February 2017

CEO's Outlook

I wish all stakeholders of the CLINUVEL Group a healthy, mindful and successful 2017.

After a Christmas break CLINUVEL started 2017 with fervour and '*en bon esprit*'. We look forward to an exciting year.

During a meeting on 4 February in London international expert physicians, senior and paediatric patients, family carers and advocates gathered to further characterise the disease erythropoietic protoporphyria (EPP). Our teams witnessed how traumatised and affected EPP patients are, and we were abruptly reminded of the privilege to supply treatment to EPP patients who had not received a diagnosis for, in some instances, more than four decades of their lives.

A common theme that was expressed by patients at the meeting was how they have not been taken seriously by society, by those within their immediate environment, and by their general physicians. In many ways their ordeal is confronting, invisible and not understood. All attendees came away with the conclusion that EPP patients have not been given the credence by healthcare providers, their families, or by society at large. Many patients did express in different terms how they had been labelled "insane", "unstable" and "non-credible" for most of their lives. Patients had told us that for years they had been suffering from an invisible disease for whom physicians had been unable to find a diagnosis. During the London meeting it was mentioned again how patients had recognised each others' life stories of hiding and withdrawing from light and, therefore, from a normal life. It was also said by a number of patients that those in their immediate environment had not fully accepted their condition and trauma until the moment they serendipitously stumbled across a physician who had set the right diagnosis, albeit without available therapy, or (a more recent phenomenon) self-diagnosed online. This meeting was the most humbling of all I have attended since being introduced to EPP and it left us all with much to think about, not least the commitment to make SCENESSE® (afamelanotide 16mg)[1] available for children with EPP.

For 2017 we have self-imposed a number of deliverables, while for other matters we are subject to external reviews, audits and inspections. The teams' performances are always under ongoing appraisal.

In the excitement of establishing a team which oversees the European distribution of SCENESSE®, we are now arriving at a juncture where CLINUVEL is managing intricate systems and processes to comply with the post-authorisation rules and regulations.

Our series of bimonthly news bulletins starts today and these communication pieces serve as an insight to CLINUVEL's approach and relevant thought processes.

PHARMACEUTICAL PRESS AND STATUS QUO

It is apparent that the change of US administration and upcoming elections in France, Germany and the Netherlands are causing uncertainty on the future direction for our industry, and the potential impact these uncertainties may have on CLINUVEL. Without being speculative, I would like to put forward a few comments on the evolving political climate.

Since the emergence of specialty treatments and orphan drug companies, we had anticipated a growing sentiment in favour of pharmaceutical companies entering a market where little competition existed by virtue of lack of available treatment. As I have stated previously, including during the 2016 AGM, scientific innovation comes in

multiple forms, and genuine R&D efforts will need to be recognised by trendsetters in healthcare, politics, and governmental advisory bodies. Society expects pharmaceutical companies to justify their endeavours throughout the entire research and development phase to the point of market access. The trend is set for decision makers to assess companies to ensure their R&D targeting medical demand is well defined and R&D has been executed through the lowest cost model possible. Policy makers incorporated these factors in their decision paradigms. CLINUVEL anticipated the evolving economic modelling and developed a first-in-class orphan product well below the median industry cost to come up with a new pharmaceutical.

At the moment the obvious challenge – for society and those decision makers influencing bodies outside of pharmaceutical development – is to arrive at a model where true galenic innovation is to be distinguished from those who merely reformulate existing therapies with little innovation or research input.

"...when pharmaceuticals are being assessed by politicians, press, and the public, then R&D context, historical expenditures, and differentiation is mandatory..."

This risk of failing to differentiate is highlighted when the media is quick to tar everyone with the same brush. A minority of companies in our sector has attracted attention and taken advantage of the system by increasing the price of their therapies without justification for the minimal R&D expended.

In order to meet these challenges with greater sophistication, I would refer one back to the December 2016 Newsletter, the comments of NICE's Chief Executive Sir Andrew Dillon, where he advises that when pharmaceuticals are being assessed by politicians, press, and the public, then R&D context, historical expenditures, and differentiation is mandatory.

