 questionnaire was used. This questionnaire consists of two, seven-item subscales measuring negative affectivity (NA) and social inhibition (SI). Items are scored on a five-point rating scale, with total subscale scores between 0 and 28. Individuals scoring high (>10) on both NA and SI scales are defined as having type-D personality.<sup>22</sup>

## 2.2 | Statistical analysis

Categorical data are described with frequencies and percentages. Continuous variables are expressed as mean and standard deviation (SD) for normal distributed variables, or as median and interquartile range (IQR) for non-normal distributed variables. A McNemar test, Wilcoxon test and Mann-Whitney-*U* test were used for comparisons of non-normally distributed data. *p*-Values were corrected for multiple testing using the Benjamini-Hochberg procedure. Missing data (only the missing values) and outliers (definition  $\pm 4$  SD) were excluded from analysis. Statistical analyses were performed with IBM SPSS statistics for Windows (version 25.0). All statistical tests were two-sided with a significance level of 0.05.

## 3 | RESULTS

Of the 146 adult patients with EPP known at the Erasmus MC Rotterdam, 128 were included in the study. For 121 patients the baseline information and questionnaire were collected between May 2014 and August 2020. For 105 patients on afamelanotide treatment the information and follow-up questionnaires were collected between January 2019 and October 2020, baseline data was missing for seven of these patients.

### 3.1 | Demographics

Details of the baseline characteristics of the EPP patients and reference values of the Dutch population are presented in Table 1. The marital status of EPP patients appears comparable to the Dutch population; 42.5% of the EPP patients were married, 30% were unmarried, 18.3% were living together and 7.5% were divorced. In total 52.6% of the patients has children, and in patients older than 30 years, 75.0% (60/80) has children. None of the patients younger than 30 years old has children (0/34).

The educational level of EPP patients seems higher compared to the Dutch population, 36% vs. 30% had a high educational level, and 42% vs. 37% had a middle educational level.<sup>19</sup> Five percent of the patients (6/121) were medical practitioners, compared to 0.44% in the Dutch population.<sup>23</sup> The EPP patients consumed a median of 4 units of alcohol per week (IQR 2–7), and 5.7% of EPP patients consumed excessive alcohol which is lower compared to the Dutch population with 8.2%.<sup>19</sup> Of the EPP patients 21.4% had ever tried drugs compared to 35.1% in the general population.<sup>19</sup> Current drug use was reported by 5.1% of the patients, mostly cannabis (66.7%) (Table 1).

### 3.2 | Employment and income

At baseline 59.5% of the EPP patients worked full-time or part-time. Of all EPP patients 5.0% reported to be unable to work due to their EPP and light exposure limitations. That EPP influenced their career

**TABLE 1** Baseline characteristics of patients with erythropoietic protoporphyria in comparison to the general Dutch population.

	<i>n</i>	EPP patients	Dutch population <sup>15</sup>
Age (y) <sup>a</sup>	121	39 (27–50)	42.0
Male (%)	57	47.1	49.7
PPIX level (μmol/L ery) <sup>a</sup>	119	37 (26–59.7)	<1.5
Country of birth (%)	118		
Netherlands	107	90.7	86.2
Europe	5	4.2	5.9
America	2	1.7	2.4
Other	4	3.3	5.5
Marital status (%)	120		
Married	51	42.5	38.6
Unmarried/living together	58	30.0/18.3	48.7
Divorced	9	7.5	7.8
Other	2	1.7	4.9
Educational level (%)	119		
Low	26	21.8	30.9
Middle	50	42.0	37.3
High	43	36.1	30.3
Income based on postal code			
Disposable income (euro) <sup>a</sup>	117	34.400 (27.950– 41.700)	34.100 (33.000– 43.200)
Intoxications			
Alcohol			
Alcohol intake (% yes, <i>n</i> )	121	79.3 (96)	80.4
Excessive alcohol use (% <sup>a</sup> , <i>n</i> )		5.7 (5)	8.2
Total units/week <sup>a</sup>	88	4 (2–7)	–
Smoking			
Current % ( <i>n</i> )	121	22.3 (27)	22.4
Cigarettes/day <sup>a</sup>	27	1.0 (0.5–5.0)	–
Drugs use			
Ever (% <sup>a</sup> , <i>n</i> )	117	21.4 (25)	35.1
Current (% <sup>a</sup> , <i>n</i> )	118	5.1 (6)	11.6
Skin type (Fitzpatrick scale; %)	121		
Type I	11	9.1	–
Type II	42	34.7	–
Type III	55	45.5	–
Type IV	12	9.9	–
Type V	1	0.8	–

