CLINUVEL Communiqué

15 January 2019

CLINUVEL

Dear patients, shareholders, friends,

I wish you all a year in good physical and spiritual health, and a year in which we anticipate further progress of SCENESSE® (afamelanotide 16mg)[1] and CLINUVEL's other products and activities. We look to a rather full year of events affecting CLINUVEL in one way or the other: firstly, the direct drivers such as US regulatory, European clinical, and UK geopolitical (read Brexit); and secondly, the indirect events such as the domestic financial regulatory reviews (Australian's Royal Commission report on 1 February), and the release of US key financial data. We are looking forward to 2019, undoubtedly requiring us to navigate all known and new challenges which lie ahead of us and which, by now, has become part of our team's DNA: anticipating and reacting to resistance, obstacles, and legislative and regulatory changes. I wish my team and all of our audiences a successful year in optima forma.

PDUFA DATE

We learnt on 9 January that the US Food and Drug Administration (FDA) has now completed its filing review of the New Drug Application submitted in 2018 and set a target review date of **8 July 2019** under the Prescription Drug User Fee Act (PDUFA). The agency also provided a target date of **8 April** to communicate labelling and any possible post-marketing requirements and commitments, as well as advising that it did not plan to hold an advisory committee meeting to discuss the product.

This landmark step provides our teams with a clear timeline to an FDA decision on the overall benefit-risk assessment of SCENESSE®. During the coming months the frequency and intensity of interactions between CLINUVEL and the FDA is expected to increase. A number of issues have already been addressed through answers provided by CLINUVEL to the agency to not only to ensure the completeness of the dossier, but also in anticipation of the product's use in the US EPP patient community. All our team members play a part in the final dialogue with the FDA. All the cogs of the Company need to function to meet the demands of the set 8 July timeline.

As illustrated in the December 2018 News Communiqué and reiterated in the flow chart below, the options for the FDA with regard to the dossier on SCENESSE® are multifarious.

The FDA has already conducted an inspection of the US manufacturing facilities of SCENESSE®, part of the expected quality assessment of the innovative product. As the European Medicines Agency (EMA) – in the presence of the FDA – had already performed a manufacturing (GMP) inspection early 2013, the manufacturing team had been familiar with the regulatory processes expected. Further inspections of US clinical sites are now underway to determine GCP compliance as part of the comprehensive review.[2]

FDA TIMELINE SCENESSE®

9 **JAN** PDUFA date set for 8 JUL

JAN FDA Clinical inspections

MAR Quality assessments

8 **APR** FDA communication on labelling, post-marketing authorisation

MAY Final communication, Q&A clinical use post-MA

8 JULY 2019: PDUFA DATE

FDA RISK-BENEFIT SCENESSE®:

1. Marketing Authorisation (Approval)

OR

2. Complete Response Letter (Rejection)

During the filing review interval – from 10 January until 8 July – the FDA will be able to pose questions on the individual scientific modules submitted: pre-clinical and clinical product data, manufacturing and the distribution of the product in the US. The active pharmaceutical ingredient, manufacturing processes and quality aspects of the product have been the focus of the Division of Dermatology and Dental Products of the FDA to date.

The synchronous supply of SCENESSE® under Real World conditions in the European Union uniquely enables the FDA to evaluate the quality management systems, pharmacovigilance system and controlled distribution (under "PASS")[3] of the product as it takes place. This situation, whereby a product for an orphan indication is simultaneously being prescribed commercially to a similar patient population and supervised by a leading regulatory agency (EMA) under strict post-marketing protocol, is relatively new for the FDA and adds information to the clinical data generated during the pre-marketing clinical development programme.

Finally, as stated before, using a controlled-release formulation of a hormone to mitigate and annihilate the impact of visible light in a genetic disorder which renders patients phototoxic and anaphylactoid is wholly innovative, and requires the FDA to review a dossier without precedent or template.

While we share the frustration of American EPP patients about the regulatory review process taking much time to be completed, progress has been made whilst we all need tp patiently wait and the Company works towards an outcome. Taking another perspective, the FDA is also to be publicly commended for its ability to evaluate a novel technology.

A positive from the extended filing review is that our clinical and pharmacovigilance teams have been able to add more safety data to the overall SCENESSE® dossier. The increase in patients exposed to the drug longitudinally provides the necessary data to assess – in regulatory terms – the long-term safety profile of a first-in-class drug. We gradually witness the increase in number of injections among European EPP patients who have remained on treatment for more than five years without significant side effects ('treatment related adverse reactions'). Indeed, a number of Swiss and Italian patients have received more than a decade of treatment with SCENESSE®, having been administered individually over 50 controlled release injectable implants each at the porphyria centres of expertise.

Controlled-use of novel technology is central in our thinking and led to the current product presentation. Our scientific team consciously took the step to formulate afamelanotide 16mg as a controlled-release formulation rather than as a self-administrable oral formulation. The latter would have provided additional risks to patients and carers since oral formulations can lend themselves to abuse, as seen in many as seen from pharmaceutical products in the US.

