CLINUVEL

ASX ANNOUNCEMENT

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Afamelanotide in fair-skinned Parkinson's patients

Preclinical models show benefit of afamelanotide as MC1R therapy in Parkinson's Disease

*CLINUVEL has released a separate **Technical Note** to accompany the announcement of its new program in Parkinson's Disease (PD), see here*

EXECUTIVE SUMMARY

- Phase IIa CUV901 study receives ethics, regulatory approval for 2024 start
- Loss of function of melanocortin-1 receptor (MC1R) found in PD patients
- First time evaluating patients with early PD symptoms
- PD models show benefit of MC1R therapy with afamelanotide in PD

CLINUVEL today announced a novel clinical program evaluating afamelanotide as a treatment in early-stage Parkinson's Disease (PD or Parkinson's) in fair-skinned patients. The program objectives are to determine whether afamelanotide – through melanocortin-1 receptor (MC1R) activation – is able to lower α-synuclein (a toxin) in blood levels in PD patients, and positively affect neurons of the midbrain. MC1R is known to be a key receptor in brain and skin cells.

In large studies, it was found that fair-skinned patients have a higher risk of PD associated with a malfunctioning MC1R.[a, 1-2] Since afamelanotide is known to optimise the function of the MC1R, it is hypothesised that the drug treatment would have a positive effect in PD by lowering α-synuclein, as recently demonstrated in preclinical studies.[2–3] Afamelanotide is marketed in Europe and the USA as SCENESSE® for patients diagnosed with erythropoietic protoporphyria (EPP).

Evidence for use of afamelanotide in Parkinson's Disease

Worldwide, individuals born with red hair and fair skin are found to have a loss of function of MC1Rs – expressed on skin and brain cells – and to carry an increased risk of Parkinson's and melanoma.[4 – 5]

In various Parkinson's models it has been illustrated that an MC1R-binding drug – such as afamelanotide – enables cellular protection against α-synuclein, a toxic substance found in the neurons of PD patients. In preclinical models, the use of afamelanotide has been shown to improve neurodegenerative conditions.[6]

Following decades of human use, it has been well established that afamelanotide strongly binds to MC1R and optimises cellular functions (signalling) through pharmacological activation.

The CUV901 study is the first human study evaluating the effect of afamelanotide in PD as a therapeutic option.

Study design – CUV901

The Phase IIa CUV901 study will evaluate six fair-skinned patients with early symptoms of PD who are not yet receiving medicinal therapy.

The first objectives of the open-label study are to focus on the safety of afamelanotide, while determining α-synuclein in blood, and assessing visual changes in the midbrain. Secondary endpoints are to assess cognitive functions. The study design has obtained ethics and regulatory approval.[b]

Patients between 40 and 85 years old will receive 11 doses of 0.08 mg per kilogram body weight of afamelanotide on each day of drug administration, over a study duration of 56 days. The first patients are expected to enrol before the end of 2024.

Commentary

"We are immensely pleased to initiate a highly innovative study for afamelanotide," CLINUVEL's Chief Scientific Officer, Dr Dennis Wright said. "It marks a real breakthrough to conduct this study in Parkinson's after lengthy regulatory discussions and preparation.

"At the heart of the problem in Parkinson's lies the loss of dopamine producing neurons in the brain due to toxicity caused by α-synuclein. There is now evidence that afamelanotide – by binding to MC1R – could maintain stability and integrity of the affected neurons and slow down progression of the disorder.

"By analysing blood and brain scans of the substantia nigra, we will learn of afamelanotide's potential effect in Parkinson's. The ability to do something for this group of patients results from decades of clinical research and a focus on translating inhouse knowledge," Dr Wright concluded.

About Parkinson's Disease

Parkinson's Disease is a progressive and degenerative disorder caused by oxidative stress and neuroinflammation. Symptoms consist of progressive loss of motor functions and increased tremor, as well as dementia, depression, sleep disorders and a range of autonomic dysfunctions. Ultimately PD can result in adverse clinical outcomes, contributing to over 200,000 deaths annually.

PD is characterised by the loss of dopamine producing neurons predominantly in the substantia nigra (SN) of the brain, while a high accumulation is seen of the neurotoxin α-synuclein.

It is thought that treatment of patients with early symptoms provides a better prognosis.

The current standard of care in PD is levodopa, monoamine oxidase B (MAO-B) inhibitors or dopamine agonists, which all aim to provide symptomatic relief but are not able to slow neurodegeneration. These medications become less effective as the disease progresses and escalating doses may be required.

– END –

Notes

[a] Epidemiological analyses from 120,000 US individuals revealed that fair skinned Parkinson's patients have an increased risk of developing melanoma in a lifetime, both populations carrying a defective MC1R function.[1] Afamelanotide is known to possess very high binding property (agonist) to MC1R and offer cellular protection by overcoming a loss-of-function of the receptor in patients with fair skin with red hair phenotype.

[b] Alpha-synuclein (α-synuclein) – as a measure of disease progress - is used as a biomarker in blood samples of PD patients.

References

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6. Cai, W., et al. (2022). Melanocortin 1 receptor activation protects against alpha-synuclein pathologies in models of Parkinson's disease. Molecular Neurodegeneration, 17(1), 16.
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About CLINUVEL PHARMACEUTICALS LIMITED

CLINUVEL (ASX: CUV; ADR LEVEL 1: CLVLY; Börse Frankfurt: UR9) is a global specialty pharmaceutical group focused on developing and commercialising treatments for patients with genetic, metabolic, systemic, and life-threatening, acute disorders, as well as healthcare solutions for specialised populations. As pioneers in photomedicine and the family of melanocortin peptides, CLINUVEL's research and development has led to innovative treatments for patient populations with a clinical need for systemic photoprotection, assisted DNA repair, repigmentation and acute or life-threatening conditions who lack alternatives.

CLINUVEL's lead therapy, SCENESSE® (afamelanotide 16mg), is approved for commercial distribution in Europe, the USA, Israel, and Australia as the world's first systemic photoprotective drug for the prevention of phototoxicity (anaphylactoid reactions and burns) in adult patients with erythropoietic protoporphyria (EPP). Headquartered in Melbourne, Australia, CLINUVEL has operations in Europe, Singapore, and the USA. For more information, please go to https://www.clinuvel.com.

Authorised for ASX release by the Board of Directors of CLINUVEL PHARMACEUTICALS LTD.

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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; the COVID-19 pandemic and/or other world, regional or national events affecting the supply chain for a protracted period of time, including our ability to develop, manufacture, market and sell biopharmaceutical products; competition for our products, especially SCENESSE® (afamelanotide 16mg), PRÉNUMBRA® or NEURACTHEL®; our ability to achieve expected safety and efficacy results in a timely manner 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, Israel, China 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®, PRÉNUMBRA® or NEURACTHEL® 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 and consumer based products; decisions by regulatory authorities regarding approval of our products as well as their decisions regarding label claims; our ability 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 2023 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 preliminary and uncertain forecasts and estimates is available on request, whereby it is stated that past performance is not an indicator of future performance.

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