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Phase II study: SCENESSE® in combination with narrowband ultraviolet B (NB-UVB) achieves repigmentation in vitiligo

A new observation in the CUV103 study conducted in Singapore is that overall skin darkening is culturally and socially unacceptable among patients of Asian origin

Melbourne, Australia and Singapore, 19 December 2018

SUMMARY

- Phase II study in vitiligo, a treatment-resistant disease[1]
- n=21, patients of Asian ethnicity, darker skin complexion
- Pooled analysis of data collected on all patients who received SCENESSE® with NB-UVB (n=18)
- Six doses of SCENESSE® subcutaneously administered monthly in combination with NB-UVB twice a week
- Repigmentation therapy with SCENESSE® in combination with NB-UVB effective and safety profile maintained:
  - Statistically significant increase in pigmentation on areas of vitiligo for total body, areas of head and neck (VASI, $p<0.001$ at Day 196), as well hands, upper extremities, trunk and lower extremities (VASI, $p<0.05$ at Day 196), with exception of the feet
  - Maintenance of pigmentation observed at Day 280, three months after the end of the treatment
  - Combination therapy of SCENESSE® with NB-UVB well tolerated

CLINUVEL PHARMACEUTICALS LTD today announced results of the CUV103 phase II clinical trial conducted at the National Skin Centre in Singapore which evaluated the use of SCENESSE® (afamelanotide 16mg) in vitiligo patients of Asian ethnicity.[2] The results of the pooled analysis of all patients (n=18) who received SCENESSE® (systemic treatment) plus narrowband ultraviolet B therapy (NB-UVB) showed that the combination therapy was clinically effective in achieving repigmentation in patients with vitiligo, a treatment-resistant disease which causes loss of pigmentation and has an intense psychological and social impact on patients.

However, for the first time since the start of the CLINUVEL's programme, the cultural aspects of skin darkening in patients of Asian origin were observed during the CUV103 trial. The overall darkening of the skin was considered to be undesirable and this had an impact on recruitment and willingness of some patients to undergo therapy.

OBJECTIVES AND DESIGN

Afamelanotide, an analogue of alpha-melanocyte stimulating hormone, activates the production of melanin in skin, with the SCENESSE® controlled-release injectable implant formulation having an affect across the total body surface area (pandermally). Earlier studies in vitiligo patients showed SCENESSE®, in combination with NB-UVB, could induce faster and deeper repigmentation in patients compared to NB-UVB alone.[3]

Patients enrolled in the CUV103 trial were planned to receive total body irradiation with NB-UVB twice per week for a duration of seven months along with SCENESSE® or placebo every 28 days for six months (six doses in total).

In this Phase II exploratory study in Asian vitiligo patients, *the scientific hypothesis* was to test whether:

a. following a month of NB-UVB monotherapy the administration of SCENESSE®, in combination with NB-UVB, would result in follicular repigmentation (through the induction of dermal stem cells); and
b. the administration of six doses of SCENESSE® in combination with NB-UVB would lead to repigmentation as assessed over time at seven timepoints in comparison to baseline values.

The Vitiligo Area Scoring Index (VASI), a standard validated scoring system for measuring the repigmentation (extent and degree of pigmentation) achieved was used to assess the efficacy of the intervention (a decrease in VASI score corresponds to repigmentation).

Included in this study were patients of Asian ethnic origin with darker skin complexion categorised as Fitzpatrick skin types IV to VI (including Chinese, Indian and Malay origin) who had 10% or more body surface area (BSA) affected by vitiligo and had not received NB-UVB treatment in the six weeks prior to study start.

RESULTS

Recruitment of patients of Asian origin who would accept temporary pandermal skin darkening during treatment was slow and the study design was modified from a randomised controlled (SCENESSE® plus NB-UVB versus placebo plus NB-UVB) to an open label study (SCENESSE® plus NB-UVB). A pooled analysis of all patients who received SCENESSE® plus NB-UVB (n=18) was undertaken and the results are presented below.

Out of the 21 patients who were enrolled in the trial, three patients receiving treatment with SCENESSE® and NB-UVB decided to withdraw consent and discontinue treatment. Withdrawal was mainly due to concerns with experiencing much darker constitutional skin following drug administration compared to baseline, despite this having been explained during the patient consent process. During clinical consultation these patients expressed concerns at the overall temporary epidermal darkening activated by SCENESSE® in combination with NB-UVB as skin darkening is culturally and socially unacceptable in certain Asian populations.

