CLINUVEL Communiqué V

11 July 2019

CLINUVEL

Dear patients, shareholders, friends,

In this Communiqué we turn our attention to the most recent news communicated to the Company on 31 May by the US Food and Drug Administration (FDA): an extension of the scientific review time for SCENESSE® (afamelanotide 16mg) by three months.[1]

To those new shareholders who recently asked for more background information on CLINUVEL, we provide context to the Company's regulatory pathway and the long-awaited **FDA outcome expected on 6 October 2019 (the Prescription Drug User Fee Act ("PDUFA") goal date)**. We also discuss the history and context of CLINUVEL's mission to serve the clinical needs of US erythropoietic protoporphyria (EPP) patients, the FDA's possible outcomes, and the scenarios under which the Company would progress its lead technology.

US FDA REVIEW PROCESS SCENESSE®

Following requests from new shareholders, we clarify some of the facts pertaining to the US dossier of SCENESSE®. As stated in News Communiqué IV, at this stage of the regulatory process there is no information which can indicate or hint at the FDA outcome.

The regulatory review of a **new molecular entity (NME)** is expected to be more comprehensive and more challenging than a new drug application (NDA) of a known molecular entity.

The complexity of the review process is compounded by the use of a novel formulation, eluting the drug in a specific targeted manner, a new way of administering the hormone including injection site, and last, but not least, the *novel pharmacological concept of systemic photoprotection*. With regard to all these novel aspects, it is to be expected that regulatory authorities will have more internal debate compared to dossiers on known concepts and therapeutic modalities. The deliberations on novelty may also differ within each FDA division. This presumption has been confirmed by the lengthy deliberations of the European Medicines Agency (EMA) during their review of the SCENESSE® dossier from 2012 to 2014.

FDA TIMELINE 2019 SCENESSE®

9 Jan	PDUFA date set	✔
Jan	FDA clinical inspections	✔
Mar	Quality assessments	✔
8 Apr	FDA communication on labelling, post-marketing authorisation	Outstanding
May	Ongoing communication	✔
	Q&A clinical use post-MA	Outstanding
31 May	FDA extends PDUFA date by three months	✔
6 Sept	FDA communication on product labelling, post-marketing authorisation requirements, CUV commitments	
6 Oct	PDUFA DATE	

FDA RISK-BENEFIT SCENESSE®:

1. Marketing Authorisation (Approval)

OR

2. Complete Response Letter (Rejection)
   - Appeal grounds, Formal Dispute Resolution (FDR)
   - Timeframe for FDR
   - Further communication with DDDP

The ultimate mandate of the FDA is to weigh up the risks of the proposed product versus the benefits offered. The latter is expressed as overall effectiveness of the proposed therapy.

The balance between risk and benefit of the newly proposed pharmaceutical product is considered in the context of the patient population to be served, in this case the adult EPP community. Here it is imperative to reflect on the '*unmet medical need*', that is the unserved population awaiting an effective and safe treatment. Along these lines the FDA may have a considerable advantage over the EMA as the American agency is privy to longer-term and *continuous* safety data provided by ongoing use of the product in European patients. In 2014 the EMA had no access data from another continent where patients could be monitored in **real-time**, whereas the FDA benefits from the periodic safety update reports and Annual Reports submitted to the EMA since 2015. It is widely known that both the FDA and EMA share and exchange information on novel products, hence it is presumed that the FDA is fully aware of, and up to date on, the status of the SCENESSE® dossier.

Additionally, the FDA may be burdened by the past experiences of being too risk averse and withholding drugs from patients where there is a need and where no significant adverse safety risks exist to date. The results from the "thalidomide" era reverberated for a long time and the regulatory agencies worldwide recognised that they themselves were prone to "*Type I*" errors, allowing drug therapies on the market when more harm was being done to patients than good. Vice versa, as time lapsed, this decennium the regulatory agencies have acknowledged the existence of "*Type II*" errors, withholding a drug from the market when more benefit than harm could be expected based on the underlying data.

Procedurally, the FDA is bound to observe the set PDUFA dates during its review process, and, in case of doubt of being able to complete the work, it is free to extend the review timelines.

