
Foto: Daniel Aufdermauer

Outsourcing in Clinical Trials DACH
29th-30th October 2024, Zurich

Developing the first treatment for my own ultra-rare disease – lessons learned

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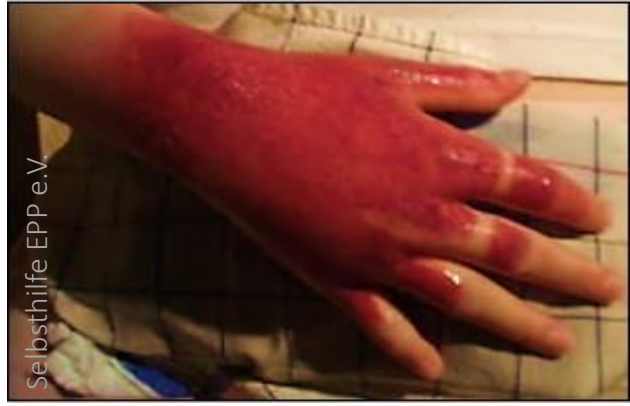
International Porphyria Patient Network (IPPN)

No conflicts of interest to declare

Erythropoietic Protoporphyria (EPP): When the sun hurts

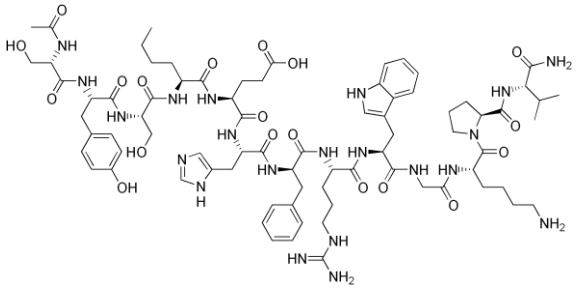


- Ultra-rare genetic defect of the heme biosynthesis
  - Accumulation of a phototoxic heme precursor in the red blood cells
  - Phototoxic burn injuries after 10 min exposure to the visible light
- Severe and long-lasting (days) neuropathic pain
  - 2006: No medication to either treat or prevent the symptoms

- Avoidance of light:
  - Social isolation and stigmatisation
  - Low quality of life, depression and suicidal ideations
  - Not compatible with a normal life
- «Hiding from the sun, at home, alone»

A ray of hope

- Dr. Rocco Falchetto
  - Biochemist from Basel/Bellinzona
  - Patient with EPP
- Suggests «afamelanotide» for treating EPP
- Prof. Elisabeth Minder, MD
  - EPP expert in Zurich
  - My PhD supervisor
- Starts a trial including 5 Swiss patients
- Jasmin
  - Recently diagnosed with EPP
  - Molecular biologist and PhD student with Elisabeth
- Inputs on endpoints for efficacy and QoL



https://de.wikipedia.org/wiki/Afamelanotid#/media/Datei:Melanotan.png

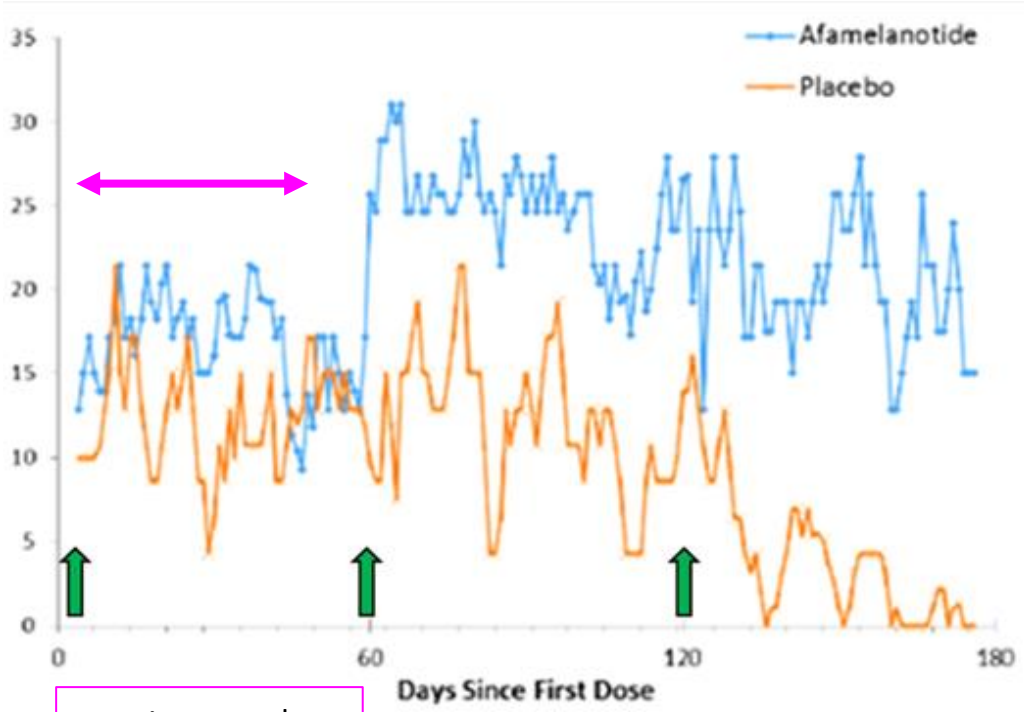
- Afamelanotide
  - Moderately increases skin pigmentation
  - Strong anti-inflammatory properties
- Two months, slow-release implant formulation developed around 2000 by an Australian biotech