Note: Excessive alcohol use was defined as more than 14 alcoholic units per week reference data of the Dutch population is presented as prevalence (%) or mean values.

Abbreviations: EPP, erythropoietic protoporphyria; IQR, Interquartile range; *n*, number; PPIX, protoporphyria IX; y, years.

<sup>a</sup>Data presented as Median (IQR) unless otherwise mentioned.

choice was reported by 60.4% of patients, and specific adjustments at work to prevent EPP symptoms was reported by 58.7% (e.g. workplace far away from windows, yellow foil on windows and options

to work indoors instead of outdoors). Three years after initiation of afamelanotide treatment, none of the EPP patients reported unemployed due to their EPP, compared to 5% at baseline. Unemployment for other reasons was still reported after initiation of afamelanotide treatment (16.5% at baseline vs. 12.6%, respectively). Full- and part-time employment rate increased from 59.5% to 69.9% on afamelanotide treatment ( $p > 0.05$ ), which seems a normalization compared to the percentages in the Dutch population (67.8%). Following initiation of afamelanotide treatment patients reported significantly fewer adjustments at their work (40.2%,  $p = 0.023$ ) and 10% of the patients reported they were considering a career switch due to the positive treatment effects (Table 2). The estimated disposable income of EPP patients, based on postal code was €34.400 (27.950–41.700) and is equivalent to the Dutch population.<sup>19</sup>

### 3.3 | Clinical features

The median age of first EPP symptoms was reported to be 1.8 years (IQR 0–3.1). The median age at diagnosis was 8 years (IQR 4–17.3) with a median diagnostic delay of 6 years (IQR 2–15.3) (Table 2). The only factor associated with a shorter diagnostic delay was having a sibling without EPP ( $r = -0.214$ ,  $p = 0.037$ ). The duration of the diagnostic delay was not associated with parents or siblings with EPP, time in bright sunlight, PPIX level and age of first symptoms ( $p > 0.05$ ). The older EPP patients (>40 years) reported a statistically significantly longer diagnostic delay, compared to younger EPP patients (median 9 years; IQR 2–20.5 vs. median 4 years; IQR 2–11; Z-score –2.137,  $p = 0.033$ ).

Patients were asked to report which periods during their life they experienced the highest burden of their EPP (multiple periods were possible). Most EPP patients reported the burden was greatest when they were young teenagers: 10–14 years old (76.1%), thereafter when they were children: 0–9 years (71.8%), followed by late teen age: 15–19 years (68.4%). With increasing age EPP patients reported fewer problems (Figure 1). EPP patients reported a median time to onset of phototoxic symptoms after exposure to sunlight of 15 minutes (IQR 5–30), which significantly improved after initiation of afamelanotide treatment to 60 min (IQR 30–180, Z-score –6.057,  $p < 0.0001$ ).

Several patients (36%) reported having EPP symptoms throughout the entire year. Most patients reported experiencing EPP symptoms during early and late spring (88.2% and 84%) and early and late summer (96.6% and 83.2%, Figure 2). During treatment fewer patients reported symptoms during spring and summer (73.3% in early spring, 76.2% late spring, 85.7% early summer, and 74.3% late summer).

