A Phase III, Multicentre, Randomised, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Subcutaneous Bioresorbable Afamelanotide (CUV1647) Implants in Patients with Erythropoietic Protoporphyria (EPP) CUV017 - Results

CLINUVEL PHARMACEUTICALS LTD conducted a study which investigated SCENESSE® (afamelanotide 16mg) as a systemic photoprotectant in a 12 month, multicenter, randomised, double-blind, placebo-controlled Phase III crossover study (CUV017) in erythropoietic protoporphyria (EPP). In one Australian and seven European centres, SCENESSE® was evaluated for its ability to provide preventative pharmaceutical therapy in adult EPP patients who are known to suffer from phototoxic reactions following exposure to light (>400 nanometres wavelength). The independent members of a Data Safety and Monitoring Board have reviewed the study results and have confirmed the conclusions.

Sponsor	**CLINUVEL PHARMACEUTICALS LTD**
Finished product	**Test product:** afamelanotide (16 mg implant) contained in a poly(D,L-lactide-co-glycolide) implant core **Placebo Product:** Poly(D,L-lactide-co-glycolide) implant
Active substance	Nle4-D-Phe7-α-MSH (INN afamelanotide)
Name of the trial	A Phase III, Multicentre, Randomised, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Subcutaneous Bioresorbable Afamelanotide (CUV1647) Implants in Patients with Erythropoietic Protoporphyria (EPP)
Protocol No	CUV017
Countries	Australia, France, Germany, Italy, Netherlands, Sweden, Switzerland and United Kingdom
Development phase	Phase III
Study period	The first subject was dosed on 14 May 2007 and the last subject completed the study on 9 December 2009. The study participation period was approximately 360 days for each subject.
Objectives	**Primary endpoints** a) The mean number of phototoxic reactions that occur whilst patients are on active compared with placebo implants. b) The mean severity score for phototoxic reactions that occur whilst patients are on active compared with placebo implants. **Secondary endpoints** Difference in the mean between active and placebo: a) Changes in melanin density (measured by spectrophotometry) b) Amount of sunlight exposure, as recorded in diary card c) Change in quality of life (measured with SF36 questionnaire) d) The mean "time taken to develop provoked symptoms" following photo testing (in a subset of patients only)
Methodology	This was a phase III, multicentre, randomised, double-blind, placebo-controlled study to evaluate the safety and efficacy of subcutaneous bioresorbable afamelanotide implants in patients with Erythropoietic Protoporphyria (EPP). The study was conducted with two parallel study arms with crossover between treatments every 60 days.

Number of patients (planned and analysed)	Approximately 70 eligible patients were planned to be enrolled in total, across all sites. The number of subjects actually enrolled was 100, of whom 93 completed the study.
Diagnosis and Main Criteria for Inclusion	a) Male or female subjects with a positive diagnosis of EPP (confirmed by elevated free protoporphyrin in peripheral erythrocytes) b) Aged 18-70 years
Study Treatment	Active: Afamelanotide (16 mg implant) contained in a poly(D,L-lactide-co-glycolide) implant core Placebo: Poly(D,L-lactide-co-glycolide) implant Formulation: subcutaneous resorbable implant formulation
Criteria for Evaluation	*Efficacy Endpoints:* Efficacy will be assessed by: • Number and severity of phototoxic reactions • Melanin density (measured by spectrophotometry) • Duration of sunlight exposure, as recorded in patient diary • Quality of life measured with SF36 questionnaire • Time taken to develop provoked symptoms following phototesting (in a subset of patients only) *Safety and Tolerability Endpoints:* • Treatment-emergent adverse events (coded as MedDRA Preferred Terms). • Changes in haematology, serum chemistry and urinalysis measurements from Screening to Study Days 1, 61, 121, 181, 241 and 301.
Statistical Methods	**<u>Efficacy Analysis</u>** *Primary Efficacy Endpoints* Active treatment (Group A for Days 0-60, 121-180, 241-300 plus Group B for Days 61-120, 181-240, 301-360) was compared with placebo (Group A for Days 61-120, 181-240, 301-360 plus Group B for Days 0-60, 121-180, 241-300). • The mean number of phototoxic reactions that occurred whilst patients were on active compared with placebo implants. • The mean severity score for phototoxic reactions that occurred whilst patients were on active compared with placebo implants. *Secondary Efficacy Endpoints* • Changes in melanin density (measured by spectrophotometry) • Amount of sunlight exposure, as recorded in a diary • Change in quality of life (measured with SF36 questionnaire) • The mean "time taken to develop provoked symptoms" following phototesting (in a subset of patients only) – this was an interim analysis at the Zürich site only, and is not included in this report. **<u>Safety and tolerability:</u>** The number of participants with treatment-emergent adverse events (TEAEs) was summarised by MedDRA preferred term and body system for each treatment group. TEAEs were further summarized by intensity, seriousness, outcome and relationship to study drug. Participants who prematurely terminated treatment due to adverse events related to study medication were listed.
Results	**Primary Efficacy Analyses** The primary efficacy objectives were to determine whether afamelanotide could reduce the number and severity of phototoxic reactions. An 11-point Likert scale