The efficacy evaluations showed statistically significant improvement (i.e. decrease in the VASI scores) from baseline (Day 0) to end of the treatment (Day 196 – after six doses of afamelanotide and seven months of NB-UVB) for the total body surface ($p<0.001$) as well as individual body areas: head and neck ($p<0.001$) and hands, upper extremities, trunk and lower extremities (all $p<0.05$).

The evaluations showed statistically significant decreases (improvement) in the VASI scores compared to baseline (Day 0) and at subsequent timepoints throughout the study; for the total body surface at Day 84 ($p=0.001$) through to Day 168 ($p<0.001$), for the head and neck, upper extremities and trunk at Days 112, 140, Day 168 (all $p<0.05$) and for the hands and lower extremities at Day 140 and Day 168 (all $p<0.05$). No differences in VASI over time were seen for the feet, an area that is quite resistant to repigmentation.

There were no statistically significant changes in pigmentation, as measured by VASI, between the end of the treatment (Day 196) and the follow-up visit (Day 280) (all $p>0.05$). This finding suggests that repigmentation had remained stable for the three months following completion of the treatment.

Patients' total body surface and head were exposed to a median of 48.0 and 43.0 total NB-UVB sessions, respectively, during the study. Median cumulative doses of 50,125 mJ/cm^2 and 45,229 mJ/cm^2 of NB-UVB radiation were received for the total body and head, respectively.

The repigmentation therapy of afamelanotide in combination with NB-UVB was shown to be tolerable and acceptable to all patients remaining in the trial. No serious adverse events were reported in the study.

There was no statistically significant difference in the change of quality of life over time as measured by the VitiQoL questionnaire (total score).

COMMENTARY

"At this institute, we all have been occupied by a most fascinating study with this potential new drug treatment," Professor Steven Thng, principal investigator at the National Skin Centre in Singapore said. "Having worked for a large part of my career in treating the entire spectrum of dermatology patients, this is the first time we have observed how strong cultural aspects dominate patients' perception of skin colour and repigmentation, even though they suffer from vitiligo. Since there had been no effective systemic repigmentation therapy, patients' anxiety for overall darkening of the skin had never been communicated and was a real surprise to us. This new finding indicates

that dark skin versus whiter skin in vitiligo patients in Singapore is regarded quite differently than in other parts of the world.

"The treatment with SCENESSE® was remarkably effective in achieving repigmentation in those patients who chose to overcome their anxiety of darkening and significantly improved their appearance. I can see a great application of this new therapy in the future, but it will need to be restricted specifically to those patients of Asian descent who do not suffer the psychological distress of overall temporary darkening caused by the hormonal treatment. As a clinician I am primarily looking at the extent of repigmentation achieved, patient burden from the treatment and ease of use of a new therapy. SCENESSE® seems to meet most of these criteria," Prof Thng said.

"We are observing similar efficacy results following the use of afamelanotide as we have found from the CUV102 study conducted in 2011-2012 in North America," Dr Pearl Grimes, Director of the Vitiligo & Pigmentation Institute of Southern California, Los Angeles said. "However, the cultural aspects dominating the behaviour of patients of colour in Asia is not a surprise to me, since skin colour is an important perceived determinant of social mobility and self-esteem.

"The results of the CUV102 and CUV103 studies are the foundation for the combination therapy with afamelanotide in vitiligo and our Institute is ready to engage in the next steps of this exciting and promising clinical program in the United States," Dr Grimes said.

"Much has been learned during this trial, including about the perception by vitiligo patients of various cultures and on a different continent," CLINUVEL's Director of Clinical Affairs, Dr Emilie Rodenburger said. "It is known and reported that NB-UVB can lead to unsatisfactory results for vitiligo patients, and this study seems to confirm the previously reported safety and efficacy of the combination therapy of SCENESSE® with NB-UVB. Together with the CUV102 study results, this study outcome has fortified our first objective to pursue the clinical program in vitiligo in North America.