Holidays were reported to be affected by EPP related phototoxicity in nearly all patients (98.3%), their destination had to be adjusted in 23.3%, specific activities in 27.5%, and both destination and activities in 35.0%. After initiation of afamelanotide treatment 19.8% did not need adjustments during holidays, 17.8% adjusted the destination, fewer patients reported the need to adjust their activities (25.7%), and fewer patients adjusted both activities and destinations (19.8%). At baseline, most patients spent their holiday in Northern-European countries (33.3%), or remained in the Netherlands (17.1%), while only 20% went to the sunnier Southern European countries. On treatment, Southern Europe was reported as the most frequent destination

	Baseline	n	On treatment	n	p-Value
Employment and career					
Employment (%)		121		103	
Full-time or part-time <sup>a</sup>	59.5%	72	69.9%	72	0.078
Cannot work due to EPP	5.0%	6	0%	0	0.063
Cannot work for other reasons	16.5%	20	12.6%	13	1.000
Other (e.g. retired)	19.0%	23	17.5%	18	0.678
Adjustments at workplace (yes, %)	58.7%	109	40.2%	94	<b>0.023</b>
EPP effect on career choice (yes, %)	60.4%	111	–		
Considers a career switch	–		10.0%	90	
Clinical features					
Age first symptoms (years) <sup>b</sup>	1.8 (0–3.1)	110	–		
Age at diagnosis (years) <sup>b</sup>	8 (4–17.3)	106	–		
Years of delay to diagnosis (years) <sup>b</sup>	6 (2–15.3)	101	–		
Time spent in bright sunlight (minutes) <sup>b</sup>	15 (5–30)	111	60 (30–180)	86	<b>&lt;0.001</b>

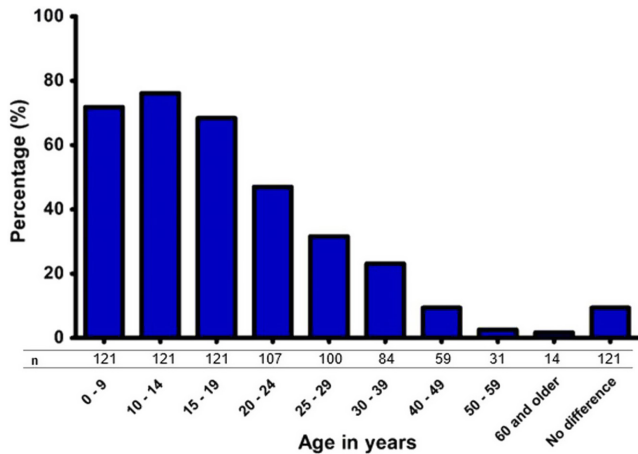
**TABLE 2** Characteristics regarding employment, career and clinical features of patients with erythropoietic protoporphyria in the Netherlands, before and on afamelanotide treatment.

Abbreviations: EPP, erythropoietic protoporphyria; n, number; IQR, interquartile range.

Significant differences p-value level < 0.05 in bold.

<sup>a</sup>The employment rate in the general Dutch population is 67.8%.<sup>15</sup>

<sup>b</sup>Data is presented as median (IQR).



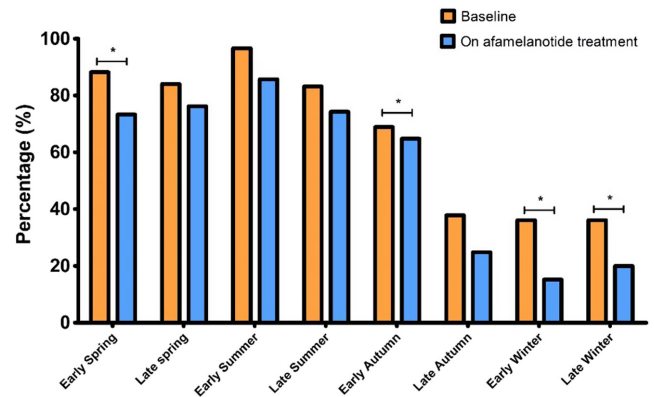
**FIGURE 1** Erythropoietic protoporphyria patients reported age periods with the highest burden of their disease. Patients were asked the following question: “At which age did you experience the highest burden of your EPP (you can answer multiple age categories)”.

