# CLINUVEL Communiqué

02 May 2019

CLINUVEL

**Dear patients, shareholders, friends,**

In this Communiqué we concentrate on CLINUVEL's programs and US market access for SCENESSE®.

As the European season unfolds, we report on the back of quarterly financials (released 30 April) which are on track against our own projections. Importantly, our commercial teams and finance staff are performing well in keeping our expenses in balance, very much reflected in the company's profitability and tight control of expansion.

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## BREXIT AND EU DISTRIBUTION SCENESSE®

At midnight on 29 March the UK was due to leave the European Union (EU) as per Article 50 of the Treaty on European Union. After suffering three consecutive defeats in the House of Commons for a proposed Brexit deal, Theresa May obtained an extension until 12 April to reach a compromise within her own party. As the Tory backbenchers and hard Brexiteers could not agree any exit deal, European Council President Donald Tusk and European Commission President Jean-Claude Juncker persuaded the European Council to grant the UK a further and last extension until 31 October to come up with a final plan which would be acceptable to EU member states. The disruption to UK and EU business is vast, to say the least. Many companies and organisations have already shifted their operational hubs from the UK to the continent in anticipation of import duties and new regulations imposed on cross-border trade.

As to the life sciences sector in the UK, one can imagine the uncertainty about tariffs on goods, hospital supplies and medications. For CLINUVEL, Brexit has had a number of consequences which required our full attention and allocation of manpower. I reiterate some of the activities.

Since our second manufacturer (an EU obligation) is located in the UK, the recognition of batch testing in the UK by the EU would become a point of contention under a Brexit scenario. Hence, we were forced to seek solutions for current EU batch testing and release, a mandatory requirement from EU regulators. Equally, we needed to find options for transporting our stock into the EU prior to being subject to import duties on the medical product. One can only imagine the costs and logistics involved to reorganise the route of SCENESSE® (afamelanotide 16mg) under cold transport.[1] In the midst of the Brexit turmoil when suppliers changed their operations, the new Falsified Medicines Directive was introduced in early February, forcing manufacturers to provide anti-tampering devices and barcodes on their individual products.

Since CLINUVEL had invested significantly in operating and pharmacovigilance systems, we needed to adapt our systems and personnel to remain in compliance. We opened our sixth office in Dublin to accommodate all future changes, and a seventh CLINUVEL office is to be opened on continental Europe. Simultaneously, key European Medicines Agency (EMA) personnel familiar and charged with supervising SCENESSE® post-

authorisation were no longer in their roles and changes were seen. Two changes were made to the EMA rapporteurs appointed, and the latter requires our staff's attention and renewed introduction to CLINUVEL's dossier.

In providing a high-level overview of how political decisions directly impact the operations, workload and additional costs to a pharmaceutical company, I see how these changes unfortunately take time away from the development and research of our teams. However, ultimately our task during the geopolitical turbulence is to prevent disruption of EU supply and lead a commercially viable operation. Therefore, after gruelling recent months I am pleased to state that our teams have come through miraculously well and have been able to supply each single centre thus far without any treatment disruption. Our quality control and pharmacovigilance are of a high standard and, in cooperation with regulatory bodies, we have managed to transition out of the UK. The visits to the European Commission as well as collaboration with the EMA and UK regulator, MHRA, have been very positive to date.

As part of our EU supply, two porphyria expert meetings were held in Berlin and Florence in March and April. During this valuable interchange our teams received firsthand information on treatment, clinical observations and response rate. There is really no substitute for learning directly from trained medical staff about their onsite experiences and patients' response to the treatment. In Berlin we learned how the therapy continues to impact patients and their immediate families and partners, while questions were raised about the dose frequency, including whether patients could receive more implant injections per year, i.e. annual continuation of treatment. Subsequent analyses will be made by the centres to investigate the effectiveness of the desired increased treatment frequency.

In Florence, the Italian expert physicians and medical staff stated that patient demand remained high year on year, with the repeat prescriptions per annum unchanged. While patients were travelling long distances, the Italian centres expressed high patient satisfaction.

Further expert meetings are being held year on year to receive comments on CLINUVEL's clinical supply. CLINUVEL will be prominently represented during a number of conferences and meetings in 2019. We encourage our staff to present the Company actively during these meetings for wider audiences to learn about our story.

