Clinuvel communique

2018

We started this year with limitless optimism and energy, and I attribute this to a foundation of internal changes made over the past 16 months. Our fascinating journey is marred with frequent need to reflect on how to anticipate and respond to a ceaseless flow of changes in CLINUVEL's clinical, regulatory and reimbursement ecosystems. Consequently, we were compelled to redefine our business objectives continuously, and therefore we posed the question what one would want the Group to be by 2020. On the 14 February our teams intend to adopt new guidelines, values and direction to achieve our objectives "CLINUVEL 2020" as explained during the recent AGM, and on 20 February we aim to unveil our new website. The new staged communication strategy aims to be fully implemented by 20 May, when we disclose our complementary product lines and new markets to be served.

Our managers are constantly required to overcome unfamiliar and unforeseen challenges which come with exploring new avenues in taking SCENESSE® (afamelanotide 16mg) and other novel products to patients. In 2018, we will need to pass all these challenges for the US regulatory dossier to be reviewed by the Food and Drug Administration (FDA). In other jurisdictions such as Australia and Japan we target to submit dossiers for the ultra-rare disorder erythropoietic protoporphyria (EPP).[1]

With the recent appointment of Dr Agersborg as a knowledgeable US medical specialist, the Company leads by example in the life science sector by diversity represented on its Board of Directors. In 2017 the percentage of women represented on the ASX-200 was still 26.2%, and still nine Boards had no women at all.

FINANCIAL PERFORMANCE

As the 29 March 2019 comes closer, the BREXIT conditions of obtaining a favourable European deal are as complex as one could have expected. While the negotiations about membership of a single market and customs union are ongoing, it has been confirmed that the European Medicines Agency (EMA) has chosen Amsterdam as its headquarters, decamping from its current base in Canary Wharf, London. The UK regulatory agency, MHRA, will most likely gain a status as preferred affiliate to the EMA, while the transition will impact all pharmaceutical companies operating in Europe.

CLINUVEL's immediate concern relates to the role of the MHRA as co-rapporteur of our continuous regulatory dossier of SCENESSE®. Our teams are preparing the necessary changes of the dossier needed following the UK's departure from the EU, while we are all eager to find out which national competent agency will be replacing the MHRA.

On a practical level, since CLINUVEL's wholly owned UK subsidiary entity is the SCENESSE® license holder within the European Union, it is apparent that in the next months we will transfer the marketing authorisation to a new European subsidiary while our activities will be split between the UK and continental Europe. Naturally, these changes will have an impact on our obligations to adhere to pharmacovigilance, distribution, manufacturing, and financial operations. Of significant practical consideration is our need to anticipate and prepare numerous European regulatory inspections which our teams are subject to annually and which will need to be coordinated before and during the BREXIT transition.

As demonstrated in November 2017, our finance teams closely monitor how we track against our own internal benchmarks, whereby we aim to achieve the long-term business objectives of financial independence,

diversification of the Group, and vertical integration of key functions.

In expanding the business functions, we have resisted taking on debt, even at times when 10-year treasuries were priced at 1.367% (in 2016, CLINUVEL's last capital raise). While the European Central Bank and the US Federal Reserve are expected to continue to raise interest rates, we do not see the need for debt finance to facilitate expansion, and we presently find ourselves in a position where we can balance our capital needs to achieve further research & development of follow-on products. We intend to replicate the controlled distribution of SCENESSE® in the US in a similar manner as we are currently managing in Europe. We will implement final decisions on CLINUVEL's US operations from June 2018 onwards. In projecting the growth of the Group, cash flow management and profitability remain key components.

The current cash reserves aid to protect against unforeseen systemic events and – importantly in pharmaceuticals – are part of an armamentarium of strategic defence. Finally, depending on the financial performance during the next calendar year, we will be formalising CLINUVEL's dividend policy and strategic objectives associated with it.

CLINUVEL's financial result for the six months ended 31 December 2017 is due for release prior to the end of February 2018. As was stated in our 2017 AGM presentation, while the market access of SCENESSE® is being negotiated and discussed in individual countries in Europe we are not providing financial guidance as yet. The Company's financial result is currently dependent on one commercial product and under one regulatory approval. Negotiations with key European countries to set a uniform price are ongoing or yet to commence. At this stage CLINUVEL does not consider its earnings to be sufficiently predictable to provide reliable guidance for the current and future reporting periods.

