Clinuvel communique

GLOBAL UPDATE

The CLINUVEL team is looking with much optimism and energy to the start of 2018. I believe the year ahead is one where the Company will make great strides on various fronts: research, product development, distribution, and restructuring of the Group of companies. We all eagerly await the day our teams can supply SCENESSE® (afamelanotide 16mg)[1] to US erythropoietic protoporphyria (EPP) patients who endlessly request updates on progress. That very day will be the epitome of CLINUVEL's lengthy crusade, and a most fulfilling professional moment.

The period following the November Annual General Meeting (AGM) is the optimum time for our teams to regroup and finalise planning for the next calendar year.

US PROGRAM

As the interest in CLINUVEL's rolling submission of the New Drug Application (NDA) increases, we prepare ourselves for an intense year of advanced scientific discussions with the US Food and Drug Administration (FDA). As found on the AGM information slides (28 November), the first important event in this sequel will be the completion of the US filing with the supplement of European data generated from real-time use of SCENESSE®. The aim is to gain further knowledge on patients' behaviour under real world conditions which often differs from that recorded during clinical trials.

Naturally, CLINUVEL is currently focussing on the US distribution. Many of the post-marketing measures we have implemented in Europe are being replicated and synchronised in the US.

SCENESSE® TECHNOLOGY

A theme which we will repeatedly discuss the coming year, reflecting my personal research interest, centres around *priming and readiness of the environment*. Early in the planning of the development program for SCENESSE®, we reflected on the question: what would it take to introduce novel technology in an environment not yet prepared to accept the scientific concept? At Board level we agreed that time would be required for the field of endocrinologists to mature on the notion to deploy melanocortins for systemic use to elicit systemic photoprotection – that is to the entire body surface. In going through various other sectors, I draw many parallels with our industry. Radical changes to prevailing beliefs requires concomitant communication and challenging of the targeted environment where the technology ultimately needs to be accepted to attain success. Most often the field is loaded with incumbent motives to maintain its traditional beliefs. All innovators have to penetrate some barriers, large or small.

This notion is applicable to the automotive industry where driverless vehicles are predicted to dominate our streets, and gradually change the concept of transportation as we had known it since the introduction of the Ford Model T. The long-announced disruption is raising questions of control, liabilities, costs, power supply, and infrastructure, to name a few. Only eight years after the Google car was announced to the world are politicians and industry willing to entertain and embrace the notion of dramatically redefining transportation.

Similarly, at CLINUVEL we had long anticipated that changing common medical thinking and the perception of the use of melanocortins as a biomimicry to an endogenous stress response, would pose challenges. We have challenged the notion of endocrine versus paracrine response of the epidermis to alpha-Melanocyte

Stimulating Hormone (α-MSH), the former very much part of long held and established beliefs in endocrinology.

CLINUVEL's emphasis here had been on allowing gradual adoption by consistent communication and proof of principle of SCENESSE® in EPP, but also in other indications we had evaluated. We have taken giant leaps since 2005. During global conferences from 2005 to 2008, clinical experts were eagerly taking the public microphone, posing questions on whether afamelanotide would be safe for long-term use, or whether the medicine would provide any clinical benefit at all. We have systematically eroded, and therefore overcome, the anticipated resistance and this has led to where CLINUVEL is today. Patience borne by all has been worthwhile, as we see how eminent scientists, established editorial boards of prominent journals and heads of university departments have turned their attention to our field of focus. I predict that melanocortins will be deployed in many areas of medicine. CLINUVEL is obliged to be at the forefront of this wave of attention to melanocortin 1 receptor (MC1R) function, melanocyte biology and proopiomelanocortin (POMC). The present status of melanocortins is positive as the environment has been primed and is ready to accept a once-so-alien concept.

Notwithstanding, in some cases of disruptive technology there is the risk that the passing of time alone makes novel technology obsolete, inherent to entrepreneurship and the flip side of the pursued reward. However, in CLINUVEL's case we have witnessed the reverse phenomenon; the medical community and scientific researchers latching on to the concept of melanocortins, and the family of POMC now actually becoming a growing field of interest among a varied medical community and start-ups. The pendulum could have swung both ways, but all stakeholders of the Company have gradually realised that these molecules have now obtained a place in clinical research. It is the direction for which CLINUVEL had fought.