First off one ought to do proper in-depth research and establish an understanding of the context in which a novel drug has been developed. As in our case the lack of available therapy, the absence of companies willing to invest R&D monies in EPP, the innovative model of developing a new therapy at minimal cost, and lastly the forgone opportunity costs to society and investors must also be considered. In healthcare, one is obliged to separate the chaff from the wheat to succeed and maintain a competitive advantage in this field.

Our Board has always endeavoured to foster an open dialogue with active investors who funded the Company to enable SCENESSE® to be developed as the first systemic hormone, serving EPP patients. CLINUVEL's management was selective and cautious in its introductions to active investors, and took into account their investment horizon, and expectations on profitability and returns, while it tempered expectations in a changing political environment since the global financial crisis 2007-8.

It is management's task to serve and placate many interests while at the same time looking after CLINUVEL's assets. SCENESSE® as a systemic photoprotective drug, an immune modulator and neuroprotective drug has a significant place. We are convinced that many other applications and analogues will enter the field of medicine in years to come. If we momentarily ignore CLINUVEL's inherent bias in favour of melanocortins – our field of expertise and attention – evidence is being provided by the world's most renowned experts spending their careers on further exploring the role of melanocortins, the molecular effects of UV cytotoxicity, and molecular signalling. As protective agents against trauma, stress response, environmental factors or stimulants in deficient hormonal axes and systemic tracks, the POMC[2] group of drugs will come to the clinical fore. SCENESSE® is merely the first one to have gone through a comprehensive and lengthy R&D program, and others will follow in decades to come. Today there are more than 6,000 peer-reviewed papers on POMC (the gene coding for melanocortins), 5,000 publications on the hormone alpha-MSH, 5,000 more on melanocortins, and more than 117 on SCENESSE®. The field constantly evolves and scientific evidence on clinical need and applications is rapidly emerging. Usually society (including decision makers) trail scientific research as was seen in BRAF and PD-1 check point inhibitors, JAK inhibitors, and most recently in the CRISPR gene editing.

There is a time lag of several years before central agencies and insurers realise that new science will be applied in hospitals; in the case of SCENESSE® one UK agency started scoping the treatment before the drug was approved, all

others were reactive and only showed interest in the treatment once it has received CHMP approval.

I view it as our collective task, – CLINUVEL, physicians, patients, researchers – to provide a genuine account of benefits, risks, long term use and prospective use of the product. In traversing the innovation cycle our teams engage with decision makers to articulate the historical context, the benefits and future direction while we witness a populist movement against pharmaceutical companies. Genuine intent, and clear and consistent messages win over an audience, hence my optimism about the current sentiments which will eventually be able to distinguish and appreciate scientific breakthroughs.

CHARACTERISATION OF ERYTHROPOIETIC PROTOPORPHYRIA

In 2012, as part of our entry to market, CLINUVEL's teams had identified and articulated ten objectives for which to deepen and clarify further due to the lack of general understanding on a number of novelties surrounding SCENESSE® and erythropoietic protoporphyria:

I. EPP as an example of a genetic chronic disease, and lifelong impairment;
II. EPP as an example of a most debilitating light disorder causing second degree burns due to exposure to all light sources (artificial and environmental);
III. the novel medical concept of hormonal protection from within (endogenous) against external/ environmental insult/damage;
IV. patients' conditioned behaviour to avoid the known insult (light) against all costs and unwillingness to expose to light sources in lieu of being at risk of incurring burns and "scars" for life;
V. the psychological impact of being deprived of light lifelong;
VI. the impact on parents' and families' lives;
VII. the introduction of proper nomenclature in optical physics to clinically express a chemical reaction in human tissue elicited by protoporphyrin IX;
VIII. the therapeutic impact and freedom provided by afamelanotide to EPP patients;
IX. the distinction between phototoxicity, anaphylactoid reaction and any other form of pain due to the lack of responsiveness of EPP patients to all forms of analgesics;
X. the psychological impact reported by patients after withdrawal of afamelanotide following long term use.

With each innovative technology a set of new parameters is expected to be introduced, novel nomenclature and the need to change an unprepared environment. We long anticipated the post-marketing phase where we believed that the introduction of SCENESSE® would need to be accompanied with novel models, and novel sets of medical coding and diction, since no other similar therapy had existed. Protecting endogenously ("from within") against light sources eliciting a chemical organic reaction has not yet been covered in medical textbooks, therefore the weight to characterise the disease further rests on CLINUVEL beyond its role of drug supplier. Consistent and long term communication and education of policy and decision makers is key to success. We need to stick our head above the parapet and others will jump on the proverbial bandwagon.