SPONSORED PILOT STUDIES

In November 2005 we asked the cardinal question: how does a company maximise information from clinical data while minimising expenditures? Better put, how should it arrive at decisions which traditionally cost millions of dollars in pharmaceutical exploration? The clinical proof of principle of testing a novel molecule in an indication transcends in CLINUVEL's model the traditional search for 'endpoints' to arrive at cardinal development decisions. There are many parameters evaluated by our scientific teams which are aimed at gaining sufficient information to decide whether to progress in a clinical direction or to abandon early on in a program, thereby saving substantial funds. In modelling stochastic outcomes we realised that smaller pilot studies could be designed to derive and extract information beyond the classical endpoints (clinical study objectives) expected in larger clinical trials. At the time this was a radical departure from conducting larger clinical trials at high cost, but one approach we took courage to.

Over the years, CLINUVEL obtained many requests from academic physicians, research institutions, and companies for making SCENESSE® available for small scale studies. The requests were unsurprising, given the body of preclinical work in melanocortins, and how few *genuinely new* drugs are available each year. However, we have remained selective in choosing exploratory studies to evaluate the benefits and risks of the sought-after product. In a limited number of physician-sponsored pilot studies CLINUVEL assessed and allowed the use of the product so it could obtain pharmacological, safety and effectiveness data. In parallel, Company sponsored pilot trials had other specific objectives such as patient and physicians' request and prescriptive behaviour, or intensity of symptoms. In some instances, we use these exploratory studies to compare disease characteristics, to investigate biochemical parameters and review surveys to arrive at clinical, regulatory, and long-term commercial decisions. However, at all times we looked to manage and protect data generation, medical information and, importantly, intellectual property and rights originating from the use of our main asset. As is custom in this particular sector, not all of these exploratory data can be published or made available, in order for us to maintain advantage from our investments. There has been a public debate whether exploratory studies are sufficient in orphan drug development, however for CLINUVEL the pilot programs played out well, yielded much valuable information, and have proven cost-efficient.

The exploratory work on the current afamelanotide molecule is continuing. For 2018 year we have specific

objectives. One is to determine whether dermal fragility leading to ulceration and bullous exacerbation in other *cutaneous porphyrias - such as variegate porphyria and porphyria cutanea tarda* - is being addressed by our melanocortin. Here our teams are investigating the reparative properties of the pharmaceutical formulation to provide a clinically significant benefit to patients. The introduction of dermal fragility needs to be distinguished from phototoxicity and anaphylactoid reactions seen in EPP. An exploratory study will give us insight for the possible label-extension for SCENESSE®, while other objectives are being explored at the same time, very much following the similar adage of maximum intelligence from limited exposure to the drug.

Simultaneously, we are compelled to provide full-proof assurance to the supervising regulators that off-label prescription (use outside EPP) will not take place with SCENESSE®, even when the exploratory studies would show to be of obvious benefit in the new patient population. The commercial supply of SCENESSE® – as a first-in-class molecule – is strictly policed and remains laborious in maintaining one European registry, one retrospective Chart Review and three PASS studies.

US MARKET ACCESS

With much interest the industry has noticed how the FDA's commissioner, Dr Scott Gottlieb, leads the agency to look at *innovative ways* to gain earlier insight on a therapy's benefits to outweigh its risks benefit. It is yet a prime example of the US regulatory environment which is perhaps forced to rethink *how to fix a broken clinical trial model,* as FDA Center for Drug Evaluation and Research Director Dr Janet Woodcock publicly expressed.[2]

However, President Trump recently stressed at State of the Union that prescription drug prices would need to be reduced. Whereas Trump had, in 2017, called on the industry to reduce the 'artificially high prices of drugs', the Congress had not passed any bill covering this concern in 2017. However, it had become increasingly obvious that the pharmaceutical industry would be facing resistance in the commercial launch of new products. The populist message of the need to reduce drug prices in the US was recently expressed by Alex Azar, sworn in as US Secretary of Health and Human Services. I am not alone in the notion that the current political agendas do not address the need to look at drug pricing case by case and weigh up relevant factors per therapeutic domain. This discourse has led to our current successes in obtaining market access and pricing in Europe, while several other countries might argue that pricing of all products coming to market are too high from the onset. It is not surprising that many of our peers are therefore inflating the prices to anticipate stark reductions during protracted negotiations. We refrain from these practices.