As this Communiqué goes to print, the SCENESSE® treatment can most likely be argued to fall under the latter regulatory category, and denial of market access would need to be founded on the basis of risk assessment, less on the grounds of effectiveness as experienced by European patients and prescribing physicians during years of controlled use.

However, the benefit-risk assessment reaches much further than as described above, with deliberations on CMC (including manufacturing processes) post-marketing licensing obligations and commitments, product claims, labelling and longer-term use weighing heavily on an agency. To the defence of the US FDA, it has been familiar with the afamelanotide product since 1988, the first occasion when US physicians obtained an investigational new drug (IND) approval for the product, albeit based on different chemical synthesis and final formulation. In essence, the historical context and development plan are equally important factors in the integral approach to grant the proposed therapy a license or not.

A **US marketing authorisation** would come in the form of specific labelling, possibly a *black-box warning* if the FDA deems the product of risk to public health, or when the risk profile is not yet sufficiently known. To put these considerations in perspective, the EMA provided SCENESSE® in 2014 a *black triangle* classification, indicating this medicinal product to be monitored more closely. In Europe, the Company has implemented a strict system of pharmacovigilance under an agreed Risk Management Plan. Counterintuitively, CLINUVEL embraces these measures since it lowers longer term clinical risk and provides more certainty on controlled use of the product. The FDA's proposed labelling can be expected – as per FDA's correspondence of 31 May – by **6 September**.

PROCESS IN EVENT OF COMPLETE RESPONSE LETTER

In the event the FDA would issue a **Complete Response Letter (CRL)** denying marketing authorisation, several procedural steps need to be followed by the FDA and the applicant company. Section 562 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bbb-1) directs the FDA to have dispute resolution procedures in place. An appeal by the applicant is considered by the FDA as a request for **Formal Dispute Resolution (FDR)**. The actual submission of an appeal is known as a **Formal Dispute Resolution Request (FDRR)**. Such matters pertain to scientific / medical disputes.

An FDR needs to contain basic elements:

- prior to submitting a FDRR, the applicant is recommended to ask the FDA review office responsible for the decision to reconsider.
- no new data should be submitted in the FDRR.
- the applicant can request a meeting with the deciding official for the appeal, to discuss the appeal issue(s).
- either the applicant or FDA can request the scientific dispute to be referred to an Advisory Committee.
- once an FDRR is submitted, the FDA has 30 calendar days to respond.
- if an applicant's FDR is rejected, the applicant can appeal the same matter to the next higher management level, and so forth all the way to the FDA Commissioner.
- an End of Review Conference (Type A meeting via teleconference or face to face) can be requested by the applicant within three months of a CRL.

SUMMARY OF FDA POSITION

In previous communiqués we have commented on the frequency of interaction with the FDA on the NDA for SCENESSE®. This is routine during the evaluation of any application. The agency asks questions and the Company provides written and verbal responses. Following a recent response, the FDA deemed the amount of documentation provided such that they required additional time for evaluation. According to the FDA guidelines, they have the discretion to extend the PDUFA date at any time.

Although the extension of the evaluation of CLINUVEL's NDA for three months is not our favoured outcome, we remind all stakeholders that if insurmountable outstanding scientific issues were identified during the filing stage, and/or major deficiencies were identified during their due diligence to date, the FDA has always been able to issue a **Refusal to File (RTF)** and/ or recommend a withdrawal of the NDA. Since these events had not occurred, we embrace a cautious optimism and bear the patience to a long-awaited outcome.

I conclude by expressing my gratitude to our global teams who are working incessantly to gain approval of SCENESSE® for the US EPP patients. Sadly, there remains treatment inequality at present, whereby those US EPP patients who can afford the international journey continue to seek bi-monthly treatment in Europe. However, for a large majority of US patients, this option is too burdensome and unfortunately, they remain untreated.

We all look forward to the user fee goal date of **6 October** and are hopeful that the treatment will eventually come to patients in the United States.