	and physician assessments through case report forms (CRF) were used to evaluate "pain" as a principal symptom of phototoxicity. The duration of daily (sun)light exposure was used to assess the willingness of patients to expose themselves during all seasons. Melanin density (reflecting changes in skin pigmentation, measured by spectrophotometry) and quality of life (Short Form 36 surveys) were also evaluated. In an analysis of the total number of days (frequency distribution) on which patients experienced pain in the specific pain severity categories (severe, moderate, mild and none), a significant reduction of frequency was observed in patients on active drug [p=0.0023]. Characteristic to EPP, the majority of phototoxic reactions occurred during spring and summer. In analysing the average pain severity experienced by the total number of patients, the assessment of all individual daily pain scores was significantly lower in patients receiving SCENESSE® compared to those receiving placebo [p=0.0017]. An additional evaluation of the pain scores in patients willing to modify behaviour by continuous exposure to daily (sun)light showed a positive trend toward a reduction in average pain score following active drug treatment [p=0.1654]. **Secondary Efficacy Analyses** Clinically relevant daily exposure of longer than one hour per day symptom-free was recorded by the trial physicians (CRFs) at the end of each 60 day treatment. In assessing the duration of sunlight exposure per patient, there was significantly more sun exposure in patients receiving SCENESSE® [p<0.0001]. These analyses strongly indicate that patients receiving drug increased their confidence to engage in outdoor activity. In assessing skin pigmentation (melanogenesis as function of the drug's pharmacological activity), a distinct clinical effect was recorded following administration of active drug, and in both treatment arms absolute melanin levels rose in one group by 29.1% and in the other by 28.4%. The quality of life (QoL) observations of clinicians did not reflect the patients' response to treatment. Quality of life assessment over the entire 12-month study was determined to be inappropriate for this population. Since the majority of patients wished to continue use of the drug after the end of the studies, alternative and disease specific quality of life measurements are being employed in the ongoing studies. SCENESSE® was well tolerated, none of the patients who completed the study requested the treatment to be discontinued and no serious adverse event was reported to be drug-related. **Summary:** Reduction in the severity and frequency of episodes of pain associated with phototoxicity: • Significant difference in pain scores p=0.0023 • Reduction in the average overall daily pain severity score p=0.0017

	• Reduction in the average patient's daily severity score p=0.1654 [CI 95% range 94.9% to 98.8%] Increase in sun exposure tolerated by patients: • Significant difference in sun exposure in active group [p<0.0001] Increase in the average skin melanin density level: • from 3.13% to 4.04% (Group A) and 3.06% to 3.93% (Group B) Quality of Life (SF-36) • Determined inappropriate QoL instrument, disease-specific QoL used in compassionate program <u>Safety and tolerability:</u> In total, eight serious adverse events were reported, of which four occurred in placebo recipients. None of these events were considered to be related to study medication. Most adverse events were mild or moderate in severity, with headache, nausea, flushing and gastrointestinal events reported most often.