March 2018

CLINUVEL *Communiqué*

CLINUVEL

SCENESSE® LONGER TERM FOLLOW UP

The erythropoietic protoporphyria (EPP) Expert Meeting in Vienna on 16 March has had quite an impact on our global teams working in the fields of photomedicine and melanocortins. The interest in SCENESSE® (afamelanotide 16mg)[1] was high and, without exception among all delegates from 12 countries and 21 expert centres, the feedback was very positive.

Under the Post-Authorisation Safety Study (PASS) the high percentage of patient continuation after 13 months of treatment – 06 June 2016 to 30 June 2017 – was discussed in Vienna, as well as the unexpectedly high demand for further treatment during autumn and winter. The earlier hypothesis that light emitted along the Soret band (>408 nanometres) is affecting patients all year round is increasingly supported by the experiences from the medical community. It is during these scientific meetings where colour and nuance are provided on a novel treatment used under real-world conditions.

One cannot escape the impression that clinical trials under restricted conditions only provide a bleak picture in rare genetic disorders such as EPP. The progressive understanding of patients' conditioned behaviour, characteristic symptomatology and, in our case, the gained freedom to participate in full life is of immense worth in light of further developments underway.

The Viennese discussions were significant in that one is able to compare the opinions and professional attitude from clinicians to an innovative therapy over a long duration. In listening to the exchanges between academic professionals specialising in metabolic and genetic disorders, one is able to assess the direction a global scientific discussion is taking. The latter theme will be the subject of a series of Scientific Communiqués in April and May 2018. While scepticism and reservation had dominated the views of a few national experts as early as 2006 and later in 2010, in Vienna we witnessed how the same porphyria experts had now fully embraced the novel systemic photoprotective agent providing clinical benefit which is now, more importantly, seen as a first-line therapy. I see the attendance of meetings by physicians as a mandatory exercise from which one can truly obtain a reaction to a company's choices from those who professionally matter most.

As a red line through CLINUVEL's program, and with clear foresight, we had remained aware in the past that expert porphyria physicians had to remain independent and unbiased towards the prescription of CLINUVEL's drug. Whereas it is documented in our industry that senior scientists may become a member of Scientific Boards and Advisory Panels, at CLINUVEL we intentionally did not want to establish these Boards to prevent inequality among the medical community and to avoid a selection bias. Instead, in 2005 we opted to incorporate independent feedback as one of the main instruments for us to decide whether or not to prolong the development of SCENESSE® in EPP. Fast forward the timeframes, and the independent response from the academic community has significantly influenced our team's decisions at critical points in time, in 2008 and 2011. I support the view that it is best for expert physicians not to become engaged with pharmaceutical companies, allowing them to freely form their own professional views to offer or decline a treatment to their patients. While our managers and staff are always nervous to face the relevant medical experts in vivo, the meeting in Austria provided a forum where one witnessed enthusiasm for the treatment on offer solely based on the European and Swiss experiences over the past decade.

A number of experts expressed that the overall administrative burden of introducing an innovative first-

line pharmaceutical treatment is considerable. More specifically the PASS was taking considerable time away from clinical work elsewhere, and therefore requiring a specific EPP-infrastructure within hospitals. CLINUVEL assists where it can in setting up the "SCENESSE® infrastructure" and ensures that EPP expert centres as required are trained, accredited, equipped, sufficiently staffed and, at all times, compliant to participate in the multidisciplinary care for EPP patients. It is indisputable that the PASS obligations translate to an administrative and clinical load. However, these obligations also provide a regimen for safety long-term. I have emphasised throughout the years the *non-negotiable* aspect of guarding safety of a novel molecule which eventually determines overall success of treatment and value.

Our own teams commit to the post-marketing authorisation commitments for each individual patient – on a non-identifiable basis – to be followed up at inevitable cost. CLINUVEL's approach to the global distribution of SCENESSE® is to 'passively' let the prescription and use (demand) for the drug occur, whereby the Company is not actively promoting the prescription of the treatment. The results to date from Europe are most encouraging.

With some pride and utmost modesty, we can state that the second PASS Annual Report and latest six-monthly Periodic Safety Update Report have both been submitted to the European Medicines Agency (EMA). Our scientific teams have learned that the use of the drug has not altered the safety profile of SCENESSE® during the first 13 months of prescription under real-world conditions. While CLINUVEL has now facilitated the administration of approximately four thousand controlled release implant formulations across the overall program, and a longer-term safety pattern has emerged, however the need to remain vigilant is required from our teams.