Afamelanotide for treating EPP

- Clinical trials testing afamelanotide in EPP
  - Cross-over (n=100, 360 d.)
  - Parallel design (n=77, 180 d.)
  - Parallel design (n=74, 270 d.)
  - Long-term observational study (n=115, eight y.)
  - Pivotal study (RCT, n=93)

- Results pivotal study:
  - Primary endpoint: Median additional 20 min/day in sunlight as compared to the placebo control group
  - Less phototoxic recations, less severe and shorter
  - Normalisation of the time spent in sunlight
  - Increase in QoL as measurde with the disease specific questionnaire

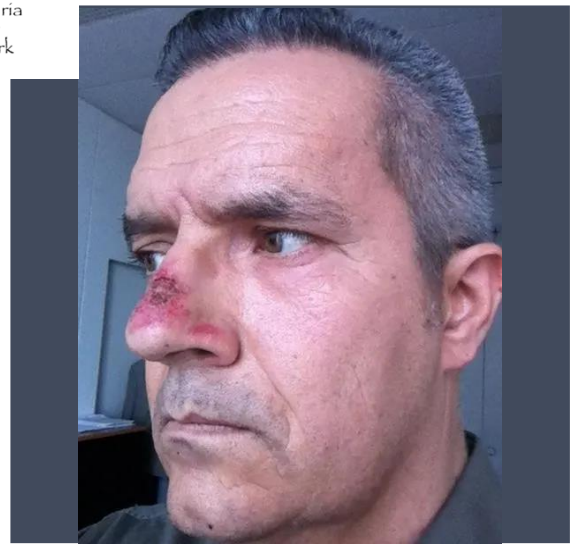
Time in sunlight without pain (min/day)



Anxiety to be exposed to sunlight

Langendonk, J. G., Balwani, M., Anderson, K. E., Bonkovsky, H. L., Anstey, A. V., Bissell, D. M., ... & Desnick, R. J. (2015). Afamelanotide for erythropoietic protoporphyria. *New England Journal of Medicine*, *373*(1), 48-59.

International Porphyria Patient Network




Photos: privat





Long-term studies: Median <u>additional 180 min</u> maximum time possible in direct sunlight

Wensink et al. (2021). *Genet Med*. 2021;23(9):1616-1623. doi:10.1038/s41436-021-01176-z
Barman-Aksözen et al. (2020): Orphanet J Rare Dis. 2020;15(1):213. doi:10.1186/s13023-020-01505-6

Quality of Life: If in a hurry, taking a taxi even if it is a Tesla!

Berlin, Mai 2024

Quality of Life: If in a hurry, taking a taxi even if it is a Tesla!

Home > Journal of Patient-Reported Outcomes > Article

Validation of a novel patient reported tool to assess the impact of treatment in erythropoietic protoporphyria: the EPP-QoL

Research | Open access | Published: 03 August 2021
Volume 5, article number 65, (2021) Cite this article

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

Scientific and ethical issues when testing afamelanotide

https://www.medizin.nrw/news/neue-aufgaben-fuer-die-ema/

- No validated efficacy endpoints and QoL instruments etc. → development of new instruments and endpoints, but challenge to convince regulatory and HTA agencies

« […] it is not clearly evident from the clinical trials whether the apparently small increase in sunlight would translate into a meaningful change in the patients' life.»
EMA European Public Assessment Report, p. 104.

To: Dr Tomas Salmonson, Chair Committee for Medicinal Products for Human Use (CHMP)
Cc: Dr Patrick Le Courtois, Head Pre-Authorisation Unit
Cc: Dr Juan García Burgos, Head Public Information and Stakeholder Networking, Medical Information, Patient Health Protection

Basel, June 17th 2013

Regarding: Porphyria patient input in CHMP review of Scenesse

Dear Dr Salmonson,

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Dear Dr Falchetto,

Subject: Your letter of 17 June 2013 regarding porphyria patient input in CHMP review of Scenesse

Thank you for your letter dated 17th June 20013 about Scenesse, medicine for the treatment of erythropoietic protoporphyria.

«However, patient and EPP experts have confirmed that the increase in outdoor light exposure possible with Scenesse [afamelanotide] was enabling to alter patients' quality of life and translated in the uptake of outdoor lifestyle.» EMA European Public Assessment Report, p. 104.

