



Clinuvel communications

Live on <http://www.clinuvel.com/> today:

- Webcast: EPP – “A life in the shadows”
- Webcast: Clinuvel CEO Dr Philippe Wolgen discusses results from the CUV017 trial

Live on <http://www.clinuvel.com/en/blog> today:

- Insight to Clinuvel’s first Phase III results

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## Company Announcement

Tuesday 13 July 2010  
Melbourne, Australia

# CLINUVEL REPORTS POSITIVE RESULTS IN PHASE III PORPHYRIA (EPP) CLINICAL TRIAL

Clinuvel Pharmaceuticals Limited (**ASX: CUV; XETRA-DAX: UR9; ADR: CLVLY**) today announced that it obtained positive results in a study which investigated SCENESSE® (afamelanotide) as a systemic photoprotectant in a 12 month, multicenter, randomised, double-blind, placebo-controlled Phase III crossover study (CUV017) in erythropoietic protoporphyria (EPP). In one Australian and seven European centres, SCENESSE® was evaluated for its ability to provide preventative pharmaceutical therapy in EPP patients who are known to suffer from phototoxic reactions following exposure to sun and light (>400 nanometres wavelength). The independent members of a Data Safety and Monitoring Board have reviewed the study results and have confirmed the conclusions.

### Results

#### Primary Efficacy Analyses

A total of 91 patients completed the 12-month study, in which an 11-point Likert scale and physician assessments through case report forms (CRF) were used to evaluate pain as a principal symptom of phototoxicity. The duration of daily (sun)light exposure was used to assess the willingness of patients to expose themselves during all seasons. Melanin density (reflecting changes in skin pigmentation, measured by spectrophotometry) and quality of life (Short Form 36 surveys) were also evaluated.

In an analysis of the total number of days (frequency distribution) on which patients experienced pain in the specific pain severity categories (severe, moderate, mild and none), a significant reduction of frequency was observed in patients on active drug [ $p=0.0023$ ]. Characteristic to EPP, the majority of phototoxic reactions occurred during spring and summer.

In analysing the average pain severity experienced by the total number of patients, the assessment of all individual daily pain scores was significantly lower in patients receiving SCENESSE® compared to those receiving placebo [ $p=0.0017$ ].

An additional evaluation of the pain scores in patients willing to modify behaviour by continuous exposure to daily (sun)light showed a positive trend toward a reduction in average pain score following active drug treatment [ $p=0.1654$ ].

#### Secondary Efficacy Analyses

Clinically relevant daily exposure of longer than one hour per day symptom-free was recorded by the trial physicians (CRFs) at the end of each 60 day treatment. In assessing the duration of sunlight exposure per patient, there was significantly more sun exposure in patients receiving SCENESSE® [ $p<0.0001$ ]. These analyses strongly indicate that patients receiving drug increased their confidence to engage in outdoor activity.

In assessing skin pigmentation (melanogenesis as function of the drug’s pharmacological activity), a distinct clinical effect was recorded following administration of active drug, and in both treatment arms absolute melanin levels rose in one group by 29.1% and in the other by 28.4%.

The quality of life (QoL) observations of clinicians did not reflect the patients' response to treatment. Quality of life assessment over the entire 12-month study was determined to be inappropriate for this population. Since the majority of patients wished to continue use of the drug after the end of the studies, alternative and disease-specific quality of life measurements are being employed in the ongoing studies.

SCENESSE® was well tolerated, none of the patients who completed the study requested the treatment to be discontinued and no serious adverse event was reported to be drug-related.

Complete results will be presented at the 19<sup>th</sup> Congress of the European Association for Dermatology and Venereology in October 2010.

### **Regulatory relevance**

The genetic disease EPP – also described as absolute light intolerance – is known to impact patients from childhood onwards as they learn to adapt behaviour when experiencing the skin effects following UV and sun exposure.

The results from this trial demonstrate for the first time that patients who are able to overcome their anxiety to expose themselves to sunlight receive beneficial photoprotection from SCENESSE® reducing or abrogating the severity and frequency of cutaneous symptoms.

The study also demonstrates that the lifelong conditioned behaviour of patients remains a challenge in a placebo-controlled trial in which patients are uncertain whether they receive active treatment or not. Despite this uncertainty, only nine patients did not manage to complete the entire trial.

