July 2018
CLINUVEL *Communiqué*

CLINUVEL

US REGULATORY PROGRESS

On 25 June 2018 CLINUVEL announced its New Drug Application (NDA) for SCENESSE® (afamelanotide 16mg) for adult erythropoietic protoporphyria (EPP) patients had been submitted to the US Food and Drug Administration (FDA). It has been imperative for our teams to thoroughly prepare the scientific write-up and analyses of the use of afamelanotide 16mg while taking into consideration the learnings from our submission to the European Medicines Agency (EMA) back in 2012. The ensemble of data managers, statisticians, regulatory experts, pharmacovigilance and clinical managers – without short changing the back-office and supporting staff – have worked tirelessly towards this landmark submission.

The validation period is under way. This in itself is an equally challenging time since correspondence between agency and Company intensifies to ensure the various sections of the FDA's review division have the opportunity to send out specific questions on the documentation provided. Scenarios on the FDA's validation outcome range from an applicant passing validation at first submission to being requested to file an entire or partial product submission once again. When all questions and additional information during the validation period have been addressed, all section heads need to communicate to the project manager and director of the relevant division that the complete clinical data package, comprising all aspects of the proposed pharmaceutical product, are covered. From then onwards, the validation is deemed to be concluded and the review clock is started by the project manager of the division. As stated, subject to the status granted – Standard or Priority Review – the regulatory review is expected to take between 6 and up to 24 months in similar cases depending on the further rounds of questions posed by the FDA during the analytical process. In contrast to the impression one may have, the regulatory review period is an active one. The applicant has much work to do to clarify, analyse and take positions on questions or comments received from the FDA.

The CLINUVEL Board, its senior managers and a number of key investors had long made it clear that following the missed opportunities to arrive at a submission under previous managements, the priority for CLINUVEL had been to submit a comprehensive dossier to the FDA to enable the final and decisive US regulatory dialogue on safety and effectiveness of the molecule. In having arrived at this point I congratulate all staff of CLINUVEL and shareholders who have borne the patience to see through this most challenging journey to date. In pharmaceuticals one tends to think in terms of decades rather than years, and after 13 years of concentrated work we have finally been able to deliver the substantial dossier on EPP, a most complex disorder, and by doing so introducing the novel concept of pandermal photoprotection.

With certainty, a number of companies, research groups and select parts of the medical community eagerly await the US regulatory review of SCENESSE® to start, since the review of a systemic drug aiming to photoprotect patients at risk is an unwritten chapter in medicine. A US approval of this technological innovation would be a quantum leap in the clinic and will pave a way for others in the US to attempt development of similar members of the proopiomelanocortin (POMC) family. Pioneers attract attention and competition will then emerge; this phenomenon also holds true for CLINUVEL. As long as CLINUVEL manages to keep its knowhow and technology well-controlled, and remains selective in its key choices, I am confident CLINUVEL will keep its competitive advantage.

The FDA submission contained a combination of clinical trial data, individual and combined analyses, data from Compassionate Use programs and Special Access Schemes, and the real-world experience from the ongoing European product distribution. Naturally all toxicology data from pre-

clinical studies and those obtained from human studies were incorporated. Overall more than 6,700 doses of afamelanotide in man are being evaluated by the FDA, keeping in mind that the proposed indication is a rare genetic disorder. It is fair to state that, intentionally, the extent of drug exposure – as part of our package – has been relatively large in comparison to other orphan drugs seeking review.

CLINUVEL decided to "modernise" its submission in keeping with the changing US regulatory view by including *real world experience* from patients who have received treatment in the EU and Switzerland beyond the confines of clinical trials. Although a public debate wages in the US on the precise definition of real world data, CLINUVEL believes it is one of the first companies to supply - as part of the complete clinical data package - the additional analyses of clinical experiences obtained from EU drug supply.

PHARMACOVIGILANCE

It is well documented in historical cases that the burden of proof of a drug's safety rests heavier on those drug developers who propose a *novel* molecule – previously untested and to which there is no bioequivalent or generic on the market. In the case of SCENESSE® there had been no regulatory precedent for systemic photoprotection in the US or Europe. Accordingly, our scientific teams continue to emphasise and monitor the drug's safety, and these activities will more than likely last for many years to come. The Company's willingness and commitment to be involved in a patient's long-term follow-up aims – among other objectives – to make the work of regulators much easier.