STATUS SCENESSE® IN EPP 2005 - 2018

- >3,900 implant administrations
- continuous treatment for >11 years
- European prescription of SCENESSE® (range 4 – 6 injections per annum)

The EMA's Committee for Medicinal Products for Human Use (CHMP) is issuing its Joint Assessment Report between 27 March and 05 April, after which time the safety dossier update will be complete.

EUROPEAN DISTRIBUTION

Those who follow the Company's operations will be aware of the ongoing roll out of the product in Europe, where we have had demand from patients and expert physicians in 17 different countries for access.

In recent months the team have continued engaging with governmental organisations in the United Kingdom who are responsible for facilitating access of pharmaceutical drugs on the various devolved national health services. The largest of these organisations – the English National Institute for Health and Care Excellence (NICE) – has a formal advisory role to the National Health Service (NHS) in England and effectively makes a recommendation for reimbursement of novel drugs. NICE is currently determining whether the product can be made available on the NHS England, with a planned publication date in late May. In December 2017, NICE issued its position not to recommend reimbursement of treatment of EPP patients with SCENESSE®. A decision from NICE would also impact and take precedent over any ruling from the Welsh authorities – AWMSG – which operates in parallel.

Clear from these interactions is the challenge that SCENESSE® as an innovative systemic photoprotectant poses to traditional models used in health technology assessments (HTAs). In addition to evaluating an ultra-orphan product – already a fraught space for HTAs, and one where much has been written on the usefulness of utilitarian approaches – assessors are confronted with a product approved under exceptional circumstances, with the EU's peak scientific body, CHMP, recognising the unique nature of EPP and the lack of scientific tools and instruments available to capture the true clinical benefit reported by patients and expect physicians. In the coming months we will learn more from NICE and similar bodies as to how they may overcome this confronting challenge. Our teams persist in the discussions on the basis of clear clinical benefit and therapeutic merits.

US NEW DRUG APPLICATION - SUBMISSION

Since the last safety analyses and reports are being received from the EMA, our teams are incorporating these results in the final clinical module of the US submission.

The additional European EPP data provide the Food and Drug Administration (FDA) real-time information on:

a. rate of prescription of SCENESSE®;
b. rate of clinical demand per expert centre, per country, per interval;
c. data management from the European EPP Disease Registry;
d. EPP Quality of Life and Inventory of Daily Activities questionnaires (proprietary instruments to CLINUVEL); and
e. long term safety data on SCENESSE®.

Since 2005, the Board of Directors and key active investors of the Company had mandated management to overcome previous attempts to facilitate marketing authorisation for SCENESSE® in the US. I have never made it a secret that gaining the right to distribute SCENESSE® in Europe and the US were the single most important events in the history of the Company, and we have been fully aware that this journey would be heavy on difficulties since the melanocortin analogue would pose many new regulatory and clinical questions along the way. At this point in time, I believe that most safety and effectiveness-related questions on the drug in EPP have now been addressed as best one is able to, and we feel as comfortable about the product as we may ever have been; the ultimate decision will need to be taken on rational grounds by a panel of diverse experts in Silver Spring. In the months following the submission we will learn whether the FDA's Division will grant the product a Priority Review, and whether the data package is validated. A summary of the regulatory pathway is provided in *Figure 1*.

When we initiated this new development program in 2005, our Acting Chief Scientific Officer Dr Dennis Wright and his team had inherited a series of negative regulatory outcomes based on a flawed corporate strategy which had started long before. Looking back is seldom helpful but provides one a sense of relative progress, however in overcoming – at times daunting and intimidating – obstacles our teams had to put in unspeakable efforts and work to maintain belief at times when others had not lent support for the program. I commend Dr Wright and all the CLINUVEL employees who have led the Company to an historical point in time where we will be able to file the New Drug Application for a drug which had been often derided as not finding a proper medical home. Thirteen years later, and following the treatment of more than 1,200 individuals and patients, we learn that SCENESSE® provides a life-altering benefit to EPP patients all year round, perhaps even beyond our own expectations.

In the meantime, we will continue the scientific dialogue with the FDA through rounds of questions and answers, whereby our teams are held to strict confidentiality on the content and timing of the exchanges.

Of high relevance and in view of the foreseeable economic burden of product distribution, final amendments have been made to take care of the post-marketing plan of monitoring US EPP patients longer term. Here we follow the pharmacovigilance system we have in place for the European and Swiss patients and which functions well. The establishment of a robust surveillance has amounted to several million dollars over the past few years, but the value for the Company long term is immense.

Simultaneously, discussions with US payors have started amidst broader political pressure to make provision of a novel therapy in photomedicine affordable and fair.

