

Clinical significance and benefit from SCENESSE® in US Phase III EPP study

Primary endpoint shows a strong statistical trend in pain-free exposure following the treatment of the 'orphan' disease erythropoietic protoporphyria (EPP)

Melbourne, Australia and Baar, Switzerland, November 11, 2013

Executive summary

- Endpoint analysis shows strong trend that treated patients were able to experience more pain-free sun exposure between 10:00 and 18:00; median total direct sunlight exposure was 64.13 hours in the active group compared with 47.5 hours for placebo-recipients ($p=0.107$);
- Photoprovocation, an objective measure of light tolerance, showed that SCENESSE® significantly increased time to first symptoms following light provocation (tolerance to light) ($p<0.001$);
- Validated EPP Quality of Life (EPP-QoL) instrument showed a significant treatment-related improvement in patients' quality of life ($p=0.002$ to $p=0.004$);
- Distribution of pain-free days in direct sunlight showed a statistically significant difference between the treatment groups ($p<0.001$);
- Distribution of days on which patients experienced pain of the different pain severity categories (none, mild, moderate and severe) was significantly different ($p<0.0001$);
- EMA to include review of CUV039 study results as part of marketing authorisation application.

Clinuvel Pharmaceuticals Limited (**ASX: CUV; XETRA-DAX: UR9; ADR: CLVLY**) today announced that analyses of its Phase III US study (CUV039) evaluating the administration of SCENESSE® (afamelanotide 16mg) to patients diagnosed with erythropoietic protoporphyria (EPP) had shown a clinically meaningful treatment effect. The drug was well tolerated with no safety concerns identified. The study's independent Data Safety Monitoring Board stated that the drug treatment offered had been clinically meaningful and safe for use in patients.

CHARACTERISATION OF EPP AND CUV039 STUDY OBJECTIVES

EPP is reported as a serious and very rare disabling disease, in which patients have learned to avoid light and sun exposure to prevent phototoxic pain and burns ('adapted behaviour'). Characteristic of EPP patients – and different from other photodermatoses – is that they experience prodromal symptoms upon light exposure, meaning that they are able to feel skin symptoms and burns developing. This phenomenon alerts them to shun light before their symptoms escalate. EPP patients are conditioned to avoid light from childhood and adapt their lives by remaining indoors and leading nocturnal existences.

The primary objective of evaluating SCENESSE® in EPP patients was to determine whether the prophylactic use of the drug would provide a clinically relevant benefit. The expected clinical benefit of SCENESSE® treatment was to allow patients to lead an existence which includes the ability to expose themselves to ambient light and to engage in outdoor activities which were not possible prior to treatment. A secondary objective was to assess whether treatment would improve their quality of life (QoL).

SCENESSE® is the first modern therapy to be evaluated for EPP.

STUDY DESIGN

CUV039 was a six-month, randomised, multicentre, double-blind, placebo-controlled Phase III study which recruited 93 adult EPP patients in the seven main US porphyria specialist centres (Alabama, California, Michigan, New York, North Carolina, Texas and Utah). The heads of department at each academic centre were personally involved in the conduct of the trial. Patients were randomised into two treatment groups and given either SCENESSE® or placebo implants every two months (at days 0, 60 and 120). A final visit for safety follow-up was scheduled on day 210.

Patients kept written daily diaries recording light and outdoor exposure, as well as pain data. The impact of treatment on patient QoL was evaluated throughout the study using two validated questionnaires, DLQI and EPP-QoL (disease specific). As an objective measure of efficacy, a subset of patients ($n=20$) underwent

photoprovocation testing on days 0, 30, 60, 90 and 120 utilising an artificial light source under standardised laboratory conditions to determine the tolerance to light irradiation.

ENDPOINTS AND RESULTS

In total 93 patients were enrolled and 87 completed the study (93.5%), 45 on active treatment and 42 placebo recipients. Three from each group withdrew from the study due to reasons unrelated to drug administration.

The primary endpoint was to establish the extent to which patients exposed themselves to direct sunlight between 10:00 and 18:00 as recorded daily in patient diaries. A strong trend towards greater direct sunlight exposure was seen in the active group compared to placebo recipients. Median total direct sunlight exposure was 64.13 hours (range 0 - 650.5 hours) in the active group compared with 47.5 hours (range 0 - 224 hours) for placebo recipients ($p=0.107$, Kruskal-Wallis test). The distribution of the number of days with sun exposure of various time intervals (30 min intervals) was significantly different between the treatment groups ($p<0.001$, Cochran-Mantel-Haenszel test). As an example, SCENESSE® recipients reported more days when they had pain-free exposure of 60 minutes or more (the time of greatest risk of burns).

To provide an objective measure of light tolerance in support of the primary endpoint, photoprovocation under standardised laboratory conditions was performed in 20 patients at Mount Sinai Hospital. The results showed that after receiving their second SCENESSE® administration, patients had a significantly higher tolerance to light irradiation on the lower back and back of the hand (median change from baseline in minimum symptom dose on lower back at day 90, 227.5 versus -2.4 J/cm²; $p<0.001$, Wilcoxon test). Results for the lower back at day 120 and the back of the hand at days 90 and 120 showed similar significant differences.

As a secondary endpoint, QoL was evaluated using the validated EPP-QoL questionnaire. Active drug recipients showed significantly improved QoL scores in comparison to placebo recipients on days 60, 120 and 180 of the study ($p=0.002$, 0.002 and 0.004 respectively, Kruskal-Wallis test).