Foto: Mike Day

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 October 2014
EMA/638997/2014
Press Office

Press release

Scenesse recommended for rare disease that causes intolerance to sunlight

Patients involved in discussions on benefits and risks of a medicine at CHMP for the first time

Foto: Mike Day

Currently tested pharmacotherapies in EPP

Afamelanotide: Approved since 2014 (EMA), 2019 (FDA), 2020 (TGA)

- Symptomatic treatment
- Fixed dose implant formulation
- (Increase in skin pigmentation → unblinding)
- (Testing against a placebo control group → ethically questionable)

Dersimelagon: Since 2018 phase II and III RCTs [1]

- Symptomatic treatment
- Orally available small molecule → children
- Increase in skin pigmentation → unblinding
- Inclusion of a less severly affected trial population→ not representative
- Testing against a placebo control group → ethically questionable

Bitopertin:Since 2021 phase II RCTs [2]

- Causative treatment
- Orally available small molecule → children
- Testing against a placebo control group → ethically questionable

→ As patients, we request head-to-head studies with afamelanotide!

[1] Balwani, M., Bonkovsky, H. L., Levy, C., Anderson, K. E., Bissell, D. M., Parker, C., ... & Belongie, K. (2023). Dersimelagon in erythropoietic protoporphyrias. New England Journal of Medicine, 388(15), 1376-1385.
[2] Halloy, F., Iyer, P. S., Ghidini, A., Lysenko, V., Barman-Aksözen, J., Grubenmann, C. P., ... & Hall, J. (2021). Repurposing of glycine transport inhibitors for the treatment of erythropoietic protoporphyria. Cell Chemical Biology, 28(8), 1221-1234.

Patient perspective on currently conducted clinical trials testing new pharmacotherapies for EPP

Barman-Aksözen *et al. Orphanet Journal of Rare Diseases* (2023) 18:325
https://doi.org/10.1186/s13023-023-02941-w

Orphanet Journal of Rare Diseases

POSITION STATEMENT Open Access

Current trials in erythropoietic protoporphyria: are placebo controls ethical?

Jasmin Barman-Aksözen[1], Mattia Andreoletti[2] and Alessandro Blasimme[2*]

Abstract

A new active substance called "dersimelagon" (MT-7117) is being tested as an alternative treatment option for Erythropoietic protoporphyria (EPP). At the moment, dersimelagon is being tested both in the US and in Europe in a phase III placebo-controlled RCT. However, given the availability of an already approved treatment option for EPP the use of a placebo arm is questionable from an ethics point of view. We analyze the issue and suggest that a noninferiority active-control trial without placebo is an ethically and scientifically more valid design to test the efficacy of dersimelagon as well as other EPP treatments.

Main text

Erythropoietic protoporphyria (EPP, prevalence 1:100 000) is an inborn error of the heme biosynthesis characterized by phototoxic burn injuries of the endothelial cells lining the blood vessels. The phototoxicity develops within minutes of exposure to visible light and the associated severe neuropathic pain is not responsive to pain medication, including opioids. As the visible light is causing the symptoms, UV (ultra violet)-protective measures alone, like sunscreens have no preventive effects. Patients with EPP, already in their early childhood, develop an ingrained anxiety to be exposed to light, leading to social isolation, depression, and overall impairments in their quality of life and educational and occupational opportunities [1].

In 2014, the European Medicines Agency (EMA) recommended "afamelanotide" (commercial name: Scenesse®) for approval under exceptional circumstances as the first treatment for the prevention of phototoxicity in patients with EPP. The pivotal placebo-controlled randomized clinical trial (RCT) testing afamelanotide showed statistically significant results for its primary endpoint, that is, time in sunlight without pain [2]. However, the EMA in their European Public Assessment Report outlined that it would be contrary to medical ethics principles to collect further evidence of clinical efficacy of afamelanotide in placebo-controlled trials as this would expose patients in the placebo arm to the risk of severe phototoxicity and pain [3]. In the United States, the Food and Drug Administration has granted marketing authorization to afamelanotide in 2019, followed by the approval by the Therapeutic Goods Administration in Australia in 2020.

Currently, a new active substance called "dersimelagon" (MT-7117) is being tested as an alternative treatment option for EPP. Dersimelagon is comparable to afamelanotide as to its mode of action (both are melanocortin receptor agonists), but dersimelagon has a different administration mode – being a tablet instead of a bimonthly slow-release subcutaneous implant formulation.

Dersimelagon has been tested both in the US and in Europe in a phase III placebo-controlled RCT. However,

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- We want to know how the potential new treatment options compare to afamelanotide, not to placebo!

[1] Balwani, M., Bonkovsky, H. L., Levy, C., Anderson, K. E., Bissell, D. M., Parker, C., ... & Belongie, K. (2023). Dersimelagon in erythropoietic protoporphyrias. New England Journal of Medicine, 388(15), 1376-1385.


Thank you for your attention!
International
Porphyria
Patient
Network