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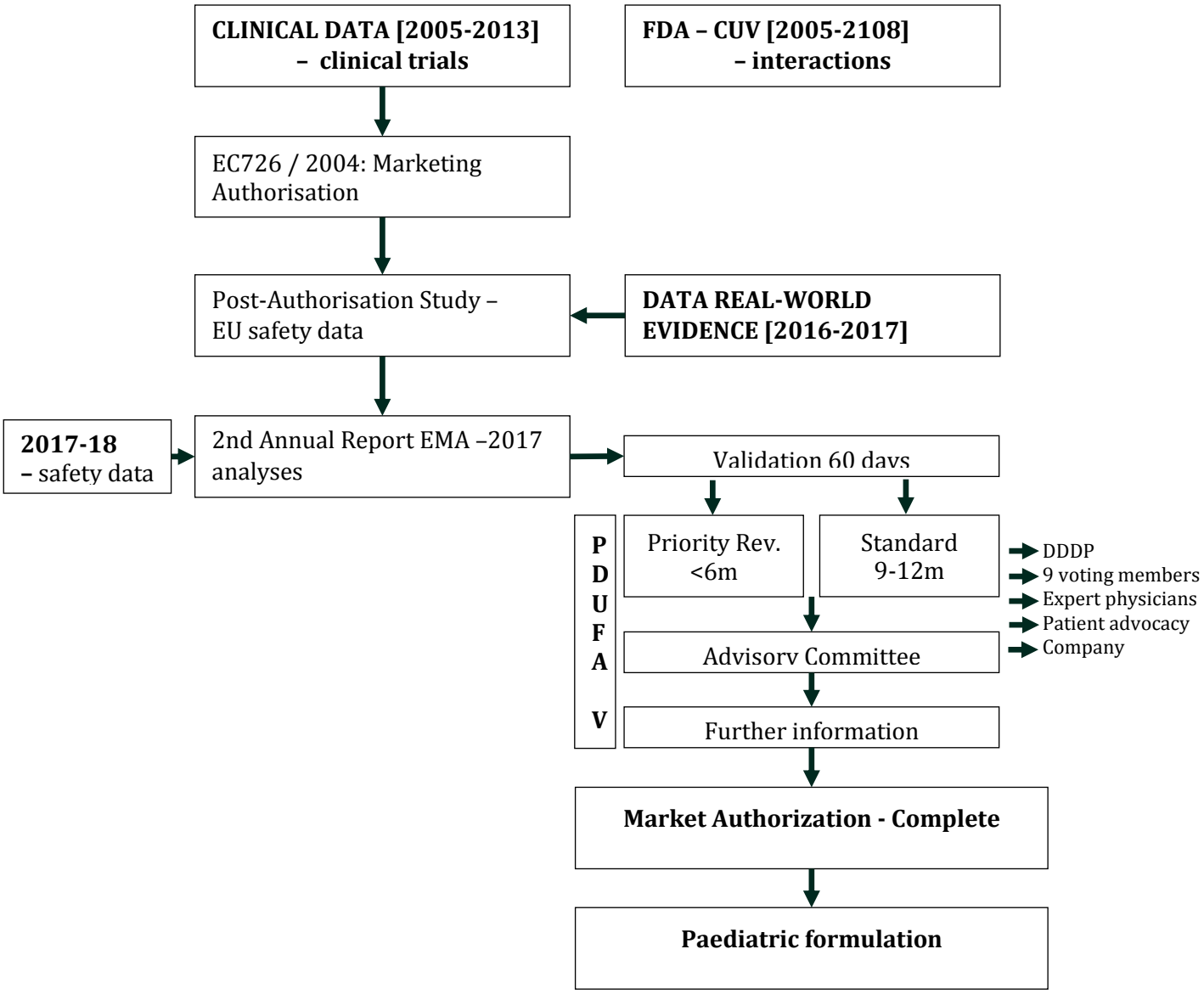
Figure 1. SCENESSE® - FDA Regulatory Pathway



DRUG-DEVICE COMBINATION

We continue to see it as our most prominent task to ensure that the safety of SCENESSE® is tested and evaluated under various conditions and in a diversity of populations. For this we have consciously and proactively undertaken a complex program over more than a decade. Given that afamelanotide is a novel chemical entity there is a regulatory need to generate data under various conditions and in various combinations (drug-drug and drug-device). Therefore, CLINUVEL's scientific leader Dr Wright and his teams undertook various exploratory and pilot studies to evaluate the drug's interaction with:

a. ultraviolet (UV) light under ambient conditions;
b. narrowband UV radiation (UVB wavelengths twice or thrice per week), and
c. immune suppressive drugs.