I stress to our operational teams to maintain situational awareness, scanning the horizon, looking and anticipating changes, remaining ahead of uncalculated events and competitors. This call keeps CLINUVEL agile and hopefully protects against complacency creeping in, all this against the background of a most successful 2017.

EUROPEAN PROGRAM SCENESSE®

Under the European post-authorisation safety study – simply PASS – our teams are working feverishly to collect, follow-up, monitor and analyse data generated by porphyria expert centres. The efforts going into the PASS are significant, and CLINUVEL has allocated a large percentage of its annual budgets to pharmacovigilance and monitoring the safety of the patient population. Essentially, CLINUVEL follows up its patients for a minimum of eight years and intensely monitors all centres for data entered and analysed, and questions arising surrounding safety. To gain understanding of what this entails, each medical episode during the supply of SCENESSE®, as diverse as a sprained ankle, flu, dental treatment, or headache is being retrieved, discussed, analysed and assessed on possible causality with SCENESSE®. The objective is to ascertain whether there could be a relation with the novel drug administered during and after the desired photoprotective treatment. As the population of EPP patients has grown, one can imagine how many cases per week need to be analysed, quantified and written up for both the team and the regulatory authorities to evaluate.

We are content with the current quality management systems as we had to set it up, and it makes CLINUVEL control the entire supply chain while retaining control of its product. Importantly, our teams remain in close contact with the medical staff administering SCENESSE® and the relationship with hospital departments is essential to the long-term success of the Company.

This month, we will receive the first analyses of the 2016-2017 year's supply of SCENESSE®, and we eagerly look to learn what patients and expert physicians 'tell' us through these data. The European information of commercial use of the drug product will serve as the last piece of the puzzle to complement the data package to the US FDA as part of the NDA.

VITILIGO

As we have stated, only when the US FDA approves the use of SCENESSE® in EPP will it be economically justifiable to expend resources on a larger vitiligo population, who would benefit from a repigmentation therapy. The vitiligo

program excites us on various grounds; *we are giving back to an ethnic community which seldom received the undivided attention of a scientific community*. *CLINUVEL will not only be repigmenting patients who have lost their colour but we will be restoring their being.* Technology drives our decisions, as it should be, and the opportunity to treat patients of colour due to the biological response elicited by SCENESSE® fits both our values, and my personal conviction to enter fields where others have not yet ventured.

Another example of environmental changes impacting corporate direction is the consensus reached by the Vitiligo Global Issues Consensus Conference (VGICC) which held its workshop in Rome last year, where many of the physicians who have collaborated on CLINUVEL's trials reached consensus on a number of issues. The discourse was of importance to the Company's direction. In anticipation of this workshop, our teams deliberated on the clinical relevance of SCENESSE® being the future standard of care. The VGICC position paper concluded that "repigmentation and maintenance of gained repigmentation are essential main outcome measures in future vitiligo trials". The workshop analysed the results from two online surveys on vitiligo repigmentation, which had been conducted during three years. Importantly, the VGICC defined a successful treatment "if repigmentation would exceed 80% and at least 80% of the gained repigmentation could be maintained for over 6 months". Unfortunately, no agreement could be found on the best outcome measure for assessing target or global repigmentation. Since CLINUVEL's design of final vitiligo trials is deemed novel, and we therefore will once again enter unchartered waters, the consensus reached by the VGICC is of interest. CLINUVEL will meet with select global vitiligo experts during 2018 to arrive at an agreement on clinical 'endpoints' (objectives), in the case CLINUVEL proceeds to further develop SCENESSE® in vitiligo. As stated, the Company focuses first on the market access of the drug in EPP before we engage in a US program in vitiligo.

To bring it all together, the VGICC is yet another example where the evolution of the environment actually benefits the clinical research of a pharmaceutical company in progressing innovation. Simply put, the scientific evidence not only comes from a company's own's dataset but also hinges on the dominant opinions of experts, those who will need to prescribe a therapy in the future. The convergence of critical minds is of immense value to CLINUVEL.

