CLINUVEL

TECHNICAL NOTE

AFAMELANOTIDE AS MC1R-TARGETED THERAPY IN PARKINSON'S [PD]

SUMMARY

In brief, key to the novel story of addressing PD with melanocortins is the finding that fair-skinned PD patients share a common trait with fair-skinned melanoma patients, in that a certain receptor, the melanocortin-1 receptor (MC1R), is malfunctioning, increasing the risk of both diseases.

In preclinical models it has been shown that rescuing MC1R function through afamelanotide treatment positively affects dopamine deficits seen in Caucasian patients at high risk of developing PD.

Afamelanotide is a commercial agent which has been shown to optimise MC1R function. It is now believed that binding of afamelanotide to MC1R may provide protection from neurotoxins like α-synuclein (α-Syn), the culprit in PD patients.

The novel objective is to develop a MC1R-targeted therapy in Parkinson's.

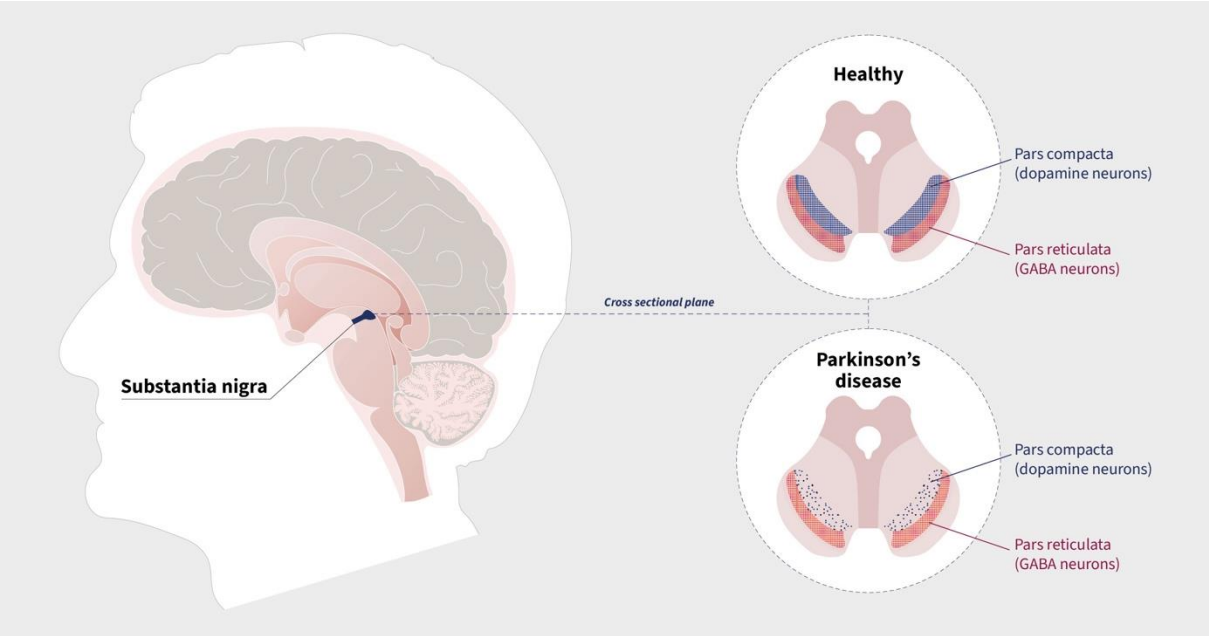
Afamelanotide is now being evaluated in Parkinson's Disease (PD), since various experiments and models have shown that the drug substance can protect fragile dopamine-producing neurons.

It is well accepted that the central problem in PD is the loss of dopamine-producing neurons in the substantia nigra (SN) due to aggregation of α-synuclein (α-Syn). Modern attempts to treat PD aim to restore neuronal integrity and the nigrostriatal pathway.

- Recent research focused on the fact that people with darker skin types and hair colour (brown/black) show lower PD incidence rates compared to people on the lighter end of the spectrum (blonde/red hair and fair/freckled skin).
- The MC1R plays a pivotal part in brain and skin, and shares its function in the UV-darkening response, anti-oxidative and anti-inflammatory effects.

Preclinical evidence has confirmed that *intact MC1R regulated cellular signalling pathways* play an important role in maintaining dopaminergic neuronal survival. This is key to arresting progress in PD. Therefore, based on in-vitro and in-vivo evidence to date, there is an evident rationale for MC1R targeted therapies for PD.

Afamelanotide is a potent MC1R agonist, activating cells of the skin and central nervous system. Effective activation of MC1R is shown to protect against alpha-synuclein (α-Syn) provoked neuronal damage in PD. Much evidence points to the unique role MC1R has in regulating brain cells.



Substantia Nigra (in a healthy individual vs a PD patient)

Afamelanotide – as an analogue of a biological human hormone produced by brain and skin cells – exerts various properties:

(i) optimisation of MC1R signalling
(ii) protection of dopaminergic neurons
(iii) strong anti-oxidative properties
(iv) anti-oncotic properties (reduces inflammatory swelling)

Afamelanotide has been found in experiments to protect against ischaemic stroke, intracerebral haemorrhage, traumatic brain injury, Alzheimer's disease (AD), and other neuroinflammation associated disorders.