Against this changing environment there is also the concern that the FDA has accelerated the approval of generic drugs to increase competitive tension and disenfranchise companies from monopolising therapeutic areas. Tarring all innovators with the same brush is hardly going to assist making novel therapies available for patient groups who have no alternative treatment, and our US dialogue at present is aimed at driving home that very argument.

In many ways Trump has been progressive in his thinking towards US healthcare. He pushed to enact "Right-to-Try" legislation for terminal disorders which offered to the Senate in August 2017 and which would prohibit the FDA from using safety or efficacy data associated with the use of an investigational drug administered outside a clinical trial to "delay or adversely affect the review or approval of the drug".[3] Importantly, the Act seeks to include an exception to the prohibition on FDA considering safety or efficacy data obtained from compassionate use experience. Under this Act allowance for such data would be considered if an FDA centre director, or a more senior FDA official, had issued a statement indicating that the data were "critical to determining the safety" of the investigational drug. In some cases the relevance to orphan drugs may be deduced and argued.

In view of the dynamic regulatory and political changes, our teams continuously analyse all possible avenues to stay ahead of the generic threats which may emerge in the future.

SYSTEMIC CONFOUNDING DOMAINS

One of the exciting aspects of CLINUVEL stems largely from what I call the use of innovative technology in *systemic confounding domains.* In choosing commercial

opportunities, one has to overcome in pharmaceuticals a number of hierarchically ranked challenges. Maximum effectiveness versus market size, safety profile versus dose regimen, and controlled prescription versus generalised access are some of the paradoxes one must reflect and decide on. Seldom can one fully reconcile these.

However, our teams proceed on the basis that we provide medical benefit to a pool of patients in a disease not yet fully characterised with the expectation to provide returns on equity to those who shared our vision more than 10 years ago, and to those who have supported our cause unconditionally. However, one obvious peril – not infrequently asked to our teams – is that of possible obsolescence of SCENESSE®. Some investors expressed the angst that there would be other products or therapies following in the wake of CLINUVEL's innovative photomedical vortex. Guarantees do not exist in our sector, but we have put all our efforts to stay ahead.

As a relevant aside, I see overconfidence as a questionable trait in commerce, and operational fear as the worst possible guide, albeit one that can motivate teams to perform. Back to my excitement, while the *systemic confounding domain* is in our case somewhat defined by the evolution of the field of endocrinology, photomedicine and – in particular – melanocortin science, we started to discern illuminating changes within the scientific community during the past decade. These changes actually gave rise to a wider acceptance of our very technology, and even opened up therapeutic opportunities as opposed to obsolescence of the technology. Here, the trade-off between time lapsed and readiness of the environment to accept novel technology worked in CLINUVEL's favour. There are quite a number of examples, but I will restrict this today to progressive intelligence on the polymorphism of the melanocortin-1 receptor and relative risk of cancer in Caucasian population, and most significantly the increased awareness that alpha-Melanocyte Stimulating Hormone was actually not a centrally regulated hormone, but one released and controlled by multiple epidermal cells; this very notion took years to be adopted and accepted. If I add the recent regulatory viewpoints on orphan drug development and trial design, we started to realise how time lapse had actually assisted our programs and progressive knowledge.

VITILIGO

The progress in vitiligo occurs at various fronts. Our statistical teams are now finalising the CUV103 exploratory study in Singapore, where 18 patients of four ethnicities suffering from generalised vitiligo (GV, formerly non-segmental) were subjected to seven consecutive doses of SCENESSE®.

Whereas we have well understood GV in Caucasian and African-American patients, in CUV103 we investigated the use of the drug in combination with narrowband ultraviolet B phototherapy (NB-UVB) in generalised vitiligo patients of Asian descent. The results will aid us in making decisions later this year together with the Global Vitiligo Expert Consortium to design the Phase IIb or Phase III study in North America. While the FDA will likely be reviewing the scientific dossier on SCENESSE® in EPP, the discussion with the same members of the regulatory division will centre around a *drug-device combination*. Here, we will once again be novel in the use of melanocortins in combination with NB-UVB in a poorly responsive patient population.

One of the key areas we deliberately quantitate early on is the commercial opportunity and target populations while balancing the patient populations diagnosed with generalised vitiligo and with the highest demand for treatment. Notwithstanding that we are once again entering an unchartered course, we find it rewarding to develop novel markets and therapeutic opportunities.