(23.0%), follow by Northern Europe (17.2%) and fewer remained in the Netherlands (13.8%). Before treatment started, 10% of the patients stayed at home during the holiday because of EPP phototoxicity, which decreased to 5.0% after initiation of afamelanotide treatment.

### 3.4 | Quality of life, health and personality questionnaires

The EPP-QoL questionnaire was completed by 119 patients; they reported a median score of 44 (IQR 21.2–69.4, Table 3), which significantly improved to 75 (IQR 63.9–88.9,  $p < 0.001$ ) on treatment. Patients reported their global health perception (VAS-score) at median 80 points (IQR 70–90), which did not change on afamelanotide treatment (median 80, IQR 70–90,  $p = 0.145$ ). A type-D personality was identified in 27.4% of patients at baseline, which did not significantly change after initiation of afamelanotide treatment (24.2%,  $p = 0.581$ ). However, social inhibition scores significantly improved after initiation of afamelanotide treatment (median 7, IQR 3–15; and median 7, IQR 2–11, respectively;  $p = 0.019$ ) (Table 3).

Details of the SF36 outcomes are presented in Table 3. EPP patients seem to score lower on the SF36 social functioning domain compared to the Dutch population ( $74.7 \pm 27.3$  vs.  $87.8 \pm 19.1$ ; respectively), this significantly improved ( $p = 0.004$ ) after the initiation of afamelanotide treatment. EPP patients seemed to score equal on the physical functioning domain compared to the Dutch population ( $91.6 \pm 13.8$  vs.  $93.1 \pm 11.8$  in the population). Patients seem to score lower on the role physical, mental health, vitality, bodily pain and general health domains compared to the Dutch population. After initiation of afamelanotide treatment there were significant improvements on the role of physical and bodily pain domains ( $p < 0.05$ ). EPP patients seem to score higher on the PCS, both at baseline ( $51.1 \pm 8.7$ ), as after treatment initiation with afamelanotide



**FIGURE 2** Reported erythropoietic protoporphyria symptoms per season. Patients were asked the following question: “During which periods do you experience EPP symptoms?” \* $p < 0.05$ .

( $53.9 \pm 6.7$ ;  $p = 0.001$ ), compared to the Dutch population. EPP patients scored lower on the MCS both at baseline ( $47.3 \pm 11.6$ ) and after the initiation of treatment ( $48.6 \pm 10.2$ ), compared to the Dutch population (Table 3).

## 4 | DISCUSSION

This large single-center cohort study provides novel insights into the impact of EPP on daily social functioning, which is often mentioned in publications on EPP but has never objectively been assessed. In summary, Dutch EPP patients have a normal income, a higher education level, but have a lower employment rate than the general population. Moreover, EPP had a large influence on career choices, and holiday destinations and activities were affected. Most parameters significantly improved after the initiation of afamelanotide treatment.

The probable higher education level in this cohort of EPP patients, compared to the general population, could be the result of having to spend more time indoors during childhood, and more time to study. However, in healthy children more outdoor time has been found to support self-regulatory capacities and cognitive development.<sup>24</sup> The educational level of the patients' parents was not taken into account in the presented study, and could be a confounding factor.<sup>25</sup> A higher education level of parents could result in an earlier diagnosis,<sup>26</sup> and it is possible that an EPP patient remains undiagnosed or untreated when the patients' parents stop seeking medical care.

