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Clinuvel Pharmaceuticals Limited (ASX: CUV; XETRA-DAX: UR9; ADR: CLVLY) recently announced that it will be filing a Marketing Authorisation Application (MAA) with the European Medicines Agency (EMA) for its photoprotective drug, afamelanotide, for the treatment of erythropoietic protoporphyria (EPP).

You previously indicated that the completion of the current Phase III EPP trials is expected in 2009. Do you remain on track to achieve this, and what were the processes involved? Has Clinuvel met its objectives to date?

**CEO Philippe Wolgen**

It looks likely we'll achieve the main objective set by this management team and under my guidance four years ago: the successful completion of a Phase III registration trial by December 2009. To find, convince, recruit and retain 101 patients with a rare disorder like porphyria to participate in a pan-European trial has been an enormous challenge out of Australia. The logistics involved in enabling this Phase III trial, in which we administered more than 600 implants, has been quite demanding.

However, to come this far – where Clinuvel now has to make decisions about filing and filing dates – is in itself noteworthy. Four years ago, when we started, there were no data generated, let alone the ability to talk about a filing prospect.

To arrive at this position we required full cooperation from numerous academic centres, pharmacies, and physicians to facilitate this trial across Europe.

We needed to oversee processes and controls to be able to pursue the development of afamelanotide as a safe pharmaceutical drug; in essence we tried to anticipate the regulatory requirements and find ways of following these porphyria patients closely across Europe and Australia. We managed to get this all done within the given timeframes, even though we're restricted to generating efficacy data on afamelanotide in spring and summer.

Initially, academic physicians globally were skeptical about introducing a novel therapy to their EPP patients. These centres had seen their patients over decades, and no effective treatment had been found to adequately treat phototoxicity induced by light. These physicians were quite disillusioned and apprehensive about introducing new hope to their patients. Our team had to overcome the defensive nature by thoroughly explaining the innovative scientific rationale for the use of afamelanotide, and by early demonstration of safety data accumulated over previous years.

The clinical risk assessment of afamelanotide occurred early on in the centres but took much time and even some delays. All physicians approached by Clinuvel needed time to make their own independent assessment of afamelanotide. Assessments were also made at local regulatory levels as well as by the multiple national ethics committees which reviewed the dossier, and the formal applications and drug safety profile. In total our team went through this evaluation process nine times.

To put the EPP trials in context we adapted the chemistry and reformulated the drug delivery and we succeeded in optimising the bioavailability and pharmacology of afamelanotide. We believed early on that the biophysical properties of afamelanotide and the resultant physiological pigmentary response would prove sufficient to neutralise and mitigate ambient radiation to the skin of EPP patients. Here, we were guided by the scientific data from physics on pharmacology of alpha-melanocyte stimulating hormone ( $\alpha$ -MSH). The net clinical effect would allow EPP patients to engage in outdoors activities, a life which had not been possible before treatment.

Now on the eve of completing the Phase III (CUV017) trial, we observe that the principal physicians and patients in this trial have been satisfied with the afamelanotide treatment over a course of 12 months.

However, one will not be able to register a drug with global regulatory agencies on positive clinical reports alone. Drug development very much hinges on demonstrating long-term safety in a disease, obvious clinical benefit in patients and statistical significance of the proposed treatment between those patients on the drug versus those on placebo. Despite the clinical significance of positive anecdotal reports, these are not sufficient proof of evidence to register a drug with global regulatory agencies. Hence, we all look forward to learning the formal analyses from these trials.

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What are the requirements for filing this application with the MAA and what are the costs?

### **CEO Philippe Wolgen**

The requirements to file stipulate sufficient data to prove that the drug under investigation provides objective clinical relief to patients against any other first line of treatment. The symptoms of phototoxicity are the result of exposure to normal daily light, where the blue and green spectrum of light from 400 to 600 nanometers provokes intense dermal symptoms. In the case of EPP, all physicians, patients and researchers involved keep reminding us that there is no effective treatment for the phototoxicity; no medicinal therapy, sunscreen or beta-carotene able to effectively assist these patients. This has been the starting point of our development of afamelanotide for this disorder, and forms the basis of our ongoing testing.

A further requirement is the demonstration of long-term safety in animals and humans. We seem to be on the right track here, as our peptide treatment provides minimal drug exposure to the patients.

The last and most important component is the efficacy of treatment reflected as a statistically meaningful difference between the two treatment groups. Supporting evidence of beneficial treatment by afamelanotide is hopefully provided by the results from quality of life surveys obtained during the trial.

The cost of filing with the EMEA is €251,600. Yet, due to the orphan drug status, the filing fee for afamelanotide is waived for the orphan indication EPP.

Therefore, and analogous to our previous approaches the past year, we will file if and when we are ready to maximise our chances of success to obtain marketing clearance. We will do everything possible to reach a successful outcome, as long as afamelanotide keeps demonstrating safety and effectiveness.

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EPP has obtained orphan drug status from EMEA, US Food and Drug Administration (FDA) and Swissmedic. How will this designation assist you if the drug successfully reaches the market?

### **CEO Philippe Wolgen**

Clinuvel is the sole company worldwide which has focused on and built up a profound understanding of photodermatoses, light-related disorders affecting skin. To our knowledge there is no other company focusing as much on all aspects of these diseases, and biophysics plays a major part in our daily activities and development. Certainly, there are cosmetic manufacturers and sunscreen manufacturers, but in the pharmaceutical sector there is no other entity where its core undertakings evolve around photobiology. We are totally focused on the use and development of  $\alpha$ -MSH and its human use. In this domain, we have a clear advantage over any other research group worldwide. In-house know-how and a strong IP portfolio provide us with a clear competitive advantage.

Additionally, the orphan drug status provides us 7 and 10 years market exclusivity in the US and EU, respectively. Further developments of the drug may provide us additional protection years in these jurisdictions.

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When does the company expect to file the MAA and what are the next steps before afamelanotide can be released to the market?

**CEO Philippe Wolgen**

Depending on the results coming from CUV017, we will assess the final compilation of the registration dossier, drug master file and will then take the decision to file shortly after. We will release our filing date in 2010. Again, absolutely safety and assurance of chance of success is mandatory to achieve the long-sought outcome in a company which has strived for more than a decade to come this far.

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Thank you Dr Wolgen

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For more information about Clinuvel Pharmaceuticals Limited, view [www.clinuvel.com](http://www.clinuvel.com) or contact Head of Global Network and Communications Lachlan Hay on +61 3 9660 4900 or via [investorrelations@clinuvel.com](mailto:investorrelations@clinuvel.com)

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