EU DISTRIBUTION

The European distribution of SCENESSE® takes place through a regimented and controlled set of measures in compliance with EMA regulations. Common for novel and innovative therapeutic products under "a black triangle" (drug subject to additional monitoring) is a risk management plan to incorporate a set of risk minimisation measures allowing teams such as ours to monitor the ongoing use of SCENESSE® and to provide periodic feedback to regulatory authorities.

We follow a Post-Authorisation Safety Study (PASS) long-term, requiring us to care for EPP patients for a minimum of eight years. Twice per annum Periodic Safety Update Reports are submitted to the EU agency and at the end of the calendar year an Annual Report is also submitted. These specialised reports are compiled by a team of experts: statisticians, and managers in quality control, clinical and regulatory affairs. With patients entering their second year of treatment under the PASS protocol in select countries, we can begin to analyse the ongoing use of the product under this protocol compared to the long term use of SCENESSE® under Special Access Schemes (2010-2015).

As to the European EPP Expert Centres (EEECs), each centre requires training and accreditation in the administration and follow up of EPP patients and in data collection, management and handling. A vast number of

patient data are being generated, ranging from biochemical (blood) analyses to questionnaires to be filled in by medical staff and/or patients. Additionally, patients themselves are asked to fill out diary cards following each implant injection to record their experiences.

Monitoring of the data handling and management of the EEECs remains the responsibility of CLINUVEL, hence the necessity for our staff to be trained, specialised and audited in these post-authorisation activities. Once these uploaded data have been verified on accuracy, they are locked into a central European EPP Disease Registry for regulatory and for analytical purposes. The data entry and management also needs monitoring by the CLINUVEL teams and overseen by an independent Governance Board. This entire system is hosted at arm's length from the Company to ensure regulatory and legal compliance and for the benefit of protection of patients' medical data.

A separate database containing safety and effectiveness data is maintained by our teams as a back up to the central European EPP Disease Registry and serves as an in-house tool for safety recording.

Lastly, pharmacovigilance systems and processes were established under the guidance of our European Qualified Person for Pharmacovigilance, a professional who is legally responsible for CLINUVEL's compliance with the expected measures. CLINUVEL has a UK-based team working around the clock to check and recheck all the processes surrounding the post-authorisation distribution of the product.

As previously stated, a novel molecule – first-in-class pharmaceutical product – is expected to be managed with the highest caution and vigilance, even though the product maintains a positive safety profile, and no medically significant adverse reactions have been observed or reported from the use of SCENESSE®. Prudence rules here, and no compromise on safety can be made. This has been our number one priority.

Needless to say, these processes pose a large workload on the CLINUVEL teams but equally on the EEECs which spend many hours on each treatment in subjecting EPP patients to additional tests and interviews.

The consequence of all additional monitoring and vigilance activities defined under the PASS protocol contribute to rising expenditures, the cost of distribution. Another way of looking at this, however, is that these measures create barriers to entry for those wishing to enter the field to compete with CLINUVEL.

As part of these anticipated processes, we recently hosted a formal regulatory inspection. While the discussions with regulatory agencies are held confidentially, it is fair to state that our teams in the UK, Switzerland and Australia have performed well to implement robust systems and processes surrounding the European distribution and administration of SCENESSE® in EPP thus far, while continuous adjustments and optimisation of the processes is expected over the next few years. Pharmacovigilance is an evolving discipline which will never be completed but requires maintenance and adjustment to changing regulations.

CLINUVEL is expected to be subjected to regular annual audits and inspections and therefore an expanding team of super specialised professionals have been added to the Company.

As to the eligibility for market access of SCENESSE®, a central criterion is access to a treatment for a disease for which there is no medical treatment. A second criterion in assessing market access is the one of the degree of medical demand expressed by patients and expert physicians. In some countries and for drugs addressing larger populations, a Quality Adjusted Life Years (QALY) model is used to assess cost-effectiveness based on a utility score, while for orphan diseases health-economic models are seldom applicable and often challenging to generate due to the small population and lack of comparators.