Our teams had long anticipated the pharmaceutical novelty of the POMC drug, and accordingly we had centred the entire development program around possible and conceivable risks. Our overall decision models reflect risk management in various aspects of the Company, and no less in the use of SCENESSE®.

Just one of the many examples is given through the formulation development which had started in late 2005. The subcutaneous injection of afamelanotide was purposefully selected and developed to retain control over the drug's route of administration. One can only anticipate the questions a drug developer would need to answer and the regulatory assurance it would need to provide if it had chosen an oral drug formulation as a systemic melanogenic photoprotective novel therapy, if this route of administration had been possible at all with afamelanotide or any other drug of the class. In opting for the current formulation and product, we steered away from further anticipated scrutiny on the possibility of off-label use and the ability to abuse its access post-marketing. The choice of developing a controlled-release formulation arguably leads to higher expenditures than other dosage forms but it does reduce the authorities' scepticism on a newly proposed molecular drug. Our teams avoided these likely pitfalls and chose the controlled-release formulation to be managed in the hands of experts, thereby taking away the anticipated regulatory reluctance towards "uncontrollable" dosage forms. Additionally, a number of arguments related to the long term financial position of CLINUVEL led us to determine the safety profile of this particular product as the key determinant of our decisions and therefore its use and formulation.

For new shareholders of the Company, it is appropriate to share some background on the pharmaceutical environment CLINUVEL finds itself in. The industry and regulatory authorities have learned from the cases of thalidomide, Tylenol and COX-2 inhibitors how safety issues emerge only following a drug's approval and commercial distribution despite these not having been observed during its clinical development. These pharmaceutical cases had caused an understandable reaction from authorities governing medicinal products by imposing strict pharmacovigilance measures. Pharmacovigilance became the discipline of surveillance of side effects recorded from new therapeutic modalities introduced to patients and the wider public. By adhering to protocolised safety surveillance measures, the aim is for the pharmaceutical manufacturer to analyse causality and expectedness of side effects reported from the use of the product. This is very much the work our EU teams have been undertaking since SCENESSE® was approved by the EMA in 2014, and to date I am pleased to report that no significant unexpected adverse events have been associated with the use of SCENESSE®. Nevertheless, we remain alert to any future event which calls our attention. Every day we analyse drug use in each patient.

In differentiating drug development, one would single out a select group of companies who develop novel molecules and innovative pharmaceutical products. Those disruptors will always face the inherent "handicap" that the novelty of the chemical entity invites a regulatory attitude of professional

apprehension. This is simply because the *ongoing* safety of these novel products is assessed within a much longer time frame, hence the need for innovators to set up elaborate and expensive pharmacovigilance systems for innovative technologies.

We have always emphasised the need to prove *safety beyond what could be reasonably expected*. A company addressing orphan diseases may never provide sufficient safety data to overcome the regulatory scepticism and apprehension, however one may adopt a strategy to ally the possible perceived risks and hesitation. Put simply: a drug developer can overcome regulatory doubts on a novel drug's effectiveness but it will never be able to overcome doubts on safety if this is not part of the corporate awareness and attitude towards risk management. At CLINUVEL we live this this culture and approach.

In regulators' reviews of the drug evaluation process one starts from the point that there is an inherent risk of allowing a pharmaceutical drug with a relatively unknown safety profile to come to market, therefore exposing the general public. Allowing unsafe drugs for the sake of providing at least some kind of therapy to untreated patients is known as a '*type I regulatory error*' to be avoided. In contrast, a so-called '*type II regulatory error*' would lead to withholding a safe drug to patients who lack treatment, or not providing them the option of treatment by being overly concerned on the lack of safety data in larger populations. We view it that in CLINUVEL's case, we have had ample evidence over the years to minimise a possible type I error in EPP patients. Our task has thus been to focus on reducing the probability of a type II error and thereby allowing light deprived patients to have access to a treatment for the first time.

