Clinuvel communique

GLOBAL UPDATE

I am addressing you during quite a turbulent period, when our teams are preparing various dossiers to meet regulatory obligations in Europe and the US.

As recently shared through the ASX, we are inching towards the complete new drug application (NDA) submission and are increasing the data package with European data from the first year of "real-life data" since SCENESSE® (afamelanotide 16mg) was launched in European markets.[1] Data analyses are under way and require our teams to critically evaluate clinical reports by hospitals and patients. Here we focus on safety data, frequency, timing, duration, and start and finish of reported side effects. The most common adverse reactions – in more than 10% of first time recipients of SCENESSE® – remain as per the EU Summary of Product Characteristics (transient headaches and nausea), although we continuously monitor the drug's safety profile. The European analyses will serve as complementary information for the US Food and Drug Administration (FDA).

CLINUVEL looks back at a successful financial quarter when our teams had to conquer every inch to get SCENESSE® to patients, and over the months I have witnessed the gratitude of patients who have spent most of their lives in darkness. The design of EPP studies and final analyses poorly reflect the real-world experience patients are actually reporting. Our teams are astounded by the physicians' reports of new found freedom by EPP patients, expressed most recently at the Bordeaux Porphyrins & Porphyrias conference (see previous newsletter). We have formed strong views on why launching a novel product meets so much resistance while the end users, prescribers, have converted to become proponents of a hormone protecting patients from light. The impact of living solely in the dark requires further evaluation in the next few years, however a systematic approach to understanding the impact of light deprivation is lacking due to the fact that no previous research group had to focus on this phenomenon.

I recently learned how the new FDA Commissioner, Dr Scott Gottlieb, takes on the established views of the FDA by proclaiming that his agency needs to "*incorporate clinical data from real life experience into regulatory decisions"* and even more refreshingly he stated that the

> "*FDA needs to think of itself as a curator of information. Not just an arbiter, where a single truth standard is secured to a fixed orthodoxy… there's often no single truth standard when it comes to the evidence used to support medical decisions."*

I can clearly discern progress in FDA's thinking and approach to innovation where conventional methods have fallen short. Dr Gottlieb is ahead of the mean regulatory curve, and his presence is sparkling but long overdue. Dr Gottlieb's public admission is tectonic in the FDA's movement and I believe may have an impact on CLINUVEL's NDA dossier.

My conviction is that decisions from regulators, advisory bodies and payors are based on historical knowledge struggling to keep pace with novel concepts. Our teams have learned over the past years that quite a number of decision makers do not take erythropoietic protoporphyria (EPP) patients seriously, or easily dismiss these patients as *those who can cope by staying indoors at home*. Gradually CLINUVEL is entering new frontiers and has introduced the innovative concept of endogenous photoprotection through a systemic melanocortin(s) and its effectiveness as evidenced by real-world data.

Dr Janet Woodcock, Director of FDA's Center for Drug Evaluation and Research drew attention by her

remarkable public comments regarding the current evaluation system of drugs:

> *"The clinical trials system is "broken" and there needs to be new ways to collect and utilize patient data".*

During a workshop on real world evidence at the National Academies of Sciences, Engineering, and Medicine in September, Dr Woodcock openly spoke out about the development of new clinical trial networks for the future, and dared to be critical of the FDA's evaluation process. Drs Gottlieb's and Woodcock's comments are very much following the European trend – which had started with SCENESSE® as a pilot project – to include patients' real-life evidence as part of the overall comprehension of challenging dossiers. We are seeing a clear evolution in regulatory thinking.

In Europe we are progressing the distribution of SCENESSE®. It must be said, however, that the burden of follow up of patients is substantial to medical staff and patients, but also to our staff. CLINUVEL attempts to alleviate the workload by assisting with administrative duties on-site – that is in hospitals – while expert clinics are often out of pocket for all the additional hours they spend on EPP patients. This is a direct consequence of the post-authorisation safety study (PASS) protocol imposed by the European Medicines Agency. This is yet another example where regulatory bodies are far removed from the reality of the practices and limited resources in academic centres, where every minute on patient care is valuable and competes with care for other diseases. Based on common clinical sense our team will attempt to evolve the PASS protocol to a more realistic one in the coming years to alleviate the administrative burden on physicians and patients which is consuming hours of scarce individual care.

The past quarter has been a successful one. The distribution of SCENESSE® has been uneventful and based on in-time-delivery. As the treatment season nears an end, we are preparing the Group for expansion in 2018, and I look forward to sharing our new plans during the Annual General Meeting on 28 November.[2]

Philippe Wolgen

[1] SCENESSE® (afamelanotide 16mg) is approved in Europe as an orphan medicinal product for the prevention of phototoxicity in adult patients with EPP. Information on the product can be found on CLINUVEL's website at www.clinuvel.com.

[2] CLINUVEL's AGM will be held at 10am on Tuesday 28 November at Arnold Bloch Liebler, 21/333 Collins St, Melbourne.

ASX: CUV