

## **New England Journal of Medicine publishes pivotal Phase III SCENESSE® studies**

*Breakthrough treatment for orphan genetic disorder presented to the general medical community*

### **EXECUTIVE SUMMARY**

- SCENESSE® published as innovative treatment in erythropoietic protoporphyria (EPP)
- Combined analyses of Phase III studies show significant improvement in the duration of patient sun exposure without phototoxicity
- New England Journal of Medicine: highest “impact factor” medical journal
- Pivotal studies led to December 2014 European marketing authorisation

Melbourne, Australia and Leatherhead, UK, July 2, 2015

Clinuvel Pharmaceuticals Ltd (**ASX: CUV; XETRA-DAX: UR9; ADR: CLVLY**) today announced that results from its pivotal Phase III studies of SCENESSE® (afamelanotide 16mg) in the orphan genetic disorder erythropoietic protoporphyria (EPP) have been published in the *New England Journal of Medicine* (NEJM, 2015, vol 375: 48-59, publisher’s embargo lifted at 17:00 EST, July 1).

### **COMMENTARY**

“Despite more than 40 years in the field it was only while participating as a senior physician in trials with afamelanotide that I gained insight into the major restrictions that EPP places on the daily activities of patients,” said Prof Paul Wilson, Emeritus Professor of Internal Medicine, Netherlands Porphyrin Centre, Erasmus MC Rotterdam, and senior co-author of the NEJM paper. “The effect of afamelanotide on diminishing these restrictions and on patient quality of life is dramatic – even more dramatic than has been captured by the trial assessment tools – and a great advantage of the drug is that side effects are minimal.”

“The approval of afamelanotide by the European Commission following these trial results represents a major breakthrough for EPP patients. As European porphyria physicians we now enter the next phase of making the drug available to our adult patients,” Prof Wilson said.

“The trial results show that the afamelanotide treatment transforms the lives of EPP patients, in essence that is the ultimate goal of having a company and academia working on new technology for 10 years,” said Dr Robert J Desnick, Dean for Genetic and Genomic Medicine and Professor and Chairman Emeritus of the Department of Genetics and Genomic Sciences at Mount Sinai School of Medicine, New York, and the corresponding author for the NEJM paper. “I’m optimistic that afamelanotide will be available to US patients in the future and delighted that European patients will soon have access to a much-needed treatment.”

“Today’s publication in the NEJM is as big an event for physicians as it is for patients: the most prestigious medical journal acknowledges a cutting-edge treatment for light-intolerant patients. Beyond EPP there is a great deal of potential for afamelanotide and similar melanocortin-based therapies. The immediate and most obvious targets are translationally photosensitive and light-induced disorders where no effective therapeutic options exist,” Dr Desnick said.

“To evaluate SCENESSE® as an innovative drug in EPP, we worked closely with the world’s leading EPP experts to develop the clinical trials’ designs and assessment tools to assess the benefits of this treatment for patients,” Clinuvel’s Director Clinical Affairs, Dr Emilie Rodenburger said. “By measuring the symptom free time patients could spend in direct light, we sought to evaluate the impact treatment with SCENESSE® could have on enabling a normal, risk-free life. Despite all the challenges faced, I am very pleased for all patients and physicians that we persevered.”

“The lead NEJM authors, Drs Langendonk and Balwani, deserve particular recognition for their initiative and expertise in rare and metabolic disorders,” Dr Rodenburger said.

### **ANALYSES OF CUV029 AND CUV039 IN NEJM**

The NEJM article, “Afamelanotide for Erythropoietic Protoporphyrria”, reviewed results from two Phase III studies, CUV029 (Europe) and CUV039 (US) conducted across 15 specialist centres. Combined analyses of 168 EPP patients showed that SCENESSE® enabled those who received active drug to expose their skin to daylight and sun without incurring characteristic phototoxic burns, with statistically significant longer exposure seen in patients who received the active drug (p=0.04 in the US, p=0.005 in Europe).

The quality of life of patients measured by an EPP-specific survey was compared between active and placebo recipients. The group receiving SCENESSE® showed marked improvement of quality of life at various time points (range of p<0.001 to p=0.06).

The NEJM authors emphasised difficulties of evaluating a novel treatment in EPP, a disease which had not previously been subject to parallel placebo-controlled randomised clinical trials.

Both studies evaluated the safety of SCENESSE®. Treatment-emergent adverse events – those considered related to afamelanotide – were mild or moderate in severity with no serious treatment-related adverse events identified.

The NEJM authors concluded that “afamelanotide had an acceptable side-effect profile and improved tolerance to sunlight in patients with erythropoietic protoporphyria”.

