A Phase II, Open Label Pilot Study to Evaluate the Safety and Efficacy of A Bioresorbable Subcutaneous Implant of CUV1647 in Patients with Solar Urticaria (SU) – Results

Sponsor	**CLINUVEL PHARMACEUTICALS LIMITED**
Finished product	**Test product:** SCENESSE® (afamelanotide 16 mg Implant)
Active substance	Afamelanotide
Name of the trial	A Phase II, Open Label Pilot Study to Evaluate the Safety and Efficacy of A Bioresorbable Subcutaneous Implant of CUV1647 in Patients with Solar Urticaria
Protocol No	CUV016
Countries	United Kingdom
Publication (Reference)	Haylett, A.K., Nie Z., Brownrigg M., Taylor R. and Rhodes L.E, Systemic photoprotection in solar urticaria with α-melanocyte stimulating hormone analogue [Nle4-D-Phe7]-α-MSH. Brit J Derm 2011; 164(2):407-414
Development phase	Phase 2
Study period	The first subject was dosed on 20 November 2008 and the last subject completed the study on 27 March 2009. The study participation period was approximately two months for each subject.
Objectives	The objectives of the study were to test the efficacy of subcutaneously administered afamelanotide as a photoprotective drug in patients diagnosed with Solar Urticaria by measuring skin reactions, characteristic 'wheal' formation and tolerance to UV and sunlight. **Primary endpoints** a) To determine whether an afamelanotide bioresorbable implant can reduce the susceptibility of patients with Solar Urticaria to provocation with a standardized light source (measured as a change in minimum urticarial dose, (MUD)). **Secondary endpoints** a) To evaluate the safety/tolerability of afamelanotide by measuring treatment-emergent adverse events. b) To determine the effect of afamelanotide on melanin density at several specified body sites. c) To evaluate a change in the MUD between Days 30 and 60.
Methodology	Solar urticaria patients received a single dose of 16mg subcutaneous afamelanotide implant during winter. Melanin density was assessed spectrophotometrically from 0-60 days. Detailed monochromated light testing to geometric dose series (increment $\sqrt{2}$) of wavelengths 300-600nm was performed at day 0, 30 and 60, with assessment of wheal and flare area and minimum urticarial dose (MUD) defined as the lowest dose at which a visible wheal response occurred. Data were analysed by repeated measures ANOVA.
Number of patients (planned and analysed)	Approximately 10 eligible patients were planned to be enrolled in total. The number of subjects actually enrolled was 5, all of whom completed the study.
Diagnosis and Main Criteria for Inclusion	a) Male or female subjects with a diagnosis of Solar Urticaria (confirmed by phototesting) of sufficient severity that they have requested treatment to alleviate symptoms; b) React to provocation with a light source;

	c) Aged 18 to 70 years; d) Fitzpatrick Skin Type I-IV.
Study Treatment	Active: Afamelanotide (16 mg implant) Formulation: subcutaneous resorbable implant formulation
Criteria for Evaluation	Efficacy was assessed by: *Efficacy Endpoints:* • Measurement of the area of the wheal and flare at all responding sites following testing. • Changes in melanin density (measured spectrophotometrically). • Changes in MUD. *Safety and Tolerability Endpoints:* • Treatment-emergent adverse events (coded as MedDRA Preferred Terms). • Changes in physical examination from Screening to Day 60. • Changes in blood pressure and heart rate from Screening to all subsequent visits. • Changes in haematology, serum chemistry and urinalysis measurements from Baseline to Study Days 1, 7, 15 and 60.
Statistical Methods	**<u>Efficacy Analysis</u>** *Primary Efficacy Endpoints* Change in MUD compared between baseline and after afamelanotide treatment at Day 30 in each patient. Secondary efficacy analysis included: • the area of the wheal and flare at all responding sites to given doses of radiation before and after treatment with afamelanotide, compared at Days 0, 30 and 60. • the level of melanin density in the skin (changes in melanin density from baseline to the post-treatment assessments at Days 0, 1, 7, 15, 30 and 60) • the change from baseline in MUD compared between Days 30 and 60. **<u>Safety and tolerability:</u>** The number of participants with treatment-emergent adverse events (TEAEs) was summarized by MedDRA preferred term and body system.
Results	**Efficacy Analyses:** In all patients, the tolerance of the skin to light of various wavelengths and intensities was increased following administration of afamelanotide. - Baseline phototesting revealed action spectra of 320-400nm (n=1), 320-500nm (n=2), 300-600nm (n=1) and 370-500nm (n=1), and on afamelanotide mean rises in MUD of 1-12 and 1-3 dose increments were seen at the individual wavelengths tested, at 30 and 60d, respectively. - The MUD was significantly increased ($p<0.001$) in all patients at 30 and 60 days and more specifically by >2-fold overall increase ($p=0.058$ vs baseline). - The size and intensity of skin reactions and wheal formation was significantly reduced ($p<0.003$) at 30 and 60 days following dosing of afamelanotide. - Mean melanin density increased by 7d, peaked at 15d and remained elevated at 60d ($p=0.03$, 0.01, 0.02 vs baseline, respectively). **Safety and tolerability:** No serious adverse events occurred during the study. A mild upper respiratory tract infection occurred in one patient that was not regarded to be related to the treatment. Pre-existing naevi were assessed prior to afamelanotide implantation and any changes noted at 60 days. Modest

	increases in pigmentation occurred in naevi after treatment, as anticipated, but this was not accompanied by alteration in size or other suspicious feature. **Conclusion:** These results indicate that afamelanotide may reduce the risk of incapacitating reactions to UV and sunlight in solar urticaria patients.