Phase II study of SCENESSE® in rare skin disorder Hailey-Hailey Disease commences

Physician-led Phase II study commences in Rome

Baar, Switzerland and Melbourne, Australia, February 10 2014

Clinuvel Pharmaceuticals Limited (**ASX: CUV; XETRA-DAX: UR9; ADR: CLVLY**) today announced that a physician-led Phase II study of SCENESSE® (afamelanotide 16mg implant) in patients with the rare Hailey-Hailey Disease (HHD) has commenced in Italy. This study will enrol ten HHD patients to be treated with twelve doses of SCENESSE® during one year, with a three month clinical follow up period. Recruitment of all patients is expected to complete by March 2014.

SCENESSE® in HHD

In 2012, the first proof of concept open-label pilot study of afamelanotide in HHD was carried out in two female patients (age 53 and 61). At the time of the start of the study, the patients both had existing skin lesions and ulcerations which had been present since their adolescent years.

Following afamelanotide treatment, the lesions began to visibly decrease in size and totally disappeared by day 60. The clinical remission was also reflected by an improved QOL measured by the Medical Outcome Survey Short-Form 36 (SF-36). No adverse reactions were reported. Both patients experienced moderate skin tanning, as expected on the basis of the secondary pharmacology of SCENESSE®. Disease recurrence was only seen in the patients eight months after completion of the treatment (Biolcati et al., 2013). By comparison, only few complete or partial remissions are reported in the literature.

Afamelanotide, the active ingredient in SCENESSE®, is an analogue of alpha-melanocyte stimulating hormone (α-MSH) and has been shown to be an effective photoprotective agent in a range of skin disorders other than HHD. Several preclinical studies have provided evidence that natural α-MSH has potent protective and anti-oxidative effects in cutaneous cells. α-MSH affects various pathways implicated in the regulation of inflammation and cytoprotection. In particular, α-MSH has been shown to increase expression of nuclear respiratory factor 2 (Nrf2), a key transcription factor involved in the expression of anti-oxidative enzymes in keratinocytes. It is therefore plausible that SCENESSE®, as a potent α-MSH analogue, could mimic its physiological antioxidant properties.

Hailey-Hailey Disease

Hailey-Hailey Disease (HHD, also known as **familial benign chronic pemphigus**) is a rare, lifelong, inherited disorder where epidermal skin cells (keratinocytes) cannot properly adhere. This causes periodic eruption of plaque-like lesions, blisters and ulcerations on areas where skin folds (flexural), often on the neck, armpits or groin. Most patients have permanent lesions. HHD usually appears in the third or fourth decade of life.

HHD is passed on as a dominant trait (autosomal dominant). In approximately 70% of all patients a positive family history can be traced. Mutations in the ATP2C1 gene (localised on chromosome 3q21-q24), encoding the Golgi secretory pathway calcium pump (Ca^{2+}-dependent ATPase), impair epidermal keratinocyte adhesion.

Current ineffective treatments include topical corticosteroids, antibiotics, and mTor inhibitors which attempt to manage minor outbreaks. There is no professional consensus on a first-line therapy as no remission has been achieved in patients. Several literature reports indicate that HHD patients being predisposed to skin cancer.

The worldwide prevalence of HHD is 1:50,000. Orphanet lists Familial Benign Chronic Pemphigus under ORPHA number 2841 (Orphanet, 2006).

Comments

"We are pleased with the results of the pilot study and look forward to the outcome of this longer-term study," Clinuvel's Acting Chief Scientific Officer, Dr Dennis Wright said. "We hope that afamelanotide provides a major

therapeutic breakthrough for HHD patients who do not have any effective treatment. The results of this study will be available in late-2015".

"From a clinical viewpoint, we have learned during the past decade that the potential of SCENESSE® to treat severe skin disorders may be quite substantial," Clinuvel's CEO, Dr Philippe Wolgen said. "We are gradually beginning to understand the positive impact SCENESSE® can have on disorders where suprabasal skin cell separation is manifest. Clinuvel's expansion in HHD speaks to the selective use of this unique drug where it is clinically most needed and this particular study assists us to establish if treatment with SCENESSE® can result in a long term remission in HHD patients."