In choosing this avenue of controlled-use we circumvented many of the future regulatory and public health concerns public health concerns.

Our thinking has always and will be geared towards safety first.

We will keep the medical community and stakeholders updated, as much as is allowed in the context of the exchange between FDA and Company, on the next regulatory steps and timeline as outlined above.

VITILIGO PROGRAM

In December 2018, we released the results of the CUV103 study in vitiligo patients (see ASX announcement and Vitiligo Communiqué from 19 December). The results show that afamelanotide in combination with narrowband UVB (NB-UVB) results in a follicular pigmentary response among vitiligo patients of Asian descent. The results of this study are prospectively of significance as the use of a drug-device combination, that is SCENESSE® and NB-UVB, is once again a scientific novelty. The FDA naturally scrutinises the introduction of a combination therapy and had asked us to simultaneously conduct a pre-clinical study to evaluate the safety of the intended combination therapy. In lay terms, a drug developer needs to simulate the use of a pharmaceutical product in models prior to using the same combination in man. The results from this pre-clinical study were favourable in that NB-UVB administered three times a week and afamelanotide 16 mg administered every four weeks over a 24-week period did not show safety issues of concern. This formed the basis for progression to the Singaporean study CUV103. Further, the study also confirmed our scientific hypothesis of melanoblasts (follicular stem cells) being able to respond to the intended combination therapy. The concept of reaching stem cells in deeper layers of the skin to repigment vitiligo patients is truly a breakthrough in medicine as we know it today and provides much hope for the future use of SCENESSE® in vitiligo. However, much work needs to be done to turn hope into reality, and this will be our next focus.

Vitiligo Program
(since program commencement)

1. CUV102 – North-America √
2. Pre-clinical study √
3. Results CUV103 – Singapore √
4. FDA outcome on EPP *ongoing*
5. Protocol agreement GVEC
6. Type-C meeting with FDA
7. Start Phase IIb North America
8. Results Phase IIb
9. Pivotal study vitiligo North America

Additionally, we published the first Vitiligo Communiqué highlighting the scientific aspects of the debilitating disease. During 2019, further vitiligo news flow and Vitiligo Communiqués will be published to keep our invested audience abreast of the developments in vitiligo and provide information to the patient community.

Following the FDA's review process in EPP, the vitiligo program will be continued in North America. The first step is for the Global Vitiligo Expert Consortium (GVEC) and our clinical team to agree a final study protocol for a pivotal study to be conducted in North America.

After the FDA's outcome on EPP, a Type C meeting will be sought with the Division of Dermatology and Dental Products to request their input on the protocol design and advanced development pathway for SCENESSE® to the US market.

VARIEGATE PORPHYRIA

CLINUVEL has announced a trial in a new indication as part of the clinical expansion of SCENESSE®. Variegate Porphyria (VP) belongs to the family of 9 porphyrias disabling patients and inhibiting them from assuming a normal unrestricted life. Due to the circulating porphyrin molecules VP patients experience lifelong *skin fragility* and suffer frequent ulcerations (lesions) and pronounced blistering, making it impossible to function properly. As lesions often occur on the hands, face and feet, patients are often severely restricted in their daily activities.

Following years of discussions with porphyria experts, CLINUVEL determined that a small-scale pilot study in VP patients was warranted, particularly given the lack of therapeutic alternatives for these patients. The Phase II study – CUV040 – will follow an open-label protocol in six VP patients for eight months, with up to six SCENESSE® implants administered over a six-month period. It is believed to be the first clinical trial since the 1970s to seek to evaluate a photoprotective therapy in VP patients. The first regulatory approvals for CUV040 have now been received, with further submissions underway to enable the study to start in 2019.

NEW INDICATION

We have previously acknowledged the potential of our lead technology to assist wider groups of patients, and we made public our plans to expand the use of the drug following US regulatory progress. The time has come for us to gradually seek further use of SCENESSE® in relevant indications of unmet clinical need – in these target disorders where there are no other alternative therapies. Our recently announced VP program is one such example.

Beyond the porphyrias, however, there are other patient populations who may benefit from the therapeutic use of melanocortins. By leaning on the expertise within our research teams and knowledge acquired through collaborations, we are now actively pursuing these opportunities in aiming to develop new clinical programs. We are awaiting the sign-off from university centres on protocols, budgets and ethics committee submissions before we can disclose the next therapeutic target for SCENESSE®.

EXPANSION CLINUVEL

Our research operations in Singapore continue to progress the multiple projects with which they have been charged to pursue. The expanded laboratory facilities have enabled the team to expedite their analytical development work, having been fully integrated into the Group in 2018. We are on track to unveil further work from the VALLAURIX team in late 2019, ever vigilant that other groups are seeking to claim advances in the same space. I fully support the notion that knowhow and expertise needs to remain inhouse. By necessity this sometimes means that our stakeholders cannot be made privy to exciting progress. As a public company we serve many interests, however in this tumultuous world of open communication the interests of patients and shareholders prevail and therefore CLINUVEL will only share meaningful progress when we have secured

positions which cannot be compromised by our competitors in the space.