INVESTOR AND PUBLIC RELATIONS

Due to the ongoing progress of the Company and interest in the upcoming FDA news, the demand for our teams to present at conferences and seminars has increased in recent months. As an update on CLINUVEL's active presence globally, we share with you our progress against the calendar for 2019.

CLINUVEL PRESENCE 2019		
Mar	Global Vitiligo Foundation Annual Meeting	✔
	American Academy of Dermatology	✔
	German EPP Expert Meeting	✔
Apr	Goldman Sachs Emerging Leaders Conference	✔
	Italian EPP Expert Meeting	✔
	HC Wainwright Healthcare Conference	✔
	BioCentury Future Leaders	✔
May	UBS Global Healthcare Conference	✔
Jun	15th Sun Protection Conference	✔
	Jefferies Healthcare Conference	✔
	World Congress of Dermatology	✔
	British Porphyria Association meeting	✔
Aug	World Congress of Light and Life	
Sept	International Congress on Porphyrins and Porphyrias	
Nov	German EPP patient association meeting	

These presentations enable CLINUVEL to brief a wide range of stakeholders. These specialised conferences provide the Company with wider exposure, as well as the opportunity to obtain feedback from the sector analysts.

When updates to news flow are discussed the international presentations are posted to the Australian Securities Exchange and on our website (www.clinuvel.com). The dual publication enables all our stakeholders to monitor the latest information available. On this note, I thank all those who have supported the Company.

Philippe Wolgen

[1] Media Release - US FDA extends PDUFA date for SCENESSE® Melbourne, Australia 3 June 2019 (https://www.clinuvel.com/media-release-us-fda-review-for-scenesse-extended-3-months).

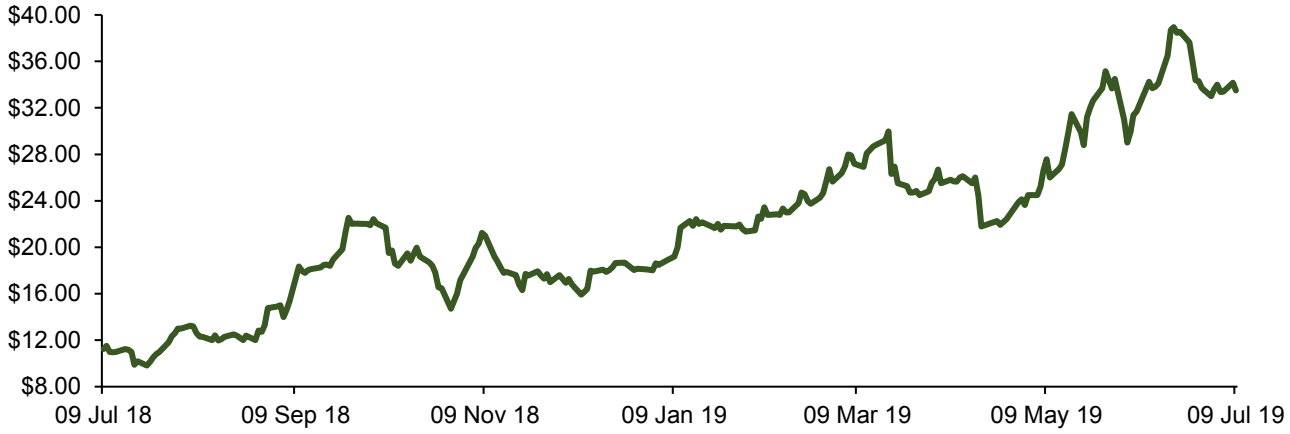
SCENESSE® (afamelanotide 16mg) is approved in Europe as an orphan medicinal product for the prevention of phototoxicity in adult patients with EPP. Information on the product can be found on CLINUVEL's website at www.clinuvel.com.

ASX: CUV

Shares on issue	48,960,633
Fully diluted	49,608,546
Market cap (9 July 2019)	A$1.64b

Share price

(ASX: CUV 9 July 2018 - 9 July 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.

Contact

Level 11, 535 Bourke St
Melbourne, 300 Vic, Australia

+61 3 9660 4900
+61 3 9660 4909

www.clinuvel.com