Positive preliminary results in Singaporean vitiligo study

Preliminary results of Singaporean Phase II study CUV103 in patients with naturally darker skin are consistent with results from the previous US Phase II trial (CUV102)

EXECUTIVE SUMMARY PRELIMINARY RESULTS CUV103

- Positive pigmentary response to SCENESSE® in combination with narrowband ultraviolet B (NB-UVB) in patients of darker skin complexion
- Combination therapy appears safe and effective
- Physicians' and patients' assessment of SCENESSE® is positive

Melbourne, Australia and Leatherhead, UK, December 3, 2015

Clinuvel Pharmaceuticals Ltd (**ASX: CUV; XETRA-DAX: UR9; ADR: CLVLY**) today announced positive preliminary results from a Singaporean Phase II trial (CUV103) evaluating its drug SCENESSE® (afamelanotide 16mg) as a repigmentation therapy in patients with vitiligo (a depigmentation disorder). The results are consistent with earlier findings from the US Phase II trial (CUV102).[1] In both studies SCENESSE® was well tolerated and increased repigmentation in patients with darker skin complexions, for whom vitiligo has an intense psychological and significant social impact.

CURRENT STANDARD OF CARE IS UNSATISFACTORY

No effective pharmaceutical therapy has yet been developed for vitiligo patients. Vitiligo therapy is primarily intended to arrest the loss of skin pigmentation and to stimulate repigmentation of affected skin as a secondary action. The current standard of care for vitiligo globally is treatment with narrowband UVB (NB-UVB) light, a controlled light therapy administered in the clinic in two to three sessions per week over the course of 12 to 18 months. The response rate to NB-UVB therapy alone is reported to be low and clinically unsatisfactory to patients and physicians.

COMMENTARY

"Together with the leading clinicians from two continents we are evaluating SCENESSE® as a new treatment for patients who have lost their pigmentation and which often affects their lives through a permanent change in appearance," Clinuvel's Director of Clinical Affairs, Dr Emilie Rodenburger said.

"From the encouraging results in two Phase II studies in the US and Singapore, and our ongoing safety program, we are confident that we have sufficient data to optimise the further development of SCENESSE® in vitiligo in specific populations," Dr Rodenburger said.

"Vitiligo has a high impact and is associated with a tragic stigma in our US population of various ethnic descent," Dr Mark Lebwohl, Professor and Chair of Dermatology at Mount Sinai Medical Center in New York, said. "We look forward to playing a part in developing the SCENESSE® therapy for the US patients with darker skin colour where the disease has a significant effect on their identity and lives."

PRELIMINARY SINGAPOREAN TRIAL RESULTS

The preliminary results of the Singaporean Phase II trial (CUV103) showed that increased repigmentation occurred in the four patients who received the SCENESSE® and NB-UVB combination treatment in comparison to the three patients who received NB-UVB with placebo treatment only. The physicians' assessment of vitiligo treatment offered was positive and in favour of the patients who received SCENESSE®.

Although first analyses were made on a small number of patients, preliminary statistical analyses (intention to treat population) comparing the change from baseline over time in the Vitiligo Area Scoring Index (VASI[2]) score (all body surfaces) between the treatment groups showed a positive trend in favour of SCENESSE® ($p=0.052$ at Day 168; Wilcoxon test). The analyses showed a higher decrease of the average VASI scores (indicating an increased

repigmentation) after the second SCENESSE® dose for the trunk, lower and upper extremities compared to placebo. Overall, these patients with Fitzpatrick skin types[3] V and VI showed a good clinical response to SCENESSE® in combination with NB-UVB.

The safety of SCENESSE® in combination with NB-UVB was good and no serious drug-related adverse events were reported in the preliminary analysis cohort. All reported drug-related adverse events to date have been in line with previous clinical experience with SCENESSE®.

The preliminary observations seen in the CUV103 study are consistent with the previous experience with SCENESSE® in combination with NB-UVB in the CUV102 study conducted in the US, where SCENESSE® combination therapy seems to provide a near complete and progressive repigmentation of skin areas affected. Final results from CUV103 are expected in the first half of 2016.

Images of vitiligo patients have not yet been released due to restrictions in the newly implemented Personal Data Protection Act 2012 (PDPA) in Singapore and its amendment of 2013.

TRIAL DESIGN – CUV103

The Phase II study was conducted at the National Skin Center, Singapore's leading dermatology clinic. The objective was to evaluate the effectiveness of six doses of SCENESSE® as a combination treatment with NB-UVB phototherapy in vitiligo patients with a naturally darker skin colour. In total 21 patients were enrolled using an adaptive trial design.