VISIBILITY CLINUVEL

In 2018, the general medical community will require greater knowledge about CLINUVEL's research and output, and to this effect CLINUVEL will present its programs, treatment in EPP and prospect to more audiences than has taken place in the past years. Our managers will be attending and presenting at more scientific meetings and conferences the coming year than ever before to make sure we are communicating the relevance of our work.

One of the questions posed after the recent AGM was whether CLINUVEL, being headquartered in Australia, was being noticed by the global scientific community for its breakthrough medical product. At various occasions we have said that in today's world the launch of innovation technology is not restricted by the Company's location but rather driven by the Company's international clinical and commercial activities. As illustrated last week, CLINUVEL is obtaining ample attention from mainstream press and industry publications (see next page). We will continue to bring SCENESSE® to the attention of a broad audience in anticipation of our further development.

Reference

Gan Y et al (2017). Repigmentation in vitiligo: position paper of the Vitiligo Global Issues Consensus Conference. *Pig Cell Mel Res*. 30(1):28-40.

[1] SCENESSE® (afamelanotide 16mg) is approved in Europe for the prevention of phototoxicity in adult patients with erythropoietic protoporphyria (EPP).

GLOBAL ATTENTION CLINUVEL (as presented to 2017 AGM)

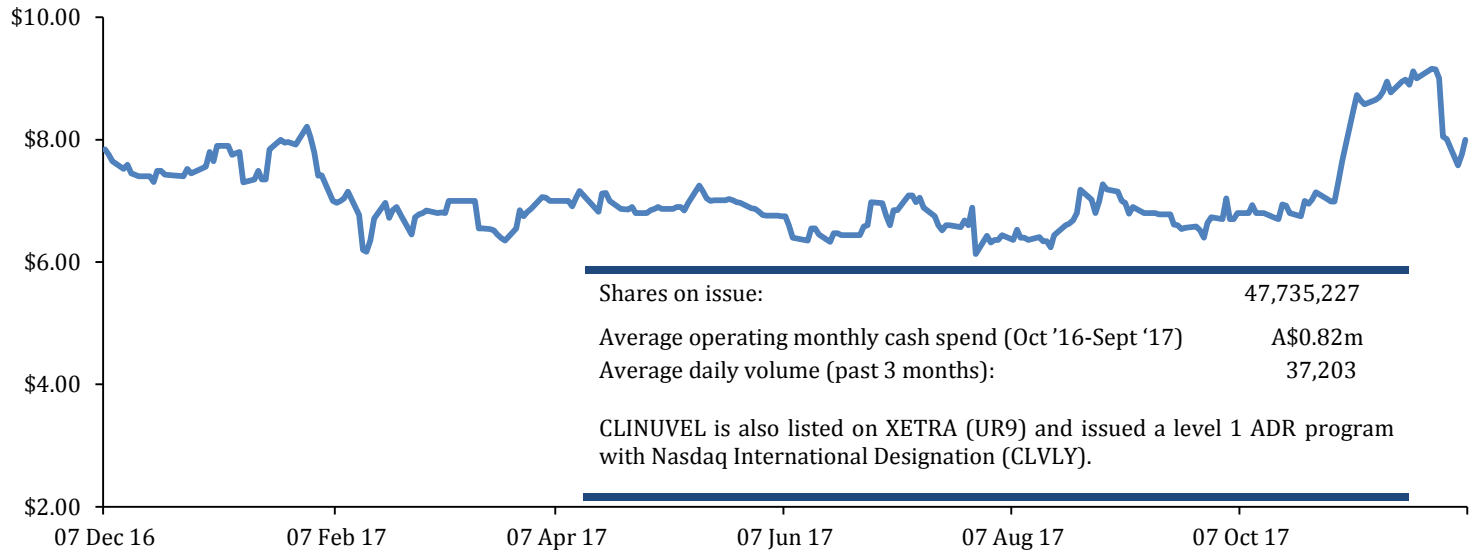
Media Coverage 2005-present

Media	Number of Titles
Industry	679
Magazine	36
Newspaper	326
Online	245
TV	60
Wire	123
Grand Total	1469

Online traffic

Website visits (since 2008)	1,867,599
YouTube video views (since 2009)	1,058,609

ASX: CUV



Shares on issue:	47,735,227
Average operating monthly cash spend (Oct '16-Sept '17)	A$0.82m
Average daily volume (past 3 months):	37,203

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