A further secondary endpoint looked at the distribution of days on which patients experienced mild, moderate or severe phototoxic pain. The difference in the distribution of days during which pain was experienced was significant between the two treatment groups ($p<0.0001$, Cochran-Mantel-Haenszel test).

The safety profile of the drug was good, consistent with all previous trials in EPP. Headaches (nine patients receiving active treatment and five receiving placebo) and nausea (seven active and five placebo) after the first implant administration were the most common adverse events.

The study's independent Data Safety Monitoring Board confirmed that these results indicate that afamelanotide 16mg provides a safe, effective and clinically meaningful treatment for patients with EPP.

REGULATORY IMPLICATIONS AND CLINICAL RELEVANCE

Clinuvel submitted a marketing authorisation application (MAA) to the European Medicines Agency (EMA) for SCENESSE® for the treatment of EPP in February 2012, with data from previous Phase II and III studies forming the basis of the submission.

As part of the final regulatory review, the EMA has requested the results of CUV039 be made available. The EMA will evaluate the latest US data in a continuum with the results reported in the CUV029 and CUV030 studies.

Clinical relevance in EPP is defined as patients' ability to engage in daily activities which were not possible prior to treatment with SCENESSE®, as well as pain-free exposure to light sources and direct sunlight.

EPP patients are conditioned from early childhood onwards to avoid light and sun, and patients fear light exposure at the risk of incurring severe skin reactions (phototoxicity). This avoidance has been reflected in all clinical studies and compassionate use programs to date, with the majority of patients avoiding exposure despite being aware that they have received active treatment. The gradual loss of anxiety and willingness to risk light and sun exposure is an essential part of the clinical relevance of the treatment offered.

The final stage of EMA review of SCENESSE® is expected to continue in January 2014. The further EMA timeline will be known by Q1 2014.

The CUV039 results together with the earlier results in CUV010, CUV017, CUV029 and CUV030 will be discussed with the FDA Division of Dental and Dermatology Products in a meeting requested for Q1 2014.

COMMENTS

“Consistent with previous EPP trials, these patients have learnt throughout their lives to avoid direct light exposure,” Clinuvel’s Acting Chief Scientific Officer, Dr Dennis Wright said. “Understandably, a deep-rooted anxiety to avoid burning reactions dominates the behaviour of these patients.

“In this statistical context, direct sun exposure between 10am and 6pm as recorded by patients, combined with the photoprovocation as an objective measure of light tolerance, confirms the scientific hypothesis that SCENESSE® provides an effective prophylactic treatment for EPP patients. These findings are consistent with the feedback we have received over the past seven years from physicians and patients,” Dr Wright said.

“This program is the first to fully and rigorously evaluate a therapy for EPP, a disease which is poorly understood globally and presents uniquely in the clinic,” 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 a lead investigator on the CUV039 study said.

“The results reflect numerically what our patients reported in the clinic: when treated with SCENESSE® they can spend more time outside, experience less pain, and lead more normal lives. Professionally this is satisfying, as we may now, finally, be able to tell EPP patients that we can manage or prevent their painful symptoms and give them a freedom never before experienced,” Dr Desnick said.

– End –

Appendix I (Following Code of Best Practice, ASX)

Name of trial

CUV039: A Phase III, Multicentre, Double-Blind, Randomized, Placebo-Controlled Study to Confirm the Safety and Efficacy of Subcutaneous Bioresorbable Afamelanotide Implants in Patients with Erythropoietic Protoporphyrria (EPP).

Primary endpoint

Determine whether afamelanotide can enable EPP patients to expose themselves to sunlight without incurring pain and phototoxic reactions, measured by duration of direct sunlight exposure between 10:00 and 18:00 hours on days when no pain is experienced (Likert pain score of 0).

Secondary endpoints

1. Determine whether afamelanotide can:
 - Increase the duration of time patients can be exposed to direct sunlight between 10:00 and 18:00 hours with no or mild pain (Likert scores of 0 to 3) and overall;
 - Improve the quality of life of patients;
 - Reduce the susceptibility to provocation with a standardised light source (minimum symptom dose).
2. Evaluate the safety and tolerability of afamelanotide implants by measuring treatment-emergent adverse events (TEAEs).

Blinding status

Double-blind.

Product development status

Good Manufacturing Practice (GMP) Standard.

Treatment method, frequency, dose levels

This was a randomised placebo-controlled study conducted in two parallel study arms for a six month period (three doses) in months when sunlight is most intense. Eligible patients received afamelanotide (16 mg implants) or placebo according to the following dosing regimen:

- Group A: administered afamelanotide implants on Days 0, 60 and 120;
- Group B: administered placebo implants on Days 0, 60 and 120.

Number of trial subjects

93 patients enrolled, 87 (93.5%) completed all patient visits.

Subject selection criteria

The participants in both groups had to fulfil all of the following criteria for study participation:

- (a) Male or female subjects with a clinical diagnosis of EPP of sufficient severity that they have requested treatment to alleviate their symptoms;
- (b) Aged 18 years old and above;
- (c) Written informed consent prior to the performance of any study-specific procedures.

Trial location

Seven trial sites across the United States of America.

Duration of the trial

Six month treatment period for an individual patient. Patients returned 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.

Appendix 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/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

About Erythropoietic Protoporphyria (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/erythropoietic-protoporphyria/>

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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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