Of further clinical relevance were the statements by all eight physicians leading the trial and declaring that the majority of patients had reported the ability to engage in outdoor activities which had not been possible prior to treatment. Significantly, these activities are not captured in current standard Quality of Life surveys.

The reported safety and efficacy data after 12-months of intermittent drug use support the regulatory criteria of clinical relevance and beneficial treatment effect for SCENESSE® as a first line therapy for EPP patients.

### **Commentary**

Clinuvel's Chief Scientific Officer, Dr Hank Agersborg said:

"Today's results are meaningful in that for the first time a mathematically significant treatment difference has been demonstrated. It is essential that we meet this EMA and FDA standard for placebo-controlled trials. It can be supported however that under realistic conditions of use simulating and approximating daily existence and risk, patients will wish to challenge themselves to risky behaviour – in this case UV exposure - only when they are assured that they will receive active drug. This is of particular relevance in EPP where patients have literally been burnt in the past.

"I am extremely pleased by these results as they will assist us in making a case to regulatory agencies on the grounds of drug safety, efficacy and need for treatment."

Clinuvel's CEO, Dr Philippe Wolgen said:

"These long-awaited results have taken us closer to our ultimate commercial objectives in the interests of both the patients as well as investors.

"In learning from pharmaceutical cases around us, and relevant to Clinuvel's drug development, I view the sequence of expected regulatory scrutiny of data generated as essential. In EPP we are treating an orphan disease for which no comparable therapy can be accessed, as such, the demonstration of both short- and long-term safety data, is the single-most important parameter in the regulatory review process.

"This statistical outcome on safety and treatment effect support in presenting efficacy data to the regulatory authorities, whereby it is relevant to our filing that no other group has ever conducted large-scale therapeutic trials in this disease or has attempted to measure the effects of light on skin. Our team can be pleased by successfully having broken new ground."

- End -

Appendix I (Following Code of Best Practice, ASX)

Name of the trial	A Phase III, Multicentre, Randomised, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Subcutaneous Bioresorbable Afamelanotide (CUV1647) Implants in Patients with Erythropoietic Protoporphyrria (EPP)
Protocol No.	CUV017
EudraCT number	2007-000636-13
Investigational medicinal product	Afamelanotide 16 mg
Formulation	Subcutaneous resorbable implant formulation
Analysis	Per protocol
Duration	12 months
Countries	Australia, France, Germany, Italy, Netherlands, Sweden, Switzerland and UK
Number of patients evaluated	91
Number of doses administered	576
Total number of days of drug exposure	Afamelanotide: 16040 Placebo: 16089
Phototoxicity measurement	<ul style="list-style-type: none"> <li>• 11-point categorized Likert pain score [per patient diary]</li> <li>• Physician's clinical assessment of phototoxicity and skin lesions per Case Report Form (CRF)</li> <li>• Daily exposure time per patient diary (PD)</li> </ul>
Overall treatment effect	<p>Reduction in the severity and frequency of episodes of pain associated with phototoxicity:</p> <ul style="list-style-type: none"> <li>• Significant difference in pain scores <math>p=0.0023</math></li> <li>• Reduction in the average overall daily pain severity score <math>p=0.0017</math></li> <li>• Reduction in the average patient's daily severity score <math>p=0.1654</math> [CI 95% range 94.9% to 98.8%]</li> </ul> <p>Increase in sun exposure tolerated by patients:</p> <ul style="list-style-type: none"> <li>• Significant difference in sun exposure in active group [<math>p&lt;0.0001</math>]</li> </ul> <p>Increase in the average skin melanin density level:</p> <ul style="list-style-type: none"> <li>• from 3.13% to 4.04% (Group A) and 3.06% to 3.93% (Group B)</li> </ul> <p>Quality of Life (SF-36)</p> <ul style="list-style-type: none"> <li>• Determined inappropriate QoL instrument, disease-specific QoL used in compassionate program</li> </ul>
<b>SUMMARY ADVERSE EVENTS</b> Serious Adverse Events [SAE] Adverse Events [AE]	<p>In total, 8 serious adverse events were reported, of which 4 occurred in placebo recipients and none were considered to be related to study medication.</p> <p>Most adverse events were mild or moderate in severity, with headache, nausea, flushing and gastrointestinal events reported most often.</p>
Data Safety Monitoring Board	<p>The study results were deemed to be consistent with the data analyses and use of SCENESSE® (afamelanotide) was recommended as potential therapy in EPP.</p> <p>On the basis of the 12-month safety reports, the use of SCENESSE® (afamelanotide) was determined to be safe for further human use.</p>