BREXIT AND IMPACT UPON CLINUVEL

As reported in previous Communiqués, the political changes caused by the outcome of the British referendum have a direct impact on the European Medicines Agency (EMA) and to pharmaceutical products licensed in Europe, and therefore on CLINUVEL. The resources associated with Brexit are potentially substantial and require much of our attention. The activities underway tend to provide a smooth transition for CLINUVEL to distribute SCENESSE® successfully throughout the European Union after 30 March 2019. There are a range of legal, pharmaceutical, financial, commercial and logistical ramifications to name a few. For instance, in order for the innovative drug to be available in the expert centres, CLINUVEL is transferring its license – its EU marketing authorisation – from the UK to a European entity within the CLINUVEL Group. Commercially, we are required to put in place the European systems to make the import of the product to EU member and non-member states as efficient as possible while taking into account taxes, import tariffs and currency exchanges. At the same time, we very much wish to preserve our dearly constructed quality and pharmacovigilance systems in the UK and retain our staff.

BREXIT

- 23 June 2016 – UK referendum to leave the EU
- 17 July 2018 – Chequers White Paper on UK's position (including on pharmaceuticals)
- 30 March 2019 – UK leaving EU – 21 months proposed transition period
- December 2021 – proposed end of transition period for UK

We have kept a close eye on the UK's Business, Energy and Industrial Strategy Committee which stated in May 2018 that it supported the UK Government in seeking a border without friction, securing minimum additional costs and bureaucracy for the pharmaceutical sector. Understandably, a large part of the UK Conservatives foresee that a hard Brexit will jeopardise European medicines remaining available under the National Health Service (NHS). Through a Chequers White Paper, British Prime Minister Theresa May has laid out the plans for Britain to exit and negotiate terms with the EU by making Britain an independent trading nation. Under these plans the British pharmaceutical regulator, the Medicines and Healthcare Products Regulatory Agency (MHRA), would no longer fall under the directives of the EMA. The headquarters of the EMA is relocating to Amsterdam as reported previously, and the Agency is gradually dismantling its UK operations.

Since our teams are cooperating intensely with the MHRA, still one of the two European rapporteurs (supervisory bodies) for SCENESSE®, the regulatory changes directly affect us. In benefiting from continuity as part of a structured surveillance system through frequent regulatory inspections

and dialogue, the change from the MHRA to a new member state rapporteur will undoubtedly cause more replicative work for us to induce the new team to the dossier and to our systems. Most importantly, the Business, Energy and Industrial Strategy Committee mirrored CLINUVEL's immediate concerns: prioritising establishing a form of UK membership with the EMA that would maintain cooperation and would not require replication of manufacturing sites, testing or roles. The latter activities are one of the most capital labour intense functions of our UK teams.

Unexpectedly, on 17 July Theresa May suffered a rare parliamentary defeat (by four votes) on an amendment tabled by Dr Philip Lee, former Justice Minister and now Member of Parliament. Under this amendment to the trade bill, the government should have to negotiate *an international agreement through which the UK may continue to participate in the European medicines regulatory network partnership between the EU*. We will report on the implications of the change in the trade bill in the next Communiqué while we continue to prepare a smooth transition of the product's license to Europe without disrupting our UK activities.

EXPANSION OF CLINUVEL

It is known that we are in the midst of preparing an extension of our product offerings. As a reminder we followed the concentric expansion of the Group organically by diversifying our knowledge in photomedicine; here, both medicinal and non-medicinal products and operations fit CLINUVEL's portfolio.

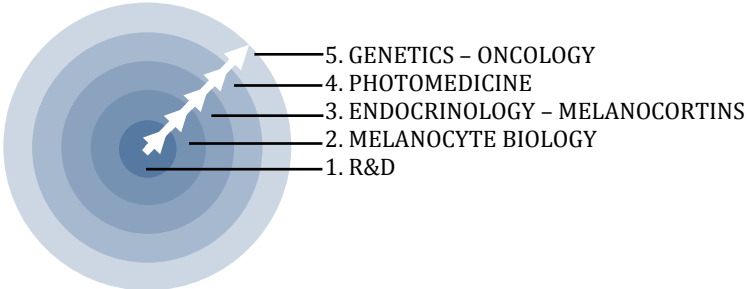


Figure 2: Expansion pathway

It is my belief that CLINUVEL's current success needs to be continued and fortified through in-house research & development, progress on US regulatory approval of SCENESSE® allowing drug access to US patients, a paediatric formulation for juvenile EPP patients, follow-on technologies, and complementary non-medicinal products. Additionally, we have well expressed publicly that the Group would need to expand to make it less dependent on one class of molecules to enhance the enterprise value. The CLINUVEL 2020 strategy is firmly dictating our objectives. The key here is the timing of growth and retention of the core group of managers and attraction of new talent in the process. The skilled people are at the core of each strategic decision we make.

