A Phase III, Multicentre, Double-Blind, Randomised, Placebo-Controlled Study to Confirm the Safety and Efficacy of Subcutaneous Bioresorbable Afamelanotide Implants in Patients with Erythropoietic Protoporphyria (EPP).

Published: 08-06-2009
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Primary objective: - To determine whether afamelanotide can reduce the severity of phototoxic reactions in patients with EPPSecondary objectives:- To determine whether afamelanotide can reduce the number of phototoxic reactions in patients with EPP...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Metabolic and nutritional disorders congenital
Study type	Interventional

Summary

ID

NL-OMON35418

Source
ToetsingOnline

Brief title
Multicentre Phase III EPP Study 2.

Condition

- Metabolic and nutritional disorders congenital

Synonym
Erythropoietic Protoporphyria (EPP)

Research involving

Human

Sponsors and support

Primary sponsor: Clinuvel Pharmaceuticals Limited
Source(s) of monetary or material Support: Clinuvel Pharmaceuticals Limited

Intervention

Keyword: Afamelanotide, alpha-melanocyte stimulating hormone (alpha-MSH), Erythropoietic Protoporphyria (EPP), implant

Outcome measures

Primary outcome

- To determine whether afamelanotide can reduce the severity of phototoxic

reactions in patients with EPP

Secondary outcome

- To determine whether afamelanotide can reduce the number of phototoxic

reactions in patients with EPP

- To evaluate the safety and tolerability of afamelanotide by measuring

treatment-emergent adverse events (AEs)

- To determine whether afamelanotide can improve the quality of life of EPP

patients

- To determine the effect of afamelanotide on free protoporphyrin IX levels

Study description

Background summary

Erythropoietic protoporphyria (EPP) is a genetic disorder in which impaired ferrochelatase activity results in the accumulation of its substrate, protoporphyrin. There are two main clinical manifestations of protoporphyrin: cutaneous phototoxicity and hepatobiliary disease. Phototoxicity is the more

common of these and it usually presents in early childhood as intolerance to sun-exposure with patients experiencing severe burning pain in the skin most often on the face and hands. It may last for several days and may be accompanied by swelling and redness on sun exposed areas.

Accumulation of protoporphyrin IX in the skin is responsible for cutaneous photosensitivity leading to (i) pain, (ii) swelling, (iii) discrete scarring and (iv) formation of ulcers. In the presence of light at 410 nm, protoporphyrin IX generates reactive oxygen species resulting in the typical phototoxic reactions. Protoporphyrin IX is eliminated exclusively via the liver. When the capacity of the biliary excretion pathway is exceeded, excess protoporphyrin IX may result in the formation of gallstones or cholestatic liver damage.

Available treatment modalities for patients with EPP are limited. Avoidance of strong sunlight, either from direct exposure or through windows glass and the use of protective clothing is essential to prevent phototoxic reactions. Systemic β-carotene has been shown to be of benefit in the treatment of EPP although good efficacy data are lacking. The clinical benefits of other treatments such as PUVA, UVB, oral cysteine5, cholestyramine and the combination thereof remain to be proven. The most effective measures are reflecting sunscreens containing titanium dioxide.

Afamelanotide is an analogue of alpha-MSH which stimulates the production of eumelanin in the skin without the specific cell damage that usually occurs when melanin production is stimulated by UV radiation. Melanin, in the form of eumelanin, is a photoprotective agent. The mechanisms proposed for photoprotection include, but are not limited to, the absorption and scattering of UV light, free radical scavenging and quenching of UV light. There is also increasing evidence that melanogenesis represents a major antioxidant defense mechanism in melanocytes, neutralising the deleterious effects of free radicals and active oxygen species9. Eumelanin acts as a neutral density filter and, unlike most sunscreens, reduces all wavelengths of light equally so that the photoprotection provided by epidermal melanin pigmentation is essentially independent of wavelength.

A pilot study of afamelanotide in EPP patients demonstrated that afamelanotide treatment increased the *time to appearance of provoked symptoms* following provocation with an artificial light source. An interim analysis conducted on 14 patients enrolled in a phase III study demonstrated that afamelanotide reduced the severity of phototoxicity, demonstrated using a visual analogue scale to measure pain intensity. The phase III study is ongoing and final data will not be available until the end of 2009.

This study aims to extend experience with afamelanotide in EPP patients by evaluating its effectiveness in EPP patients in a second phase III study.

Study objective

Primary objective:
- To determine whether afamelanotide can reduce the severity of phototoxic reactions in patients with EPP
Secondary objectives:
- To determine whether afamelanotide can reduce the number of phototoxic reactions in patients with EPP
- To evaluate the safety and tolerability of afamelanotide by measuring treatment-emergent adverse events (AEs)
- To determine whether afamelanotide can improve the quality of life of EPP patients
- To determine the effect of afamelanotide on free protoporphyrin IX levels
- To determine whether afamelanotdie can increase the duration of sunlight tolerated by patients with EPP and
- In a subset of patients (not in the Netherlands), determine whether afamelanotide implants can reduce the susceptibility to provocation with a standardized light source (minimal symptom dose (MSD) and minimal erythema dose (MED)).