The study confirms that afamelanotide treatment can improve tolerance to direct sunlight.<sup>9,11-13</sup> However, this is the first study that reports that treatment can possibly have a positive impact on employment rate. Treatment resulted in more patients reporting a full- or part-time job, and requiring less adjustment at work (e.g. blinding windows, special working hours, wearing protective clothing on their way to work), and also enabled some patients to consider a career switch. This finding can be biased by a decrease in overall unemployment rate in the Netherlands over the study period, from 6.0% in 2016 to 3.4% in 2019.<sup>19</sup>

**TABLE 3** Reported outcomes based on quality of life and type D-personality questionnaires, in patients with erythropoietic protoporphyria, before and on afamelanotide treatment.

	Before	<i>n</i>	On afamelanotide	<i>n</i>	Z-score	<i>p</i> -Value	Dutch population
<b>EPP-QoL Questionnaire<sup>a</sup></b>							
EPP-QoL score %	44 (21.2–69.4)	119	75 (63.9–88.9)	100	–6.810	<b>&lt;0.001</b>	–
<b>VAS-score<sup>a</sup></b>							
VAS (score 0–100)	80 (70–90)	99	80 (70–90)	103	–1.457	0.145	–
<b>DS-14 Questionnaire<sup>a</sup></b>							
Social inhibition (≥10)	7 (3–15)	95	7 (2–11)	95	–2.340	<b>0.019</b>	–
Negative affectivity (≥10)	8 (4–13)	95	7 (2–13)	95	1.099	0.272	–
Type-D personality (%)	27.4%	95	24.2%	95	N/A	0.581	21% <sup>19</sup>
<b>SF-36 Questionnaire<sup>b</sup></b>							
							Dutch population <sup>18</sup> ( <i>n</i> = 1742)
Physical functioning	91.6 ± 13.8	115	91.6 ± 14.9	105	–0.715	0.543	93.1 ± 11.8
Social functioning	74.7 ± 27.3	119	84.3 ± 20.9	105	–3.439	<b>0.004</b>	87.8 ± 19.1
Role physical	74.4 ± 38.2	118	86.7 ± 28.2	105	–2.745	<b>0.016</b>	86.4 ± 27.6
Role emotional	83.2 ± 34.8	113	85.4 ± 31.5	103	–0.505	0.614	85.4 ± 30.0
Mental health	74.9 ± 18.1	112	77.2 ± 17.0	102	–0.944	0.460	78.7 ± 15.2
Vitality	63.3 ± 20.8	112	66.5 ± 18.9	102	–1.098	0.435	70.7 ± 16.4
Bodily pain	73.8 ± 27.2	114	85.7 ± 18.4	104	–4.099	<b>0.004</b>	80.9 ± 19.4
General health	67.5 ± 20.7	118	69.8 ± 18.5	104	–1.469	0.284	78.2 ± 17.3
PCS	51.1 ± 8.7	110	53.9 ± 6.7	100	–3.284	<b>0.001</b>	50 ± 10
MCS	47.3 ± 11.6	110	48.6 ± 10.2	100	–1.260	0.208	50 ± 10

Note: The comparison between baseline and on afamelanotide treatment was done according to non-parametric testing. Significant differences *p*-value level < 0.05 in bold.

Abbreviations: EPP, erythropoietic protoporphyria; IQR, inter quartile range; MCS, mental component score; PCS, physical component score; QoL, quality of life; SD, standard deviation; VAS, visual analog scale.

<sup>a</sup>Presented as median (IQR).

<sup>b</sup>Data is presented as mean ± SD to compare the data to the Dutch population.<sup>16</sup>

The low QoL of EPP patients has been reported many times.<sup>2,13,27,28</sup> EPP patients in the present study, reported an EPP-QoL score of 44% which increased to 75% on treatment, this effect is comparable to reported outcome in phase III trials and observational studies. Afamelanotide treatment had positive effects on their vacations, which could positively contribute to improved QoL.<sup>29</sup>

