A Phase II, Randomised Pilot Study to Evaluate the Efficacy and Safety of Subcutaneous, Bioresorbable Afamelanotide Implants and Narrow-Band Ultraviolet B (NB-UVB) Light in the Treatment of Nonsegmental Vitiligo – Results

Sponsor	**CLINUVEL PHARMACEUTICALS LIMITED**
Finished product	**Test product:** afamelanotide (16 mg implant)
Active substance	Afamelanotide
Name of the trial	A Phase II, Randomised Pilot Study to Evaluate the Efficacy and Safety of Subcutaneous, Bioresorbable Afamelanotide Implants and Narrow-Band Ultraviolet B (NB-UVB) Light in the Treatment of Nonsegmental* Vitiligo
Protocol No	CUV101
Countries	France, Italy, Switzerland
Development phase	Phase 2
Study period	The first subject visit was in October 2011 and the last subject completed the study in December 2012. The study participation period was approximately one year for each subject.
Objectives	**Primary objective:** - To evaluate the efficacy of afamelanotide implants and NB-UVB light in the treatment of nonsegmental vitiligo (NSV). **Secondary objectives:** - To determine the short-term safety of both treatments in patients with NSV; - To evaluate the maintenance of pigmentation achieved with both treatments in patients with NSV.
Methodology	This was a 6-month pilot study, with a 6-month follow-up period, in patients with a documented history of nonsegmental vitiligo. Eligible patients were to be enrolled and randomised in equal numbers to one of the following treatment groups: **Group A** received both afamelanotide implants (one implant administered every 28 days, 6 implants in total) and NB-UVB light (administered thrice weekly, 72 treatments in total); **Group B** received NB-UVB light only (administered thrice weekly, 72 treatments in total).
Number of patients (planned and analysed)	Approximately 60 eligible patients were planned to be enrolled in total. The total number of subjects actually enrolled was 15.
Diagnosis and Main Criteria for Inclusion	Male and female subjects aged 18 years or more, with a confirmed diagnosis of NSV with 15% to 50% of total body surface involvement, stable or slowly progressive vitiligo over a 3-month period, Fitzpatrick skin types III-VI, willing and able to comply with the conditions specified in the CUV101 protocol and study procedures in the opinion of the Investigator and providing written Informed Consent prior to the performance of any study-specific procedure.
Study Treatment	Therapy with afamelanotide implant plus NB-UVB light: - Afamelanotide 16 mg implant. Formulation: subcutaneous resorbable implant formulation - NB-UVB light administered thrice weekly, 72 treatments in total.

Criteria for Evaluation	*Efficacy Endpoints:* Efficacy was assessed by: • Time to onset of repigmentation of full body, face, trunk and extremities; • Assessment of repigmentation of full body, face, trunk and extremities using the Vitiligo Area Scoring Index (VASI) and Vitiligo European Task Force (VETF) scoring systems; • Vitiligo lesion photography; • Maintenance of repigmentation of full body, face, trunk and extremities assessed on Day 336, using the VASI and VETF scoring systems; • Vitiligo lesion photography performed on Day 336; • Patient's quality of life assessed on Days 0 and 168 or Early Termination (if applicable), using the Dermatology Life Quality Index (DLQI) questionnaire. *Safety and Tolerability Endpoints:* • Adverse events recorded at each Study Visit; • Routine laboratory assessments (haematology, serum chemistry, urinalysis) performed at Screening Visit and on Days 0, 56, 112, and 168 or Early Termination (if applicable); • Full body anterior and posterior photography performed at Screening Visit and on Day 168 or Early Termination (if applicable); • Ophthalmic examination at Screening Visit and on Day 168 or Early Termination (if applicable).
Statistical Methods	This was a Phase II pilot trial, therefore statistical relevance was not expected, however, non-parametric analyses were performed. In these analyses, monotherapy with NB-UVB light was compared to combined therapy with NB-UVB light and afamelanotide 16mg. The intention to treat (ITT) principle was followed. The demographic and clinical variables are described on characteristics of study treatment groups A and B, and reciprocally compared using the non-parametric Mann-Whitney U test and chi-square test with a significance level of at least 5% (p=0.05). **Efficacy Analysis** *Primary efficacy endpoint*: The time to onset of repigmentation of full body, face, trunk and extremities from Day 0 to Day 168 between the two treatment groups. ***H0***: there will be no difference in the time to onset of repigmentation of full body, face, trunk and extremities between the two treatment groups. The primary efficacy endpoint was analysed as soon as Day 168 data become available. *Secondary efficacy endpoints:* Change from Day 0 to Day 168 between each treatment group in: • The pigmentation of full body, face, trunk and extremities • The patient's quality of life Change from Day 168 to Days 224, 280 and 336 between each treatment group in: • The pigmentation of full body, face, trunk and extremities **Safety and tolerability:** Treatment-emergent adverse events (TEAEs), including clinically significant changes in haematology, serum chemistry and urinalysis measurements from Screening Visit to Day 168 or Early Termination (if applicable), were summarised 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	**Summary and conclusions:** **Efficacy results:** 86% of the enrolled patients were Fitzpatrick skin type III (light skin) and the rest skin type IV. Analysis of the primary efficacy variable show that both groups had similar time to onset of repigmentation. However, treatment with afamelanotide implants plus NB-UVB light was associated with a higher percentage of patients with repigmentation of face and full body compared to treatment with NB-UVB light alone. With regard to the secondary efficacy variables, the VASI score showed greater mean decreases in the Afamelanotide/NB-UVB group than in the NB-UVB group at all time points. The mean decrease in VETF (extent and staging dimensions) was greater in the Afamelanotide/NB-UVB group than in the NB-UVB group from Day 112 to Day 168, and at all the time points for the VETF spreading dimension (except at Day 28). Both groups showed similar small increases in DLQI total score at Day 168, representing a slight reduction in quality of life for patients in both treatment groups. The comparisons between groups were not statistically significant for any of the efficacy endpoints at any time point. However, caution should be exercised in the interpretation of the results due to the low number of patients. **Safety results:** No deaths or serious adverse events were reported. Three adverse events were described as related to the study drug in the first group: they were one case of fatigue, one of hyperhidrosis and two of skin hyperpigmentation. Administration of the afamelanotide implant plus NB-UVB light was well tolerated in the small number of patients with lighter skin type treated in this study.

*****Vitiligo now recognised as an assembly of subsets of depigmentation disorders with a generalised or segmental character. Patients would now be categorised as having "generalised vitiligo".