**CLINUVEL PRESENCE 2019**

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| March | Global Vitiligo Foundation Annual Meeting |
| | American Academy of Dermatology |
| | German EPP Expert Meeting |
| April | Goldman Sachs Emerging Leaders Conference |
| | Italian EPP Expert Meeting |
| | HC Wainwright Healthcare Conference |
| | BioCentury Future Leaders |
| May | UBS Global Healthcare Conference |
| June | 15th Sun Protection Conference |
| | Jefferies Healthcare Conference |
| August | World Congress of Light and Life |
| Sept' | International Congress on Porphyrins and Porphyrias |

So far this year, we have seen over 40 publications on the Company and 10 peer review articles mentioning SCENESSE® as the world's first systemic photoprotective drug. The presentation of the Company and its work is part of a continuum spanning decades.

Of interest (see the March 2019 News Communiqué) is the work achieved by the International Union of Photobiology and European Society for Photobiology to host the first World Congress on Light and Life in Barcelona in August.

Our media & communications team will post the various events through the social media channels to keep all informed of our activities.

## FDA REVIEW SCENESSE®

In this Communiqué we go deeper into the subject of FDA review and possible implications if it were to issue a Complete Response Letter (CRL).

Following the 8 July PDUFA date, set on 9 January, the US Food and Drug Administration (FDA) adhered to the review processes published by the Center for Drug Evaluation and Research (CDER). A great number of questions have been sent to our teams and, on tight deadlines, we have been asked to answer and provide information on each subject under review. The FDA's Division distributes the SCENESSE® dossier to its divisional heads and lead reviewers for each to specialise on a specific subject. It is fair to state that chemistry, manufacturing and controls (CMC) has received the lion's share of the attention thus far, not unexpectedly since the FDA attributes great significance to continuation of treatment even before a product reaches the market. Equally, issues such as GMP processes receive relatively more attention in the US than in the EU during the regulatory review stage.

As communicated by the FDA, the Company was due to receive further news and/or questions on labelling and post-marketing authorisation conditions on 8 April, but thus far no further news can be reported. The FDA is simply focussed on other issues in the review of the dossier, and in the coming weeks we may receive the awaited product labelling questions.

Frequently we have been asked what would theoretically happen in the case of a CRL, where the FDA does not grant market authorisation. The answer is not straight forward, since we first would analyse the grounds of rejection prior to making a full assessment. However, if there are no surprising findings, it is reasonable to presume that CLINUVEL would lodge a formal dispute resolution request to the FDA to discuss its dossier. Generally speaking, the aim of a CRL is to communicate to the sponsor that the FDA has identified deficiencies in the dossier or evidence presented and that it is not able – in its present form – to approve the new drug application until all of the deficiencies are satisfactorily addressed, (as per 21 CFR section 314.3). In terms of timeframe, a CRL can easily consume a year's delay before the dispute is resolved or the dossier is reviewed in a second instance.

We have consistently communicated that the legacy of CLINUVEL's lead drug, the complexity of the novel pharmacological technology, as well as the lack of scientific instruments at the current state of science, all make the dossier of this drug particularly challenging. All these factors have not deterred our teams from pursuing innovation in systemic photoprotection and building a company around this proposition. The target for our teams over a decade has been on management of the safety profile of SCENESSE® since the drug's "safety" forms the basis of the regulators' scientific opinion on risk, 50% of the risk-benefit evaluation. My views are that one could overcome objections or doubts about effectiveness ("benefit"), but one may never overcome regulators' views on safety (read: risk) of a proposed novel therapy. From this point of view, I am pleased with how our Chief Scientific Officer has managed the program pre- and post-authorisation and maintained our teams' focus on this one crucially important aspect for patients and the Company.

Another reason for the extensive attention to safety lies in the patients' management once the drug is on market (post-authorisation commitments). The more a company is geared towards managing risks, the better the position of a company to minimise possible future medical liabilities. Thus, the two reasons at the foundation of our approach to risk management of the product are closely connected and dictate our daily management.

A CRL would be an enormous setback for our teams and patients, and a juncture to reviewing the US market. On the other hand, an approval would mark the collective achievement of a team willing to devote a large part of their

careers to overcome three decades of failed attempts. We shall speak about this subject later in the year once the FDA has reached its decision.

## VITILIGO PROGRAM NORTH AMERICA

In previous News Communiqués we reported on our continuing program in vitiligo (depigmentation disorder) in North America. At present, a Global Vitiligo Expert Consortium has been formed, consisting of clinical experts in hypopigmentary disorders and vitiligo. These experts are deliberating on the design of the next clinical trial in North America and advice will be sought from the FDA, once an outcome is obtained for SCENESSE® in erythropoietic protoporphyria (EPP).