"The next step will be to define the future label of SCENESSE® in vitiligo patients. It is imaginable that patients who have lost more than 10% of body surface area pigmentation would be eligible to receive the treatment. Vice versa, it is obvious that a patient who has less than 2% body surface area loss of pigmentation may not opt to receive a systemic injection of afamelanotide, but perhaps would use a topical formulation. Clearly, we are positioning ourselves at the forefront of vitiligo treatment and are developing a number of scientific tools to accompany the technological innovation we wish to introduce," Dr Rodenburger said.

– End –

[1] It has been agreed by the international medical community that 'nonsegmental vitiligo' no longer be used to describe the most common form of the disease, which is now referred to as 'vitiligo'.

[2] SCENESSE® (afamelanotide16mg) is approved in Europe as an orphan medicinal product for the prevention of phototoxicity in adult patients with EPP. Information on the product can be found on CLINUVEL's website at www.clinuvel.com.

[3] Grimes, P. E., Hamzavi, I., Lebwohl, M., Ortonne, J. P., & Lim, H. W. (2013). The Efficacy of Afamelanotide and Narrowband UV-B Phototherapy for Repigmentation of Vitiligo. *JAMA Dermatology*, 149(1), 68.

About CLINUVEL PHARMACEUTICALS LIMITED

CLINUVEL PHARMACEUTICALS LTD (ASX: CUV; NASDAQ INTERNATIONAL DESIGNATION ADR: CLVLY; XETRA-DAX: UR9) is a global biopharmaceutical company focused on developing and delivering treatments for patients with a range of severe genetic and skin disorders. As pioneers in photomedicine and understanding the interaction of light and human biology, CLINUVEL's research and development has led to innovative treatments for patient populations with a clinical need for photoprotection and repigmentation. These patient groups range in size from 5,000 to 45 million worldwide. CLINUVEL's lead compound, SCENESSE® (afamelanotide 16mg), was approved by the European Commission in 2014 for the prevention of phototoxicity (anaphylactoid reactions and burns) in adult patients with erythropoietic protoporphyria (EPP). More information on EPP can be found at http://www.epp.care.

Headquartered in Melbourne, Australia, CLINUVEL has operations in Europe, Switzerland, the US and Singapore, with the UK acting as the EU distribution centre.
For more information go to http://www.clinuvel.com.

SCENESSE® is a registered trademark of CLINUVEL PHARMACEUTICALS LTD.

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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Forward-Looking Statements
This release contains forward-looking statements, which reflect the current beliefs and expectations of CLINUVEL's management. Statements may involve a number of known and unknown risks that could cause our future results, performance or achievements to differ significantly from those expressed or implied by such forward-looking statements. Important factors that could cause or contribute to such differences include risks relating to: our ability to develop and commercialise pharmaceutical products, including our ability to develop, manufacture, market and sell biopharmaceutical products; competition for our products, especially SCENESSE® (afamelanotide 16mg); our ability to achieve expected safety and efficacy results through our innovative R&D efforts; the effectiveness of our patents and other protections for innovative products, particularly in view of national and regional variations in patent laws; our potential exposure to product liability claims to the extent not covered by insurance; increased government scrutiny in either Australia, the U.S., Europe and Japan of our agreements with third parties and suppliers; our exposure to currency fluctuations and restrictions as well as credit risks; the effects of reforms in healthcare regulation and pharmaceutical pricing and reimbursement; that the Company may incur unexpected delays in the outsourced manufacturing of SCENESSE® which may lead to it being unable to supply its commercial markets and/or clinical trial programs; any failures to comply with any government payment system (i.e. Medicare) reporting and payment obligations; uncertainties surrounding the legislative and regulatory pathways for the registration and approval of biotechnology based products; decisions by regulatory authorities regarding approval of our products as well as their decisions regarding label claims; any failure to retain or attract key personnel and managerial talent; the impact of broader change within the pharmaceutical industry and related industries; potential changes to tax liabilities or legislation; environmental risks; and other factors that have been discussed in our 2018 Annual Report. Forward-looking statements speak only as of the date on which they are made and the Company undertakes no obligation, outside of those required under applicable laws or relevant listing rules of the Australian Securities Exchange, to update or revise any forward-looking statement, whether as a result of new information, future events or otherwise. More information on the forecasts and estimates is available on request. Past performance is not an indicator of future performance.

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