Significantly, in recent preclinical models it has been found that afamelanotide peripherally administered protects dopaminergic neurons, forming a basis of making the drug substance available for evaluation in PD patients.

CLINICAL STUDY DESIGN CUV901

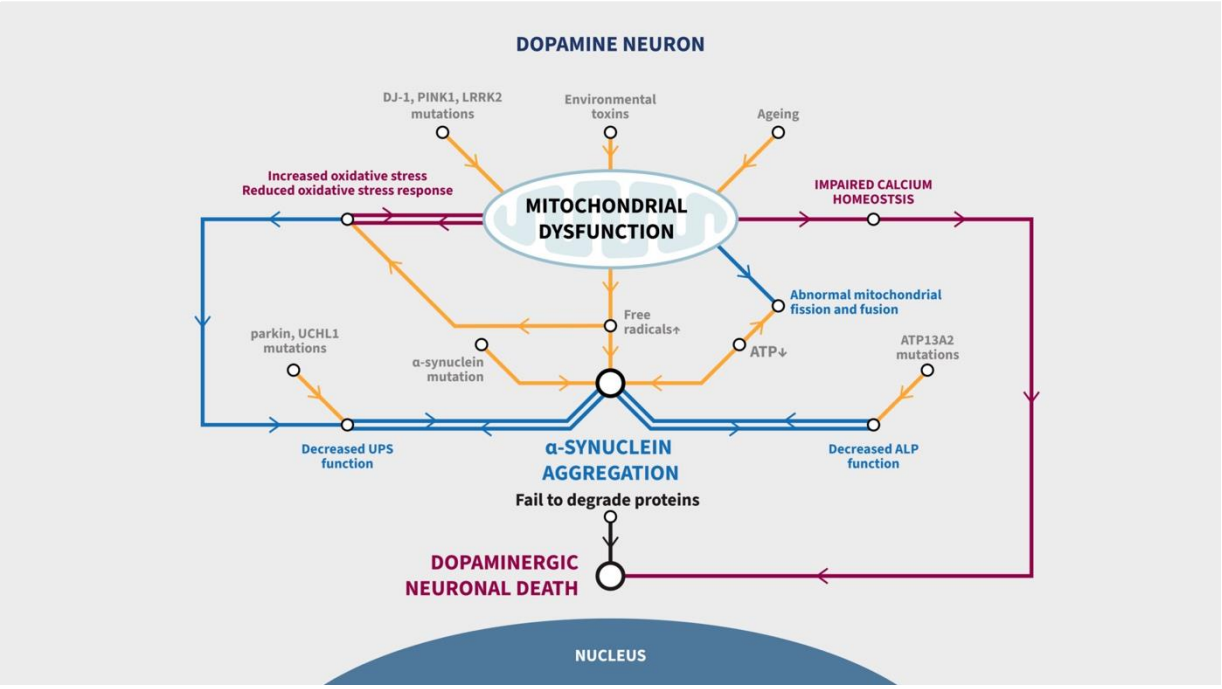
CLINUVEL has commenced a new program, focused on evaluating afamelanotide in PD. Early onset PD patients with fair skin types between 40 and 85 years will be administered 11 doses of afamelanotide on intermittent days over a total study period of 56 days.

Blood samples will be taken to measure the toxic α-Syn and inflammatory markers in blood. In addition, magnetic resonance images taken of the midbrain.

Before and during the treatment phase, patients' overall symptoms will be monitored using the Unified Parkinson Disease Rating Scale (UPDRS), with cognitive assessments made through the Mini Mental State Examination (MMSE).

PARKINSON'S DISEASE

The cause of PD remains unknown, however strong indications point to oxidative stress, mitochondrial dysfunction, neuronal network alteration, and neuroinflammation as a multifactorial cause. There is increasing evidence that peripheral, as well as central inflammation (brain) trigger the start of the neurodegeneration seen in PD.



Mitochondria dysfunction and dopaminergic cell death in PD pathogenesis.

This leads to a compromised dopaminergic system with greater susceptibility to PD-associated mitochondrial toxin α-Syn toxicity in the substantia nigra (SN). Gradual degeneration of dopamine-producing hormones is seen as neuromelanin in the brain is decreasing or lost.

Under physiological conditions, α-Syn is predominantly found in the axon terminals of presynaptic neurons. There are a number of neurodegenerative disorders with the common feature of α-Syn aggregation, commonly known as synucleinopathies. Clustering of α-Syn is found in the cytoplasm of neurons or glia. It is known from imaging that motor symptoms in PD start when approximately 50% of substantia nigra dopamine neurons are lost due to accumulation of α-Syn.

Pigment is found in the midbrain, the role of neuromelanin in the substantia nigra however remains uncertain. This pigment is markedly different from skin's eumelanin, in that neuromelanin is formed spontaneously as a chain of oligomers.

Neuromelanin has strong anti-oxidative properties in the brain, while also known to be a chelating substance binding organic amines and metal ions.

– END –

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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.

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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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