The deep-rooted distinction between non-segmental and segmental vitiligo was abandoned through the Vitiligo Global Issues Consensus Conferences. Vitiligo is now clinically being reserved for the umbrella term while the mixed types of vitiligo, segmental and non-segmental are captured under this one term. Nevertheless, the pathogenesis of all vitiligo cases differs distinctly and requires careful consideration when selecting the eligible patient populations for SCENESSE®.

With an eye on new developments in vitiligo, our teams are continuously monitoring a possible position of SCENESSE® among the disease entities of hypopigmented disorders and leucodermatoses. In our next Vitiligo Communiqué we will discuss the competitive landscape in vitiligo and the position of our lead melanocortin as well as the follow-on drug.

As it stands, it is likely that the next North American trial using SCENESSE® will be conducted in five centres. Simultaneous approval will be sought from the Institutional Review Boards, while each clinical centre is being assessed on its capacity to treat patients with a combination of narrow-band UVB (NB-UVB) light therapy. Following the results from the CUV102 and CUV103 studies, it has become apparent that the combination therapy of NB-UVB and SCENESSE® has a positive effect in Fitzpatrick skin types IV, V and VI. As time has gone by, more knowledge has emerged about the pathogenesis of the various types of vitiligo.

## INVESTOR AND PUBLIC RELATIONS

In reiteration, the programs of all teams over four continents are aligned and synchronised to ensure a consistent and global dissemination of information, and ensuring all staff within the Group of companies are abreast of all our activities. The ‘amuse de la symphonie’ is found in the planning and coordination of all our activities, while corporate news flow is incorporated in the presentations as it emerges. By executing on the annual timeline and events, we aim to address the 16 stakeholders we had identified in my 2017 AGM presentation as taking a unique interest in CLINUVEL. In differentiating these stakeholders, we seek to communicate to a minimum of 34 groups on the progress of the Company through various channels.

As our stakeholders are geographically located across the globe, the CLINUVEL website is an important channel for the timely dissemination of information on the Company’s activities and progress. Our IR team recently updated the website to improve information content and overall ease of navigation throughout the site.

As the Company grows and the FDA review progresses it is not surprising to learn that research coverage on CLINUVEL is being prepared and written by a number of buy-side analysts of mid-size to large institutions. As a

standard approach, we have publicly maintained that the Company does not commission or engage in the initiation of paid research coverage; we always held that the quality of the research coverage would follow the evolution of the Company upon its maturity. New rules were introduced in January 2017 through MIFID II (MiFID -2014/65/EU), standardising regulatory disclosures and providing investment services such as company research. The Directive was harmonised in 11 EU countries, while others are contemplating its introduction. While a number of brokerage firms and institutions had been writing short research notes for internal distribution for years, the combination of commercial use of SCENESSE®, long-term safety, first dividend in 2018, and US regulatory news flow has recently sparked the interest of Australian and US institutions.

I am confident that a possible FDA approval would further evoke the research interest in the Company, not only gauging this from the discussions our Investor Relations team is holding with various analysts.

The interest of several Australian and US institutions has also manifested during the current financial year in their investment in the Company. We welcome them as shareholders and thank them for becoming a valued supporter and part of the CLINUVEL story.

## RECENT QUESTION

I conclude by sharing the summary of a recent discussion held with a prominent fund manager in Sydney who posed following question: "*whether management had anticipated the current valuation of the Company, and whether it had taken longer to achieve than anticipated?*"

Generally speaking, one cannot predict an entity's value on the small/midcap end of the spectrum. Multiple known factors play a role – market conditions, calibre of the register, news flow and potential market size – while other unknowns can play their part. We are content with the evolution of the Company against the background of the many complex issues we have had to manage and overcome. I believe that specific and unique knowledge and information of underdeveloped scientific domains and technology will eventually lead to deeper expertise and competitive advantage, which is then possibly translated in enterprise valuation. The requisite to possible success is a monofocal and monotonous approach by a nimble team to execute in freedom. In terms of the temporal relationship between initiation of a development program and value achieved, the terminal value is relevant to make an assessment as to whether the technology is economically viable in a changing environment of pharmaceutical reimbursement.