## Appendix II (Following Code of Best Practice, ASX)

### Name of trial

CUV017. A Phase III, Multicentre, Randomized Placebo Controlled Study to Evaluate the Safety and Efficacy of Subcutaneous Bioresorbable Afamelanotide (CUV1647) Implants in Patients with Erythropoietic Protoporphyrin (EPP). Protocol No. CUV017.

### Primary endpoints

- a) The mean number of phototoxic reactions that occur whilst patients are on active compared with placebo implants.
- b) The mean severity score for phototoxic reactions that occur whilst patients are on active compared with placebo implants.

### Secondary endpoints

Difference in the mean between active and placebo:

- a) Changes in melanin density (measured by spectrophotometry)
- b) Amount of sunlight exposure, as recorded in diary card
- c) Change in quality of life (measured with SF36 questionnaire)
- d) The mean "time taken to develop provoked symptoms" following photo testing (in a subset of patients only)

### Blinding status

Double-blind.

### Product Development Status

Good Manufacturing Practice (GMP) Standard.

### Treatment method, frequency, dose levels

Multiple crossover design in which patients received alternating 16 mg afamelanotide or placebo implants once every 2 months for a total of 6 implants administered subcutaneously over a 12 months period.

### Number of trial subjects

Up to 100 patients in total.

### Subject selection criteria

- a) Male or female subjects with a positive diagnosis of EPP (confirmed by elevated free protoporphyrin in peripheral erythrocytes)
- b) Aged 18-70 years

### Trial location

Multiple trial sites in Australia and Europe

### Expected duration of the trial

12 months treatment for an individual patient.

### Trial standard

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

## Appendix III 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, SCENESSE® is a linear peptide which activates the skin to release eumelanin, the dark pigment which is known to have photoprotective properties (providing 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. SCENESSE® is a registered trademark of Clinuvel Pharmaceuticals Ltd. For more information see [scenesse.com](http://scenesse.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 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 hands and face. 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.

### About Clinuvel Pharmaceuticals Limited

Clinuvel Pharmaceuticals Ltd is a leading and innovative Australian company focused on the development of SCENESSE® (afamelanotide), its proprietary first-in-class photoprotective drug. Clinuvel has identified five groups of patients with a clinical need for photoprotection. Currently, Clinuvel is in its final stages to complete testing of

SCENESSE® in Phase II and III trials in Australia, Europe and the United States. Clinuvel's ongoing focus is to demonstrate the safety and efficacy of SCENESSE®. Pending positive clinical results, Clinuvel aims to file SCENESSE® for its first market approval for the orphan indication porphyria (EPP).

Clinuvel is currently testing SCENESSE® in five clinical indications:

Indication	Description	Clinical Trial Status
Erythropoietic Protoporphyrin (EPP)	Absolute sun/UV intolerance	Phase III trial full results reported July 2010 Confirmatory Phase III trial approved August 2009
Actinic Keratosis (AK) and Squamous Cell Carcinoma (SCC) in Organ Transplant Recipients (OTRs)	Skin cancer in transplant patients	Phase II trial started October 2007
Polymorphic Light Eruption (PLE / PMLE)	Severe sun/UV poisoning	Phase III trial preliminary results reported December 2009
Solar Urticaria (SU)	Acute anaphylactic reaction to sun/UV	Phase II trial results reported July 2009*
Photodynamic Therapy (PDT) - systemic	Phototoxicity following cancer treatment	Phase II trial results reported December 2009*

\*Program deferred February 2010.

Phase I and II human clinical trials using SCENESSE® have demonstrated that the drug is well tolerated and no significant safety concerns have been identified to date. Following successful conclusion of the development program, Clinuvel will work closely with global regulators to facilitate marketing approval of SCENESSE®. For more information see [clinuvel.com](http://clinuvel.com).

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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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