In 2019, and pending FDA's news flow, we intend to expand the Company on multiple fronts. Naturally, we will release the corporate information as it materialises, having first referred to our expansion plans at the 2017 AGM. Both by attaining independence and forming cross-border partnerships, CLINUVEL will need to fortify its position as a leading Australian drug developer for generations to come. Rather than isolated events, all our decisions to expand the Group are interconnected with each other through careful planning, choice of optimum timing to execute, these are some of the considerations needed to succeed. At CLINUVEL all our team members matter, all employees are one by one essential to continue making CLINUVEL a success story. The internal alignment takes time, but is a valuable investment for years to come. In shaping **CLINUVEL** for **2021**, we are working towards a team of new, young and together with experienced managers to complement each other in cultural diversity, skills and experience. Achieving the right balance is challenging but most exciting; seeing talent grow is the perk of my job.

As the British parliament is preparing itself to one of the most historical votes on 21 January, deciding the fate of Theresa May's Brexit plans consisting of a £39 billion exit bill for the UK, protection of citizen's rights, a debatable guarantee against a hard border with Ireland (jeopardising the UK's sovereignty) and a standstill period with the EU lasting until December 2020 (19 months). This period provides the UK cabinet with more time to pan out a more detailed deal with the EU. At the time of print, it looks like Theresa May will not obtain a parliamentary majority on 15 and 21 January. We are intimately engaged with the political events in the UK while CLINUVEL prepares itself to a 'disorderly' Brexit. The pharmaceutical industry as a whole is concerned about the supply of goods to the UK, this is at a time when CLINUVEL is still in process of requesting NICE to respect the EMA's outcome (marketing authorisation: October 2014) and make SCENESSE® available to British EPP patients. We will keep you informed later this quarter as we expect news from NICE/NHS England around this time.

Philippe Wolgen

[1] SCENESSE® (afamelanotide16mg) 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] Good Manufacturing Practice and Good Clinical Practice comprise two of the GXP guidelines designed to ensure safety and quality systems related to medical products and devices across the pharmaceutical industry.

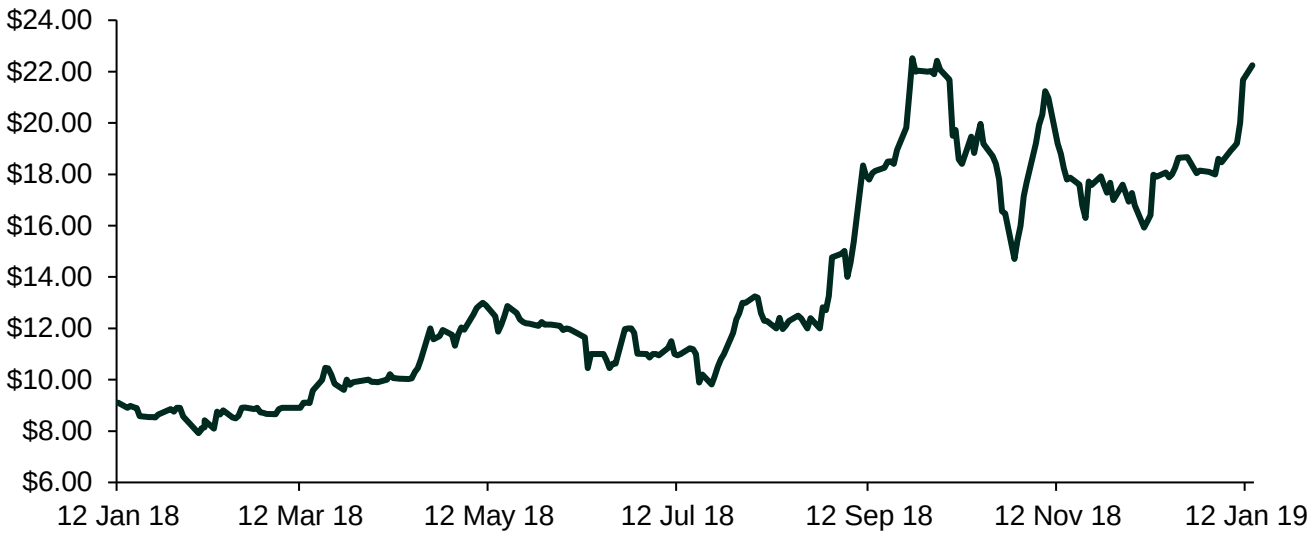
[3] CLINUVEL has implemented a risk management plan (RMP) for SCENESSE® in Europe incorporating post-authorisation safety studies and the European EPP Disease Registry. For more information on the RMP, see the Regulatory Update announcement on 14 May 2018 and News Communiqué from 16 February 2017.

ASX: CUV

Share price

(ASX: CUV 12 Jan 2018-14 Jan 2019)

Shares on issue	47,857,986
Fully diluted	49,608,546
Market cap (14 January 2019)	A$1.06b



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 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; that the Company may incur unexpected delays in the outsourced manufacturing of SCENESSE® which may lead to it being unable to supply its commercial markets and/or clinical trial programs.

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