SCENESSE®, thus far, fulfilled all criteria of a unique business case warranting, at critical points in time, the advancement of its technology for adults and for children. Surely, all of our senior managers would have desired the execution of the program in a linear and faster window, however the burden of proof and safety was always to rest on the shoulders of the first-mover, and therefore more time would be required. On balance, today's clinical and economic value justifies the development of the world's first systemic photoprotective drug in spite of all the obstacles our teams had to master. I believe the persistence displayed by our teams has become not only a recognisable trait of these professionals but also an entrenched corporate asset. Tenacity often remains underreported in business literature, but I hope this trait will form the basis for the future growth of CLINUVEL. Without falling into any sense of security, I wish to see our teams continue along this path of execution. Our task is to pass on this unique characteristic and modus operandi to the next generation of staff members who recently joined the Company. CLINUVEL's executive

management consciously tries to instil this attitude in all our staff members for them to adopt in their daily business.

In conclusion, while the probability of a US approval versus a CRL are equally weighted at this point of the Priority Review, our teams are striving to satisfy the frequent queries lodged by the FDA. As our Chair recently stated, given the legacy of the Company, we are determined to overcome all conceivable obstacles, and maintain a relentlessness in our approach.

On this note, I thank all stakeholders for your continuous belief and support.

Philippe Wolgen

[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

## ASX: CUV

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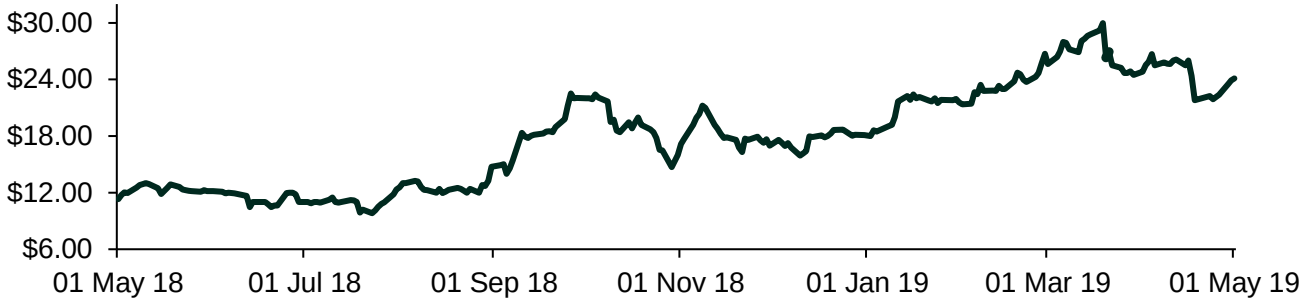
| Shares on issue | 48,960,633 |
| Fully diluted | 49,608,546 |
| Market cap (01 May 2019) | A$1.18b |

Share price

(ASX: CUV 1 May 2018-1 May 2019)




## Forward-looking Statements

This release contains forward-looking statements, which reflect the current beliefs and expectations of CLINUVEL's management. Statements may involve a number of known and unknown risks that could cause our future results, performance or achievements to differ significantly from those expressed or implied by such forward-looking statements. Important factors that could cause or contribute to such differences include risks relating to: our ability to develop and commercialise pharmaceutical products, including our ability to develop, manufacture, market and sell biopharmaceutical products; competition for our products, especially SCENESSE® (afamelanotide 16mg); our ability to achieve expected safety and efficacy results through our innovative R&D efforts; the effectiveness of our patents and other protections for innovative products, particularly in view of national and regional variations in patent laws; our potential exposure to product liability claims to the extent not covered by insurance; increased government scrutiny in either Australia, the U.S., Europe and Japan of our agreements with third parties and suppliers; our exposure to currency fluctuations and restrictions as well as credit risks; the effects of reforms in healthcare regulation and pharmaceutical pricing and reimbursement; 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; any failures to comply with any government payment system (i.e. Medicare) reporting and payment obligations; uncertainties surrounding the legislative and regulatory pathways for the registration and approval of biotechnology based products; decisions by regulatory authorities regarding approval of our products as well as their decisions regarding label claims; any failure to retain or attract key personnel and managerial talent; the impact of broader change within the pharmaceutical industry and related industries; potential changes to tax liabilities or legislation; environmental risks; and other factors that have been discussed in our 2018 Annual Report. Forward-looking statements speak only as of the date on which they are made and the Company undertakes no obligation, outside of those required under applicable laws or relevant listing rules of the Australian Securities Exchange, to update or revise any forward-looking statement, whether as a result of new information, future events or otherwise. More information on the forecasts and estimates is available on request. Past performance is not an indicator of future performance.

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