- End -

References

Biolcati G et al (2013). "Efficacy of the melanocortin analogue Nle4-D-Phe7-α-melanocyte-stimulating hormone in the treatment of patients with Hailey–Hailey disease." *Clin Exp Dermatol*. Epub 25 Oct.

Orphanet (2006). "Familial benign chronic pemphigus". Online http://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=2841.

Annex I: Following ASX Best Practice

Name of trial
Phase II study to evaluate the safety and efficacy of subcutaneous bioresorbable afamelanotide 16 mg implants in patients with Hailey-Hailey Disease (HHD).

Primary endpoint
Assess whether afamelanotide is effective in reducing or eliminating HHD-related symptoms.

Secondary endpoints
1. Assess whether treatment with afamelanotide will:
   - Improve the quality of life for HHD patients;
   - Reduce symptom severity for HHD patients.
2. Evaluate the safety and tolerability of afamelanotide implants.

Blinding status
Open-label.

Product development status
Good Manufacturing Practice (GMP) Standard.

Treatment method, frequency, dose levels
Open-label study with a single study arm. Each patient will receive afamelanotide (16mg implants) every 28 days for twelve months.

Number of trial subjects
10 adult patients with confirmed diagnosis of Hailey-Hailey Disease.

Subject selection criteria
The participant must fulfil all of the following criteria for study participation:
(a) Male or female subjects showing HHD symptoms with genetically confirmed HHD diagnosis;
(b) Clinically confirmed HHD diagnosis – stable disease (no documented remission within 30 days before screening visit) with Area Index Score ≥ 2;
(c) Aged between 18 and 80 years old;
(d) Written informed consent prior to the performance of any study-specific procedures.

Trial location
Single trial site in Rome, Italy.

Duration of the trial
Twelve month treatment period for an individual patient. Patients will return for a long term treatment follow up visit three months after the completion of the study.

Trial standard
In compliance with Good Clinical Practices (GCP) and ICH guidelines.

Annex II: About SCENESSE® (afamelanotide 16mg)
SCENESSE® is a first-in-class therapeutic being developed by Clinuvel, with the generic name (or INN) afamelanotide. An analogue of α-MSH, afamelanotide is a linear peptide which activates eumelanin of the skin, the dark pigment which is known to provide photoprotective properties (offering skin protection against light and UV radiation). SCENESSE® is administered underneath the skin as a dissolvable implant approximately the size of a grain of rice. For more information on SCENESSE® go to http://www.clinuvel.com/en/scenesse.

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 skin disorders. With its unique expertise in understanding the interaction of light and human skin, the company has identified three groups of patients with a clinical need for

photoprotection and another group with a need for repigmentation. These patient groups range in size from 10,000 to 45 million. Clinuvel's lead compound, SCENESSE® (afamelanotide), a first-in-class drug targeting erythropoietic protoporphyria (EPP), has completed Phase II and III trials in the US and Europe, and has been filed for review by the European Medicines Agency. Based in Melbourne, Australia, Clinuvel has operations in Europe, the US and Singapore.

For more information go to http://www.clinuvel.com.

Investor contacts:

Australia:	Clinuvel Pharmaceuticals Limited,	T: +61 3 9660 4900
Europe:	Clinuvel AG,	T: +41 41 767 45 45
E:	investorrelations@clinuvel.com	

Media contacts:
Lachlan Hay
Clinuvel AG
Baar, Switzerland
T: +41 41 767 45 45
Lachlan.Hay@clinuvel.com

Clinuvel is an Australian biopharmaceutical company focussed on developing its photoprotective drug, SCENESSE® (afamelanotide) for a range of UV-related skin disorders resulting from exposure of the skin to harmful UV radiation. Pharmaceutical research and development involves long lead times and significant risks. Therefore, while all reasonable efforts have been made by Clinuvel to ensure that there is a reasonable basis for all statements made in this document that relate to prospective events or developments (forward-looking statements), investors should note the following:

- actual results may and often will differ materially from these forward-looking statements;
- no assurances can be given by Clinuvel that any stated objectives, outcomes or timeframes in respect of its development programme for SCENESSE® can or will be achieved;
- no assurances can be given by Clinuvel that, even if its development programme for SCENESSE® is successful, it will obtain regulatory approval for its pharmaceutical products or that such products, if approved for use, will be successful in the market place