Patients with a type-D personality tend to experience negative emotions (high NA-score) and to inhibit self-expression in social interaction (high SI-score).<sup>30</sup> The type-D personality was present in 27.8% of the EPP patients, which is higher than in the general Dutch population (21%),<sup>22</sup> but similar to patients with coronary heart disease (28%),<sup>22</sup> and diabetes (27%).<sup>31</sup> The higher prevalence of type-D personality can be explained by the negative impact of EPP on social wellbeing from an early age. The SF36 confirmed the negative impact of EPP on social functioning. EPP patients report a high physical score on the SF36, higher than the Dutch population.<sup>21</sup> It is encouraging to see that afamelanotide treatment results in significant improvements on social functioning, giving EPP patients the opportunity to finally participate in more 'normal' activities. The findings of this study are in line with previous studies regarding the quality of life in photodermatitis in general, which has shown a very large impact on QoL, with

particular effects on employment and social and leisure activities, next to suggested higher anxiety and depression levels.<sup>32,33</sup>

This EPP cohort is comparable in age, contribution of males and females, and ethnicity to previously reported cohorts.<sup>2,28,34,35</sup> It is important to note that more than a third of the patients also report EPP symptoms during autumn and winter, considering the fact that afamelanotide prescriptions are restricted to maximum four times a year. Most EPP patients reported the first symptoms in their early years of life (0–3), however it took years to get a diagnosis since the Dutch patients reported a diagnostic delay of 6 years. The rarity of the disease and the lack of awareness amongst physicians are the common explanation for diagnostic delay in all rare diseases. The relatively short diagnostic delay in the Netherlands compared to that reported in other countries, could be explained due to the nationwide epidemiological studies by Went et al. in the Netherlands.<sup>7</sup> Although the diagnostic delay appears to have improved, there is still a need for further actions to identify patients early and to ensure referral to an expert center, since obtaining information about EPP from expert physicians is important for the wellbeing of EPP patients.<sup>36</sup>

The majority of the presented cohort are fair-skinned subjects, skin type I/II according to Fitzpatrick scale, we were unable to

correlate QoL and study differences in outcome of afamelanotide treatment in non-fair skinned EPP patients. There is no published information regarding skin type in relation to QoL in EPP. The afamelanotide study performed in healthy volunteers, demonstrated that afamelanotide resulted in a greater increase of melanin density in fair-skinned subjects, compared to darker skin subjects.<sup>37</sup>

The marital status of the Dutch EPP patients appears comparable to the general population, suggesting that EPP patients can find partners and maintain their relations long-term. The questionnaire used for this study is not designed to study the quality and happiness within relations, nor for social interactions with friends and colleagues. Besides, the observation that EPP patients have their first child at a relative old age (>30 years) is remarkable and could imply difficulty in finding relations, or postponement by other difficulties.

Afamelanotide has not been approved for children, which is very unfortunate since most EPP patients report problems during childhood which has influenced their lives the most. At present, there are no alternative treatment options for children with EPP except restriction of exposure to light. Patients report that with increasing age they learn to cope with EPP related limitations, they adapt their lifestyle, but still consider their lives as severely restricted.<sup>27,36</sup>

There are several critical notes possible on the choice of SF-36 and DS-14 questionnaires for these research questions. First, every disease, and EPP in particular, is unique in specific domains of life that is affected by the condition, we suggest to use the current outcome for additional research questions with more focus on EPP domains. Second, we are aware that what we can present is still an underestimation of the true disease burden.

## 5 | CONCLUSION

This large cohort study demonstrated that Dutch EPP patients appear to have a higher unemployment rate, despite a higher education level, that EPP has a negative impact on holidays, quality of life and social functioning. These differences diminished after initiation of afamelanotide treatment, with residual unmet need. Further research to obtain more details regarding these psychosocial consequences is needed.

### FUNDING INFORMATION

No funding.

### CONFLICT OF INTEREST


Dr. Langendonk reports contracts for phase III and IV trials with Clinuvel (the producer of afamelanotide), and Alnylam. Dr. Wilson reports travel fees from Clinuvel during the conduct of the phase III study. No disclosures were reported by Wensink and Wagenmakers.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, JGL, upon reasonable request

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