The primary endpoint of effectiveness was assessed through the Vitiligo Area Scoring Index (VASI), a standard validated scoring system for measuring the repigmentation achieved from vitiligo treatment. The secondary endpoint of effectiveness was measured through the Vitiligo Quality of Life (VitiQoL[4]).

Under a double-blind placebo controlled parallel design, eight vitiligo patients with Fitzpatrick skin types[4] V and VI involving 15% to 50% of their total body surface were enrolled. Four patients received six doses of SCENESSE® at 28 days intervals in combination with NB-UVB twice a week, and three patients received placebo and NB-UVB treatment twice a week. One patient received one dose of SCENESSE® but withdrew consent and discontinued the study early.

In an expanded open-label protocol, 13 patients with Fitzpatrick skin types IV, V and VI vitiligo involving 10% to 50% of their total body surface were enrolled. 11 patients are still being treated under this protocol, with treatment scheduled to be received up to February 2016. All patients treated under the open-label protocol are administered six doses of SCENESSE® at 28 days intervals in combination with NB-UVB administered twice weekly.

ABOUT VITILIGO

Vitiligo is a skin disorder in which particular pigment producing cells of the skin (melanocytes) appear to lose their function. As a result, lighter depigmented patches of skin (lesions) appear in different parts of the body due to the loss of melanin (pigment). Vitiligo is a disease of unknown origin which can start at any anatomical site at any age. It is hypothesised that autoimmune factors may play a role in some subtypes of vitiligo. Vitiligo often affects the face, trunk and extremities and may gradually spread over various body sites. Patients are most affected when extensive visible parts of the body show the loss of pigmentation. Although vitiligo is seen in all skin types (Fitzpatrick I-VI), the highest psychological and societal impact is seen in darker skin complexions (types IV-VI).

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[1] Lim et al (2015). Afamelanotide and narrowband UV-B phototherapy for the treatment of vitiligo: a randomized multicenter trial. *JAMA Dermatol.* 151(1):42-50. E-pub September 2014. Abstract online at http://www.ncbi.nlm.nih.gov/pubmed/25230094.

[2] The Vitiligo Area Scoring Index (VASI) is a validated quantitative scale initially developed to measure the response of vitiligo to NB-UVB treatment, but has since been used to evaluate various possible vitiligo therapies. In this assessment, the patient's body is separated into six regions: head and neck area, the hands, upper extremities (including auxiliary regions), trunk, lower extremities (including inguinal regions and buttocks), and the feet. A

decrease in the VASI score indicates an improvement in the extent and/or degree of repigmentation as a response to treatment.
Hamzavi et al (2004). Parametric modeling of narrowband UV-B phototherapy for vitiligo using a novel quantitative tool: the Vitiligo Area Scoring Index. *Arch Dermatol*. 140(6):677-683. Abstract online at http://www.ncbi.nlm.nih.gov/pubmed/15210457.

[3] The Fitzpatrick scale is a tool used to differentiate skin types based on visible melanin density and propensity for skin to burn and/or tan when exposed to ultraviolet light. It ranges from type I (very pale skin, never tans, always burns) to type VI (dark brown to black skin, always tans, never burns). For more information, see https://www.youtube.com/watch?v=HZ_LU9GtP1A.
Fitzpatrick (1988). The validity and practicality of sun-reactive skin types I through VI. *Arch Dermatol*. 124(6):869-871.

[4] The Vitiligo-specific health-related quality of life instrument (VitiQoL) is used to capture disease-targeted concerns and issues.
Lilly et al (2013). Development and validation of a vitiligo-specific quality-of-life instrument (VitiQoL). *JAAD*. 69(1):e11-18. Abstract online at http://www.ncbi.nlm.nih.gov/pubmed/22365883.

About Clinuvel Pharmaceuticals Limited
Clinuvel Pharmaceuticals Ltd (ASX: CUV; XETRA-DAX: UR9; ADR: CLVLY) is a global biopharmaceutical company focused on developing drugs for the treatment of a range of severe disorders. With its unique expertise in understanding the interaction of light and human skin, the company has identified patient populations with a clinical need for photoprotection and for repigmentation. The worldwide prevalence of these patient groups range from 5,000 to 45 million. Clinuvel's lead compound, SCENESSE® (afamelanotide 16mg), was approved by the European Commission in 2014 for the prevention of phototoxicity in adult patients with erythropoietic protoporphyria (EPP).
Headquartered in Melbourne, Australia, Clinuvel has operations in Europe, Switzerland, the US and Singapore.
For more information go to http://www.clinuvel.com.
SCENESSE® is a registered trademark of Clinuvel Pharmaceuticals Ltd.

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