

## **Clinuvel announces positive results from pivotal European Phase III study: endpoints demonstrate clinically relevant treatment effect of afamelanotide**

*Patients diagnosed with erythropoietic protoporphyria (EPP) receiving SCENESSE® (afamelanotide) were able to expose skin to direct sunlight without burns and pain and recorded an improved Quality of Life.*

Melbourne, Australia and Baar, Switzerland, December 20, 2011

### **Key results**

- Patients receiving afamelanotide reported significantly less pain associated with phototoxicity (median pain score 6.0,  $p=0.035$ ).
- Patients on active drug experienced half as many phototoxic reactions ( $p=0.044$ ).
- Afamelanotide enabled patients to experience significantly more direct sunlight exposure without pain (10 AM-3 PM,  $p=0.005$ ).
- For the majority of study days, patients treated with afamelanotide were able to spend up to seven times longer in direct sunlight without experiencing pain.
- Patients on active drug reported a greater improvement in their Quality of Life (Day 270,  $p=0.011$ ).
- No safety concerns were identified during the study.
- Clinuvel to file SCENESSE® for European Marketing Authorisation for EPP.

Clinuvel Pharmaceuticals Limited (**ASX: CUV; XETRA-DAX: UR9; ADR: CLVLY**) today announced that final analyses of its confirmatory Phase III European study (CUV029) in erythropoietic protoporphyria (EPP) has shown a clinically relevant positive prophylactic treatment effect for patients who had been administered SCENESSE® (afamelanotide 16mg controlled-release formulation).

SCENESSE® is the first photoprotective drug developed as a prophylactic treatment for phototoxicity experienced by patients with EPP, a rare light intolerance disease. Presently there is no known effective treatment for EPP, which affects approximately 10,000 people globally, of which 4,000 are in Europe. SCENESSE® has been granted orphan drug status both in Europe and the US. Clinuvel is currently finalising a Marketing Authorisation Application (MAA) for SCENESSE® for submission to the European Medicines Agency (EMA) within the next few weeks.

“To obtain these results in a relatively small orphan drug population is excellent and supports our imminent submission to European regulators,” commented Clinuvel’s Chief Scientific Officer, Dr Hank Agersborg. “We knew over the years that European patients had tolerated the drug well, and from many patient and physician anecdotes during the study we learned of the clinical benefit of the drug. Overall, results from our four EPP studies show that we have made the right decision in our development strategy and it is encouraging to see strong demand for compassionate use by patients who have completed these studies.”

“Robust data from both this European Phase III trial and our recent US Phase II trial with SCENESSE® have demonstrated major clinical benefits to patients, despite their deeply learned behaviour to avoid reactions caused by sun exposure,” Clinuvel’s CEO, Dr Philippe Wolgen said. “Our focused and cost-effective R&D program over the past six years has delivered excellent results in the initial EPP indication, and this augurs well for future delivery of value to our shareholders. I congratulate the entire Clinuvel team for their work and diligence thus far.”

### **Severe genetic disease with no current therapy**

Erythropoietic protoporphyria (EPP) is a rare life-long genetic disease found mainly in fair-skinned people. It is characterised by severe phototoxicity (intolerance to light) of the skin resulting in intolerable pain, swelling and scarring, usually of exposed areas such as the face, hands and feet. Reactions can vary from mild to extreme with hospitalisation and powerful pain killers and morphine required in severe cases.

Patients have learned to avoid exposure to the sun and bright light to prevent the emergence of phototoxic pain and burns (‘adapted behaviour’). Characteristic of EPP patients – and different from other photodermatoses – is

that they experience early-onset symptoms upon sun and bright light exposure, meaning that they very quickly feel their skin reactions developing. This phenomenon warns them to retreat from daylight before their symptoms become more severe. Significantly, EPP patients are conditioned to avoid bright light and sun from childhood onwards and through adapted behaviour have learned to live indoors and lead nocturnal existences.

### **Study objectives and design**

CUV029 was a randomised placebo-controlled trial consisting of two parallel treatment arms conducted in eight different European academic centres which recruited a total of 74 EPP patients. The drug was tested over a nine month period which included the spring and summer months. Patients were evenly distributed between the two treatment groups across all study sites, receiving either afamelanotide or placebo treatment every 60 days.

SCENESSE® activates melanin in the skin, which shields against UV radiation (UVR) and sunlight, while the drug is delivered as a subcutaneous, dissolving implant approximately the size of a rice grain. Increased pigmentation of the skin may appear after two days and the therapeutic effect lasts up to two months.

This study and its objectives were designed in conjunction with global experts in porphyria management and incorporated advice received from the European Medicines Agency (EMA) through Protocol Assistance (PA) under EU orphan drug regulations.