Study design

This is a randomized placebo-controlled study to be conducted in two parallel study arms for a 9 month period (5 doses) during Spring and Summer. Approximately 10 eligible patients per centre will be enrolled and will receive afamelanotide (16 mg implants) or placebo according to the following dosing regime:

- Group A will be administered afamelanotide implants on Days 0, 60, 120, 180 and 240
- Group B will be administered placebo implants on Days 0, 60, 120, 180 and 240

To determine eligibility for study inclusion, patients will undergo a screening evaluation 7 days prior to the administration of the first dose.

Intervention

Not applicable

Study burden and risks

(1) Prophylactic phototherapy will be withheld. Therefore there is a risk that the patients may experience EPP when the summer commences. However, this therapy is not routine for patients due to the inherent risks and the cumulative increase in the risk of skin cancer.

(2) Adverse events (AEs) or risks associated with afamelanotide. The sustained release implant alpha-MSH has been previously administered with mild AEs occuring in 10 20% of subjects. These included nausea, facial flushing and gastrointestinal discomfort experienced by 20%, 14% and 10% of subjects respectively. These AEs were generally mild in nature and usually lasted no more than 1 2 days. Other mild AEs which have been reported less commonly include headache, chemical taste in the mouth, yawning, muscle twitching, diarrhoea, light headedness and nervousness. Irregular skin tanning, darkening of moles and freckling are also reported. (NB: Darking of moles and freckling are not strictly AEs as they represent the natural effects of the drug. However the rapidity of the change was such as to be recorded as an unexpected event).

(3) The active implant is a sterile biodegradable and biocompatible poly(D,L lactide co glycolide) polymer excipient containing 16 mg of afamelanotide. The placebo implant is identical in composition except it does not contain afamelanotide. The implants contain no other excipients. These implants are manufactured by Brookwood Pharmaceuticals, Birmingham, Alabama, USA.

(4) Implant procedure the main risk is discomfort and bruising at the site of the implant. Less commonly seen side effects are infection, bleeding from the incision site, fainting and nausea. Any patient who experiences any moderate or severe toxicity (as judged from observed adverse events) considered related to the drug may have the implant removed surgically otherwise the implant will biodegrade over succeeding 2 3 months.

(5) Venepuncture the main risk is discomfort and bruising at the site of venepuncture/cannulation. Less commonly seen side effects are infection, bleeding from the puncture site, fainting and nausea.

(6) As there are currently no other prophylactic treatments available for sufferers of EPP, there are no adverse effects that may occur as a result of giving/ withholding prophylactic medication.

Contacts

Public
Clinuvel Pharmaceuticals Limited

Etage 11, 330 Collins Street, Melbourne, Victoria
3000
Australie
Scientific
Clinuvel Pharmaceuticals Limited

Etage 11, 330 Collins Street, Melbourne, Victoria
3000
Australie

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

The participants have to fulfill all of the following criteria for study participation:
- Male or female subjects with a diagnosis of EPP (confirmed by elevated free protoporphyrin in peripheral erythrocytes) of sufficient severity that they have requested treatment to alleviate their symptoms
- Aged 18 - 70 years (inclusive)
- Written informed consent prior to the performance of any study-specific procedures.

Exclusion criteria

Any of the following criteria will exclude the patient from the study:
- Any allergy to afamelanotide or the polymer contained in the implant or to lignocaine or other local anaesthetic to be used during the administration of study medication
- EPP patients with significant hepatic involvement
- Personal history of melanoma or dysplastic nevus syndrome.
- Current Bowen*s disease, basal cell carcinoma, squamous cell carcinoma, or other malignant or premalignant skin lesions.
- Any other photodermatosis such as PLE, DLE or solar urticaria.
- Any evidence of clinically significant organ dysfunction or any clinically significant deviation from normal in the clinical or laboratory determinations.
- Acute history of drug or alcohol abuse (in the last 12 months).
- Patient assessed as not suitable for the study in the opinion of the Investigator (e.g. noncompliance history allergic to local anaesthetics, faints when given injections or giving blood).

- Female who is pregnant (confirmed by positive serum β-HCG pregnancy test prior to baseline) or lactating.
- Females of child-bearing potential (pre-menopausal, not surgically sterile) not using adequate contraceptive measures (i.e. oral contraceptives, diaphragm plus spermicide, intrauterine device).
- Sexually active men with partners of child bearing potential not using barrier contraception during the trial and for a period of three months thereafter.
- Participation in a clinical trial of an investigational agent within 30 days prior to the screening visit.
- Prior and concomitant therapy with medications which may interfere with the objectives of the study, including drugs that cause photosensitivity or skin pigmentation.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	21-01-2010
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Afamelanotide
Generic name:	Nle4-D-Phe7-alpha-Melanocyte Stimulating Hormone

Ethics review

Approved WMO Date:	08-06-2009
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	06-08-2009
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	22-02-2010
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	08-06-2010
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	23-06-2010
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	18-02-2011
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2009-011018-51-NL
CCMO	NL27474.068.09