The activities around product launch of the new line are under way and pending regulatory and legal clearance the final presentation will follow. In a staged process, websites, product identity and target groups will be shared, whereby targeted distribution channels will act as pilot and feedback on the first product. This staggered approach aims to lend further visibility to the current expertise of CLINUVEL as well as expanding the Company's offerings

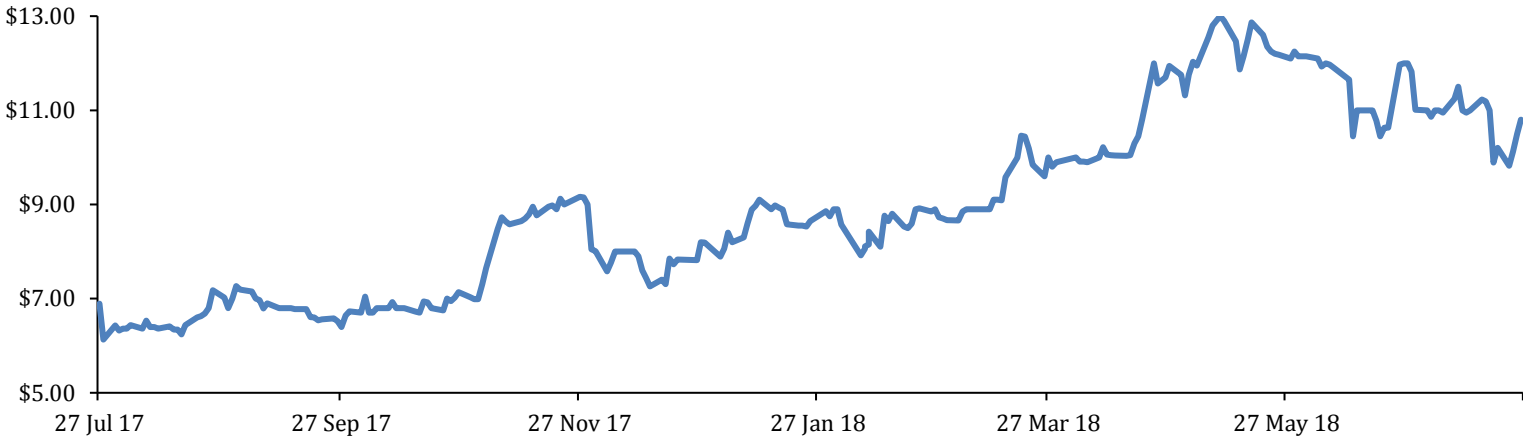
As to the expansion of indications, vitiligo results of the pilot study (CUV103) in Singapore are expected while the decision to proceed to the next trial in North America predominantly hinges on the progress of the regulatory review of SCENESSE® in EPP by the US FDA.

I send my appreciation to the entire CLINUVEL team and particularly Dr Dennis Wright, who has been working on the US dossier for more than a decade and who has had the foresight to keep the team together to see through this task of considerable proportion. The togetherness of this team is truly unique and has led to the retention of specific knowledge required to file a dossier.

I also take this opportunity to thank, on behalf of management, our Non-Executive Director Mr Willem Blijdorp who has most recently declared to have purchased 3.2% of CLINUVEL shares. It is rare in our industry to see Non-Executive Directors increasing their position at this magnitude during the commercial growth of a company. The demonstration of support is most welcome but poses an even greater expectation on our team to perform and keep delivering to advance the Company.

Philippe Wolgen

ASX: CUV



Shares on issue:	**47,824,427**
Avg approximate operating monthly cash spend (01 Jan '18-31 Mar '18)	**A$1.10m**
Average daily volume (past 3 months):	46,560
Cash/Asset Balance at Mar 31 '18:	A$28.92m

CLINUVEL is also listed on XETRA (UR9) and has on issue a level 1 ADR program with Nasdaq International Designation (CLVLY).

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.