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) - Results

Sponsor	**CLINUVEL PHARMACEUTICALS LIMITED**
Finished product	**Test product:** afamelanotide (16mg implant)
Active substance	Afamelanotide
Name of the trial	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)
Protocol No	CUV029
Countries	United Kingdom, The Netherlands, Finland, France, Germany, Ireland
Development phase	Phase 3
Study period	Date of First Subject screened: 14 Jan 2010 Date of Last Subject complete: 09 May 2011
Objectives	Main Objective: -Determine whether afamelanotide can enable patients to expose themselves to direct sunlight during the most intense periods of sunlight during the day in spring and summer. Secondary Objective: -Determine whether afamelanotide can reduce the number and severity of phototoxic reactions in patients with EPP; -Evaluate the safety and tolerability of afamelanotide by measuring treatment-emergent adverse events (TEAEs); -Determine whether afamelanotide can improve the quality of life of EPP patients.
Methodology	This was a randomised placebo-controlled study conducted in two parallel study arms (afamelanotide/placebo) for a 9 month period (5 doses). Group A was administered afamelanotide implants on Days 0, 60, 120, 180 and 240. Group B was administered placebo implants on Days 0, 60, 120, 180 and 240. To determine eligibility for study inclusion, potential subjects underwent a screening evaluation 7 days prior to the administration of the first dose (Day 0). Subjects subsequently visited the clinic on Days 60, 120, 180, and 240 for dose administration, with a final visit on Day 270 or at premature termination (if applicable). The number and severity of phototoxic reactions, the duration of sun exposure, TEAEs and the use of concomitant medication were recorded in subject diaries. Safety and concomitant medication were assessed at every clinic visit except Screening for the duration of the study. Quality of life was measured using the DLQI and supplementary EPP specific questionnaires. The DLQI questionnaire was completed every 7 days, beginning at Day 0 until Day 270 using the services of a contracted call centre. Supplementary EPP specific questions were completed at the site at Days 0, 60, 120, 180, 240 and 270.
Number of patients (planned and analysed)	Seventy-six patients were enrolled in the study, of whom 74 received afamelanotide (16 mg afamelanotide implants) or placebo.

Diagnosis and Main Criteria for Inclusion	Male or female adults subjects with a positive diagnosis of EPP.
Study Treatment	Afamelanotide 16mg in a subcutaneous resorbable injectable implant formulation or placebo.
Criteria for Evaluation	**Efficacy Endpoints**: -Number and severity of phototoxic reactions and duration of sunlight exposure, as recorded in a patient diary; -Quality of life measured with DLQI questionnaire and supplementary EPP specific questions. **Safety and Tolerability Endpoints**: -Treatment-emergent adverse events (coded as MedDRA Preferred Terms).
Statistical Methods	**Primary Efficacy Analyses**: Amount of sun exposure (primary): the difference between treatment groups in the amount of sun exposure (direct sunlight) between 1000 and 1500 hours was compared using a Kruskal-Wallis test for days on which patients experienced no pain (pain score of 0). **Secondary Efficacy Analysis**: Number of phototoxic reactions: the median number of phototoxic reactions was compared between treatment groups using a Wilcoxon rank sum test. Pain severity scores: the proportions of patients in each group who experienced a phototoxic reaction with a minimum Likert scale score of ≥ 4 and ≥ 7 were compared using a Chi-square test. Quality of Life: change in quality of life for each treatment group from Day 0 to Days 60, 120, 180, 240 and 270 were compared between groups using a Wilcoxon rank sum test. **Safety Analyses:** Descriptive methods were used to summarise the safety data. The number of subjects with TEAEs (TEAEs, including any clinically significant changes in laboratory parameters) was summarized by MedDRA preferred term and body system for each treatment group. TEAEs were further summarised by intensity, seriousness, outcome, and relationship to study drug.
Results	**Efficacy and Safety**: -Patients receiving afamelanotide reported significantly less pain associated with phototoxicity (median pain score 6.0 vs 17.5, p=0.035). Patients on active drug experienced half as many phototoxic reactions (p=0.044). -Afamelanotide enabled patients to experience significantly more direct sunlight exposure without pain (10 AM-3 PM, p=0.005). -For the majority of study days, patients treated with afamelanotide were able to spend up to seven times longer in direct sunlight without experiencing pain. -Patients on active drug reported a greater improvement in their Quality of Life (Day 270, p=0.011). -No safety concerns were identified during the study.