Under the first two categories (*a* + *b*) we have concluded three vitiligo pilot studies in three different ethnic populations. It was of great scientific interest to determine the clinical need in evaluating the potential of SCENESSE® in combination with narrowband UVB in patients of Caucasian, Hispanic, African-American, Indian, Malaysian and Chinese descent. Given the polymorphisms, genetic and anatomical variations of constitutive pigmentation is differently expressed.

In 2011, we anticipated that in light of the future regulatory discussions, CLINUVEL would need to understand the effect of frequent and intense narrowband UVB radiation in combination with our lead drug. Since narrowband UVB is a known carcinogen, safety monitoring was essential to enable us to advance to the next stage of development in vitiligo. In simpler terms, combining a new chemical entity with a known physical carcinogen required three proof of concept studies evaluating safety first before selecting the patient population that would most benefit from hormonal repigmentation therapy.

We are awaiting the final results from the third aforementioned study (CUV103) in 18 patients of Asian descent and will add the safety data to our considerations to continue the program in North America. Under category *c* (and evaluating SCENESSE® in immune compromised patients), we conducted a trial in 82 organ transplant recipients (CUV011) to evaluate the safety in combination with perpetual use of immune suppressive drugs. The significance of this trial has been to evaluate whether SCENESSE® would influence immune compromised patients who are at heightened risk of malignancy and skin cancers (non-melanoma and melanoma). The preliminary safety data from this complex study are positive and give us, thus far, no reason for concern. All these studies conclude our exploratory analyses on "drug-device" and "drug-drug" interactions in complex patient populations. We see this as part of multiple hedging strategies to understand the *extreme conditions* under which we are able to evaluate SCENESSE®. It is my professional belief from the extensive pharmacovigilance history of novel drugs that the safety of a novel molecule can never be compromised and safety should be answered as early as possible in a program, hence our approach to date. CLINUVEL set out to reduce the well-documented risk in pharmaceutical development of safety of a new chemical entity in the post-marketing phase. Many companies have fallen prey to having to answer safety concerns after the drug had been allowed on the market. At CLINUVEL we started to focus on answering as many questions as possible on safety as one could reasonably anticipate, since regulatory authorities but also insurance groups would pose these questions as part of their risk-benefit assessment and ultimate decision making. While no product can ever be declared truly 'safe', based on ample reflection and analyses, the strategy has played out well for CLINUVEL thus far.

REPOSITIONING AND EXPANSION

In the current economic climate where industry peers frequently make headlines for the wrong reasons, there is a need to publicly state one's foundation and values. In the recently published mission-vision-values of CLINUVEL's website we wish to remind the next generations of employees, stakeholders and all those who interact with us what the Company stands for.

In full leverage of our scientific knowhow we pursue a leading position in photomedicine. We identified a position where CLINUVEL will encounter minimal or no competitive pressure and to steadily progress outward to fields of related interest and where possible expansion of use for melanocortins loom.

In *Figure 2* below, one can follow the expansion of knowledge, interest and possible progression of CLINUVEL.

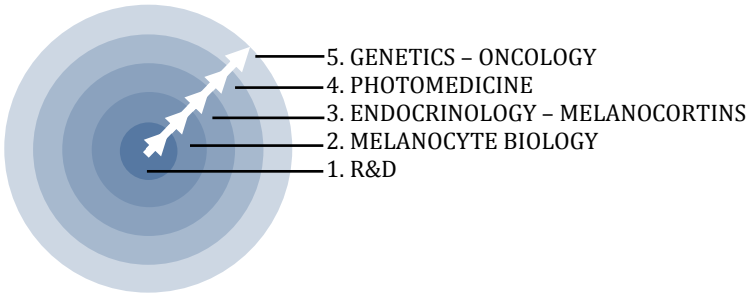


Figure 2: Expansion pathway

Our teams are in preparation to initiate a pilot study exploring the use of SCENESSE® in a new indication, whereby the support of the medical community will be required for the use of the drug in a new domain.

In all our considerations and decisions, the expansion needs to fit within the overall regulatory discussions we are holding in Europe and US.