The primary objective of evaluating afamelanotide in EPP patients was to determine whether the prophylactic effect has meaningful clinical benefit. Afamelanotide treatment aims to allow patients to lead a life which includes exposing themselves to ambient light and to engage in outdoor activities. A similar, secondary objective was to assess the effect of treatment on their Quality of Life (QoL).

### **Positive Phase III results – endpoints met**

Seventy-four patients started the study and 68 (91.9%) completed study medication and all clinical visits. In total, 17,377 days were evaluated during the study. Results of the study showed that SCENESSE® was well tolerated, allowed EPP patients to expose their skin to sunlight during the middle of the day without or with reduced pain and improved their Quality of Life (QoL). Overall the study demonstrated a strong clinical benefit to patients, despite their deeply learned behaviour to avoid reactions caused by sun exposure.

Afamelanotide recipients experienced half as many phototoxic reactions as placebo recipients ( $p=0.044$ ) and had a lower total median pain score (6.0 v 17.5;  $p=0.035$ ) and total lower maximum pain score per phototoxic episode in comparison to placebo patients (4.0 v 6.0;  $p=0.018$ ). Reduction of the intolerable pain in EPP patients is meaningful since no therapies, including analgesics, are effective in these patients.

Through recordings in patient diaries, patients in the afamelanotide group were able to spend more time in direct sunlight during periods of highest light and UV intensity, when EPP patients are most at risk of developing symptoms. Overall, afamelanotide recipients were able to spend more time in direct sunlight between 10 AM and 8 PM ( $p=0.005$ ). For the majority of study days, patients in the afamelanotide group were able to spend up to seven times longer in direct sunlight without experiencing pain.

Patients treated with afamelanotide could spend more time in direct sunlight on days when they reported no pain (10 AM-3 PM,  $p=0.005$ ; 10 AM-8 PM,  $p=0.003$ ) and on days when they reported no pain or mild pain (10 AM-3 PM,  $p=0.032$ ; 10 AM-8 PM,  $p=0.012$ ).

The impact of afamelanotide on the QoL was assessed using with a specialised EPP-specific QoL questionnaire (EPP-QoL). Patients treated with afamelanotide reported greater improvement in their QoL than placebo-recipients and the difference was significant on Days 120 ( $p=0.005$ ) and 270 ( $p=0.011$ ).

Most common adverse events were associated with implant administration (such as pain or bruising following injection), transient nausea, headache and the common cold. After reviewing and confirming all analyses and the safety data, the independent Data Safety Monitoring Board (DSMB) deemed afamelanotide suitable for further use in man. Importantly, no drug related serious safety concerns have been identified to date with SCENESSE® in all global clinical trials. To date over 600 patients have been treated with SCENESSE® across a number of indications.

Similar to the recently reported results from Clinuvel's US Phase II study in EPP, CUV030, all European study centres reported positively on their experience with afamelanotide treatment and requested the drug on behalf of

their patients for compassionate use. Following the completion of this European Phase III study, CUV029, Clinuvel has supplied SCENESSE® on a compassionate basis to Dutch, Finnish, French and German patients.

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#### **About SCENESSE® (afamelanotide)**

SCENESSE® is a first-in-class therapeutic being developed by Clinuvel, with the generic name (or INN) afamelanotide. An analogue of  $\alpha$ -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>.

SCENESSE® is a registered trademark of Clinuvel Pharmaceuticals Ltd.

#### **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), is in Phase II and III trials in the US and Europe, and is expected to be filed before the end of 2011 for review by the European Medicines Agency. Based in Melbourne, Australia, Clinuvel has operations in Europe and the US. For further information please visit [www.clinuvel.com](http://www.clinuvel.com)

#### **About Erythropoietic Protoporphyrin (EPP)**

Porphyrias are a group of inherited disorders with enzymatic deficiency in the blood synthesis pathway (also called porphyrin pathway). They are broadly classified as erythropoietic porphyrias based on the site of the overproduction and main accumulation of porphyrin. They manifest with either skin problems, neurological complications or gastro-intestinal problems (occasionally all).

EPP is a rare genetic disease found mainly in people with fair skin. It is characterised by severe phototoxicity (or intolerance to light) of the skin resulting in intolerable pain, swelling, and scarring, usually of the exposed areas such as the face, hands and feet. The pain experienced and expressed by EPP patients when their skin is exposed to light is reported as intolerable. EPP patients are often forced to remain indoors, severely affecting their quality of life.

For more information go to <http://www.clinuvel.com/en/erythropoietic-protoporphyrin/>

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

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