A Phase III, Randomised, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Subcutaneous Implants of CUV1647 in Patients Suffering from Polymorphic Light Eruption (PLE) – Results

Sponsor	**CLINUVEL PHARMACEUTICALS LIMITED**
Finished product	**Test product:** afamelanotide (16 mg or 20 mg implant)
Active substance	Afamelanotide (CUV1647)
Name of the trial	A Phase III, Randomised, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Subcutaneous Implants of CUV1647 in Patients Suffering from Polymorphic Light Eruption (PLE)
Protocol No	CUV015
Countries	Austria, United Kingdom, Australia
Development phase	Phase 3
Study period	The first patient was screened on 09 May 2007 and the last patient completed the study on 23 November 2009. The study participation was for two periods, each of approximately 150 days for each subject, in Spring/Summer in successive years.
Objectives	**Primary objectives** -Evaluate whether afamelanotide prevents episodes or reduces the severity of symptoms in patients with PLE -Evaluate the safety and tolerability of afamelanotide -Evaluate the effect of afamelanotide on the use of rescue medication for the treatment of PLE symptoms -Evaluate the effect of afamelanotide on melanin density measured by skin reflectance **Secondary objectives** -Determine whether afamelanotide has a beneficial effect on the quality of life of PLE sufferers -Determine if there are any confounding factors that may influence the severity of PLE symptoms
Methodology	In the first season, patients were randomised to active treatment (20 mg afamelanotide) or placebo in a ratio of 1:1. Patients received three implants in season 1, at an interval of 60 days (at Day 0, Day 60 and Day 120). In the second season of the study all continuing patients received an active treatment implant (16 mg or 20 mg afamelanotide) at Days 0, 60 and 120.
Number of patients (planned and analysed)	Approximately 250 eligible patients were planned to be enrolled in total, across all sites. 36 subjects received study treatment in Season 1. Of these, 23 commenced Season 2, and 19 completed Season 2 having received all 6 doses of treatment over the two seasons.
Diagnosis and Main Criteria for Inclusion	-Documented history of moderate/severe PLE as diagnosed/confirmed by a photodermatologist/photobiologist -Patients with recurrent episodes that occur at least once per year in their local environment
Study Treatment	Therapy with afamelanotide implant: - Afamelanotide 16 mg or 20 mg implant. Patients received three implants in each season (two seasons in total), at an interval of 60 days (at Day 0, Day 60 and Day 120). Formulation: subcutaneous resorbable implant formulation.

Criteria for Evaluation	*Primary Efficacy Endpoints:* -Physician's global severity assessment and patient's assessment at Days 60, 120 and 150. -Cumulative disease burden at Days 60, 120 and 150 in years 1 and 2 -Amount of rescue medication used -Changes in melanin density from baseline
Statistical Methods	**Efficacy Analysis** • Physician's global severity, cumulative disease burden and patient's assessment of global severity at Day 60, 120 and at Day 150 were presented per treatment arm, using descriptive statistics. Treatment effect was analysed using analysis of variance (ANOVA). • Change in the global severity at Day 60, Day 120 and Day 150 from Season 1 to Season 2 was presented per treatment arm using descriptive statistics. • The amount of rescue medication used between Days 0 to 120 was analysed by the Wilcoxon Rank Sum Test. **Safety Analysis** • Treatment emergent adverse events (AEs) were summarised using frequency counts and percentages. Treatment emergent AEs were presented by MedDRA system organ class and preferred term and further summarised by seriousness and causality. • Haematology, biochemistry and urinalysis data and changes from the values recorded at the screening visit were presented by visit, using descriptive statistics. The number of clinically significant results for each parameter was presented by visit. • Summary statistics for findings of physical examination, vital signs (diastolic and systolic blood pressure, pulse, temperature) and body weight were presented by visit.
Results	**Efficacy** A trend toward reduction of characteristic dermal symptoms was observed. Analysis of the physician's Global Severity Index during the 120 days and 150 days of seasonal treatment demonstrated a reduction in severity of symptoms in patients receiving afamelanotide compared to placebo (p=0.448 and p=0.077). In all sun exposed areas of the skin tested, compared to starting values, an increase in melanin density was found at 120 days (p=0.009) and 150 days (p=0.007) indicating a strong elevation in melanin density in phototype I and II patients during spring and summer. Overall the safety profile of afamelanotide administered during the trial was good.