Since vitiligo is currently not regarded as a rare ('orphan') disease, a significant part of our activities is aimed at detailing the expenditures of further and final clinical trials in vitiligo including US FDA filing costs. Nevertheless, the unmet clinical need in GV in North America and parts of Asia is well documented. More will be reported once the program resumes in North America.

SUBMISSION OF SCENESSE® NDA

The Division of Dental and Dermatology Products of the FDA has been receiving the scientific modules on a rolling basis (part of the Fast Track Designation[4]), and part of their current activities is manpower planning to allocate senior staff to each module.

At present our statisticians are pooling the European data on real-time use and clinical trial data before submission of the final clinical module. In evaluating the use of the SCENESSE® in EPP, the focus is on safety, frequency of use, altered lifelong behaviour following drug treatment, and quality of life.

Once the final module is submitted, our teams will report on the safety aspects to date as observed during last year's post-authorisation distribution in Europe.

Notes

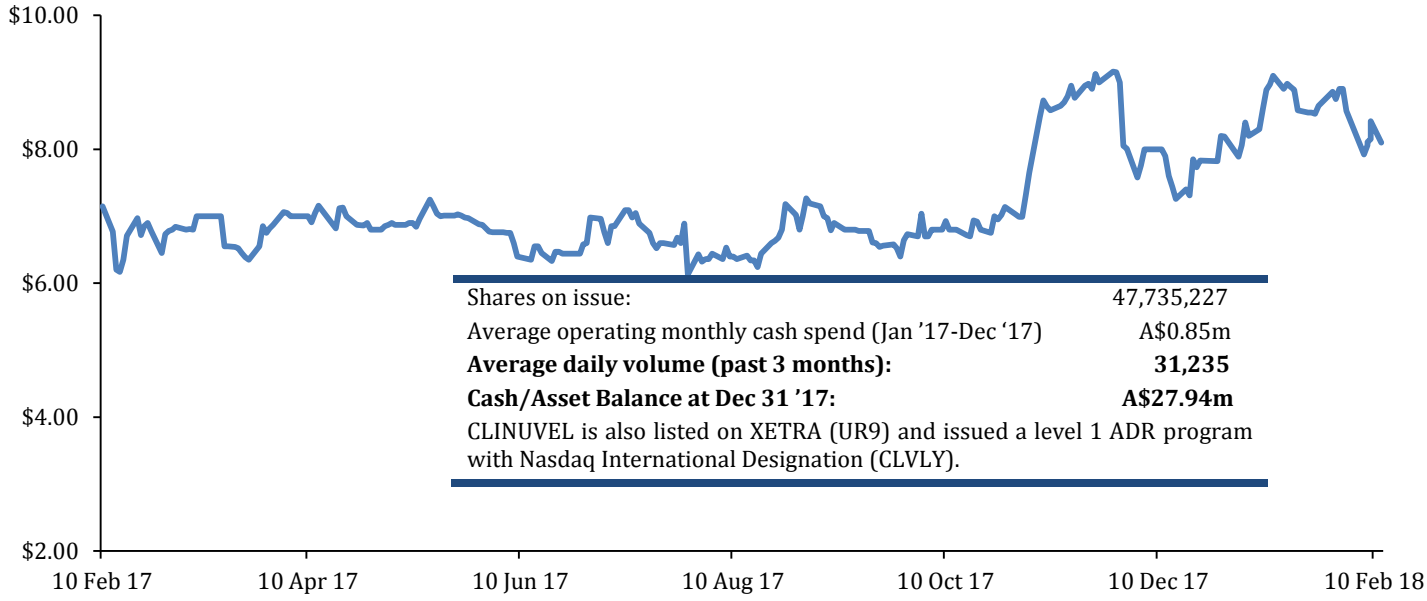
[1] SCENESSE® (afamelanotide 16mg) is approved in Europe as an orphan medicinal product for the prevention of phototoxicity in adult patients with EPP. Information on the product can be found on CLINUVEL's website at www.clinuvel.com.

[2] See CLINUVEL Newsletter 16 October 2017.

[3] Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2017.

[4] See Company announcement 6 July 2016.

ASX: CUV



Shares on issue:	47,735,227
Average operating monthly cash spend (Jan '17-Dec '17)	A$0.85m
Average daily volume (past 3 months):	**31,235**
Cash/Asset Balance at Dec 31 '17:	**A$27.94m**

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