EPP patients are conditioned from childhood to avoid the risk of second degree burn and anaphylactoid reactions. This treatment characteristic is unique to SCENESSE®, providing a seasonality to its peak use. In the months that light intensity increases, the risk of anaphylactoid reactions, burns and aversion of outdoor exposure by EPP patients is magnified. Therefore we have learned that product distribution is seen to be strongest during eight months of maximum risk. In some countries where a reflective environment dominates we observe demand for SCENESSE® also during winter months.

FINANCIAL REPORTING

At the end of February CLINUVEL will release its consolidated half-year financial statements. CLINUVEL reports its cash flow on a quarterly basis, reflecting its cash payments and expenditures incurred over the previous financial quarter in line with ASX requirements. In light of the seasonal effect of clinical demand for the pharmaceutical product, fluctuations in product supply are likely to be expressed in the sales receipts reported in the Company' quarterly financial statements. This plays a role in the Company's current policy to not provide earnings guidance.

INDIVIDUAL NATIONAL REQUIREMENTS

While European marketing authorisation is granted centrally, the authorisation holder is obliged to interact with each national competent authority before being allowed to distribute the drug within a free market zone. Furthermore, in some cases, the competent authorities are several and regional within one country.

The engagement comprises national approvals of training and accreditation materials, patients consent forms, contracts, packaging and labelling in each specific language per country, pricing agreements and volume. These administrative hurdles are necessary and can only be taken when one possesses an intimate knowledge of the product dossier.

Equally, pricing discussions with governmental representatives, ministries of health and insurers occur at an individual level in the language of origin within each jurisdiction. These activities take place among our teams, with assistance from specialised regulatory consultants in each country and from legal and health economic teams. Our teams are systematically working towards these approvals, grants, sign-offs and authorisations.

TRAINING PROVIDED BY CLINUVEL

Steadily we are growing our network of EEECs, and train and accredit the medical staff before we can initiate distribution of SCENESSE®, all pending agreements with Ethics Committees, hospitals, insurers and authorities overseeing state and private funding

US FDA PROGRESS

As previously reported, the FDA received the full EPP datasets early March 2016, and it took the relevant Division three months to assess the data package of CLINUVEL. On 18 July 2016 the Division had deemed the datasets complete and sufficient for submission of an NDA, leading to a face to face pre-NDA meeting on 7 November at FDA headquarters. The FDA clearly stipulates sponsors do not disclose the content of the discussions between the two parties and for the process to remain confidential.

While CLINUVEL is progressing on its five US regulatory modules a number of ongoing exchanges take place with the FDA.

The quality of the NDA dossier dominates our approach in order to gain time during the review process, which contrary to what the label of "rolling submission" may suggest, the FDA will only commence its review at the end of the "rolling submission" process.

EXPANSION OF CLINUVEL

CLINUVEL has expanded its pool of talent as the Company evolves to occupy and dominate a super specialised field. Obligatory for ongoing success is the transfer of intricate knowledge, hand-over of responsibilities and process management. In simpler terms more matured managers gradually need to elevate the next generation to a level where longevity and continuity of the CLINUVEL Group is maintained. Part of this current process is succession planning at all levels affecting all divisions.

The crux lies in the professionals within the Group. The teams have evolved over the years and at present there is a healthy balance between the teams in Australia, Europe, Singapore and the US. The recruitment of CLINUVEL staff has been excellent as well as the integration of the new talented and dedicated specialists. We are privileged to work with young as well as more seasoned and mature professionals. As part of our business we continuously review candidates with a specific search for deeper knowledge in our current domains of interest and with an eye to hire for the future.

In following successful business concepts in our sector, consistency is one of the main features which has our attention. Much of our daily activities consist of problem solving and/or pre-emption.

Perhaps four characteristics are symbolic for the talent CLINUVEL has attracted the past decades:

- rigor in financial execution;
- interest in novel fields of science;
- persistence and flexibility in finding solutions;
- sincerity in all aspects of the business.

A few notes on these traits:

The late Jack Wood, one of the most decorated pharmaceutical executives in North-America and well recognised in Australia, shared with our teams the eternal words: "CLINUVEL will go where nobody has gone before, face the adversity and will not freeze in the headlights". Our next generation talent is being groomed with the nexus that managing uncertainty is central to joining CLINUVEL, as this approach has stood fast since we started on a long scientific journey.