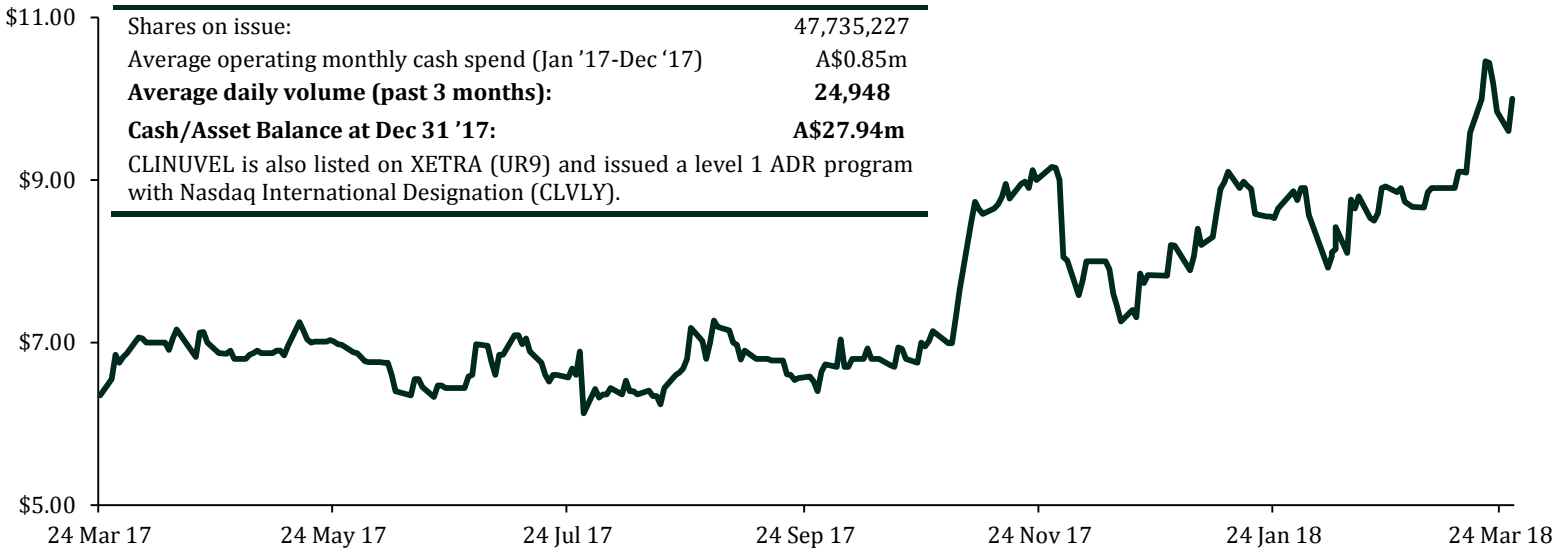
The complementary use of non-prescriptive products is aimed to fit the strategic direction of CLINUVEL and increase brand awareness of the Company.

In all our endeavours, our compassion for patients need to dominate our decisions, and doing well for patients most often will translate to long term value for all stakeholders..

Notes

[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.

ASX: CUV



About CLINUVEL PHARMACEUTICALS LIMITED

CLINUVEL PHARMACEUTICALS LTD (ASX: CUV; NASDAQ INTERNATIONAL DESIGNATION ADR: CLVLY; XETRA-DAX: UR9) is a global biopharmaceutical company focused on developing and delivering treatments for patients with a range of severe genetic and skin disorders. As pioneers in photomedicine and understanding the interaction of light and human biology, CLINUVEL's research and development has led to innovative treatments for patient populations with a clinical need for photoprotection and repigmentation. These patient groups range in size from 5,000 to 45 million worldwide. CLINUVEL's lead compound, SCENESSE® (afamelanotide 16mg), was approved by the European Commission in 2014 for the prevention of phototoxicity (anaphylactoid reactions and burns) in adult patients with erythropoietic protoporphyria (EPP). More information on EPP can be found at http://www.epp.care.

Headquartered in Melbourne, Australia, CLINUVEL has operations in Europe, Switzerland, the US and Singapore. For more information go to http://www.clinuvel.com.

Forward-Looking Statements

This release to the Australian Securities Exchange and to press may contain forward-looking statements, including statements regarding future results, performance or achievements. These statements involve known and unknown risks, uncertainties and other factors which may cause CLINUVEL's actual results, performance or achievements to be materially different from any future results, performances or achievements expressed or implied by the forward-looking statements. These statements reflect our current views with respect to future events and are based on assumptions and subject to risks and uncertainties. Given these uncertainties, you should not place undue reliance on these forward-looking statements. Some of the factors that could affect the forward-looking statements contained herein include: that the FDA may require additional studies beyond the studies planned for product candidates or may not provide regulatory

clearances, including for SCENESSE®; that the FDA may not provide regulatory approval for any use of SCENESSE® or that the approval may be limited; that CLINUVEL may never file an NDA for SCENESSE® regulatory approval in the US; that the Company may not be able to access adequate capital to advance its vitiligo programs; that the Company may not be able to retain its current pharmaceutical and biotechnology key personnel and knowhow for further development of its product candidates or may not reach favourable agreements with potential pricing and reimbursement agencies in Europe and the US.