### **RELEVANCE OF SCENESSE® IN THE TREATMENT OF EPP**

EPP is a particularly complex genetic disorder. Patients experience intense fear of incurring phototoxicity due to light exposure; severe dermal burns can result from any exposure to light, resulting in prolonged distress and incapacitation. The visible wavelengths of light cause the characteristic phototoxicity. From childhood onwards EPP patients are forced to isolate themselves from all sun and light exposure. The ingrained behaviour to minimise light exposure dictates EPP patients’ lives.

Afamelanotide, the active ingredient in SCENESSE®, acts as an agonist to the melanocortin-1 receptor and is part of the family of drugs known as melanocortins. SCENESSE® delivers 16mg of afamelanotide as a controlled-release implant activating the pathway to stimulate melanin in skin. As a result patients’ skin becomes visibly darker as soon as 48 hours after drug administration. Melanin reduces skin damage from light exposure by acting as an umbrella over cells. Afamelanotide and melanin also act as powerful antioxidants.

As previously reported by Clinuvel, the majority of patients who received SCENESSE® have expressed that the drug provided them a freedom to lead a life they had not had before, enabling them to participate in outdoor activities without fear of severe incapacitating symptoms.

### **EUROPEAN MARKET ACCESS SCENESSE®**

Based on all five EPP studies conducted with afamelanotide, in particular CUV029 and CUV039, SCENESSE® was granted European marketing authorisation on 22 December 2014 for adult EPP patients. The drug will be made available to European EPP patients as soon as the European Medicines Agency’s Pharmacovigilance Risk Assessment Committee has reviewed the Central European EPP Disease Registry.

### **NEW ENGLAND JOURNAL OF MEDICINE (NEJM)**

The NEJM currently has the highest impact factor (54.42 in 2013/14) of all medical periodicals, an independent measure reflecting the frequency of citations of its publications. The NEJM’s published articles are subject to rigorous peer review. An earlier open-label study of SCENESSE® in EPP patients was published in the NEJM in 2009.

### **CLINUVEL CONTRIBUTION**

In accordance with the NEJM Ingelfinger Rule, none of the article on both trials in EPP has been previously published in a medical journal. Although both clinical trials were sponsored by Clinuvel Pharmaceuticals, Clinuvel was not involved in the writing or editing of the manuscript. Clinuvel does not financially incentivise physicians or academics to publish its clinical trial results.

## REFERENCES

Langendonk JG et al (2015). Afamelanotide for Erythropoietic Protoporphyrria. *New Eng J Med*. 373(1):48-59. Abstract online at [http://www.nejm.org/doi/full/10.1056/NEJMoa1411481?query=featured\\_home](http://www.nejm.org/doi/full/10.1056/NEJMoa1411481?query=featured_home).

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## Media enquiries

Lachlan Hay, Clinuvel (UK) Ltd.	+44 1372 860 765	<a href="mailto:Lachlan.Hay@clinuvel.com">Lachlan.Hay@clinuvel.com</a>
Nick Miles, Cabinet Privé de Conseils s.a.	+41 22 321 4540	<a href="mailto:miles@cpc-pr.com">miles@cpc-pr.com</a>
Ted Agne, The Communications Strategy Group Inc.	+1 718 631 3117	<a href="mailto:edagne@comstragroup.com">edagne@comstragroup.com</a>
Emma Power, Monsoon Media	+61 3 9620 3333	<a href="mailto:emmap@monsoon.com.au">emmap@monsoon.com.au</a>

Media note: Dr Robert J Desnick is available for interview through the Press Office at Mount Sinai School of Medicine, please contact Sid Dinsay via +1 212 241 9200 or [sid.dinsay@mountsinai.org](mailto:sid.dinsay@mountsinai.org).

## Investor enquiries

[InvestorRelations@clinuvel.com](mailto:InvestorRelations@clinuvel.com)

## 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 another population with a need for repigmentation. These patient groups range in size from 5,000 to 45 million. Clinuvel's lead compound, SCENESSE® (afamelanotide 16mg), a first-in-class drug targeting erythropoietic protoporphyria (EPP), has completed Phase II and III trials in the US and Europe, and has been approved by the European Commission for treating adults with EPP. Headquartered in Melbourne, Australia, Clinuvel has operations in Europe, the US and Singapore.

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

Clinuvel is an Australian biopharmaceutical company focussed on developing its drug SCENESSE® (afamelanotide 16mg) for a range of clinical disorders with unmet need. 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.

Level 5, 160 Queen Street	T +61 3 9660 4900	<a href="http://www.clinuvel.com">www.clinuvel.com</a>
Melbourne, Victoria 3000	F +61 3 9660 4999	
Australia		