When the time comes for successor change in management, the Board of Directors would want to see a company with an embedded culture of tenacity and focus beyond what is generally found in our industry. The colloquial proverbs "go the extra mile, outperform quietly and persist where others would throw in the towel" are very much the features we would all want to see maintained in CLINUVEL 2020 and beyond.

Against the tide of negative press lashed out on the pharmaceutical industry the past year, I take great comfort and thereby courage in forging ahead knowing our teams as being honest in their scientific management, data handling and motives for advancing R&D.

STRATEGICALLY PRAGMATIC AND FOCUSED

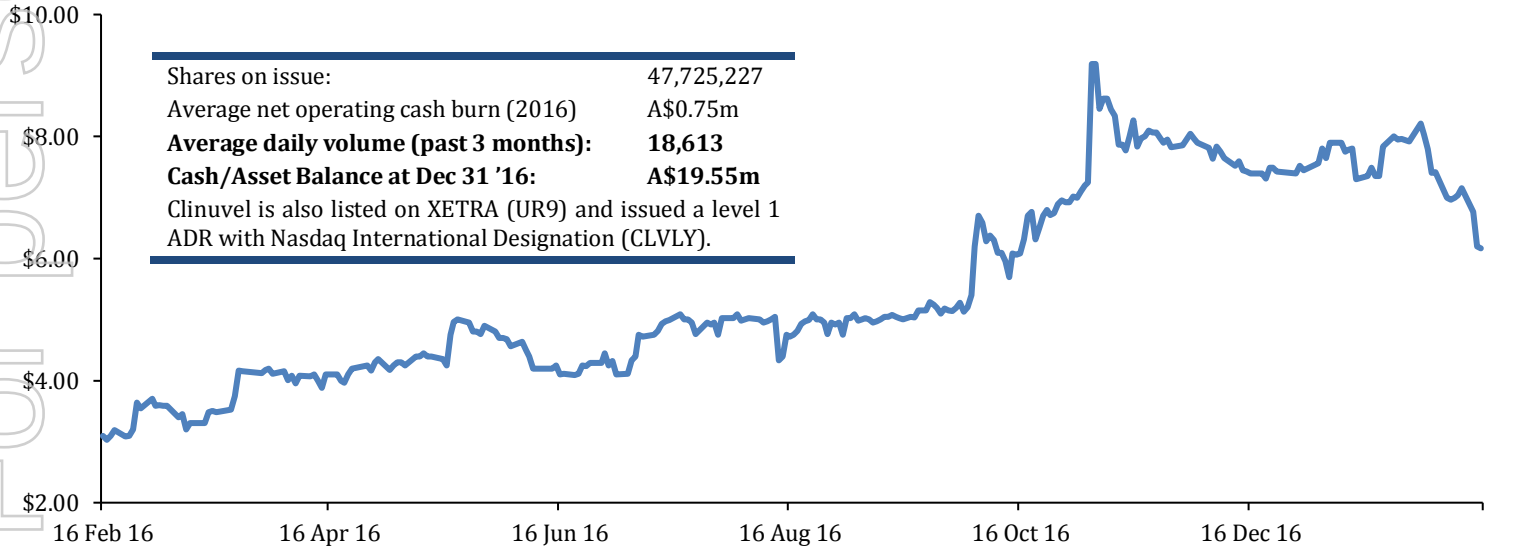
CLINUVEL remains strategically cautious and pragmatic in identifying areas where opportunities exist to leverage off the Company's expertise. It is a balance between retaining value whilst searching for synergies.

The vision of CLINUVEL being a company providing treatment to patients suffering from rare severe disorders and to patients of colour suffering from vitiligo is a clear and exciting vision to pursue. It is a legacy this team will leave behind for the next generation.

Our objectives are as strong as when they were set and have little changed. We want to see CLINUVEL grow to an established pharmaceutical company with a diversified portfolio of products and services. I look forward to sharing this progress throughout 2017 and beyond.

Philippe Wolgen

ASX: CUV



[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. Information on EPP can be found at www.epp.care.

[2] proopiomelanocortin