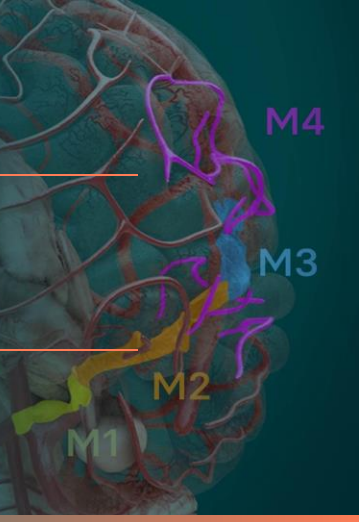
CLINUVEL

COMPANY ANNOUNCEMENT

First stroke patient treated with PRÉNUMBRA® Instant

CUV803 study evaluating new afamelanotide product in stroke patients



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	Börse Frankfurt:	UR9
	ADR Level 1:	CLVLY

Executive Summary

- First stroke patient treated with PRÉNUMBRA® Instant (afamelanotide)
- Afamelanotide as intervention for moderate to severe patients lacking treatment options
- CUV803 to focus on safety, changes in neurological and cognitive functions

CLINUVEL has started its second stroke trial (CUV803) with the first patient receiving PRÉNUMBRA® Instant (afamelanotide), a new formulation. The Phase II study is evaluating the safety and efficacy of afamelanotide therapy in arterial ischaemic stroke (AIS) patients who are ineligible for the standard of care, consisting of either intravenous thrombolysis (IVT) or endovascular thrombectomy (EVT).

In total, up to twelve adult AIS patients will be enrolled, consisting of six patients with mild to moderate, and six with moderate to severe stroke, as reflected by the National Institutes of Health Stroke Scale (NIHSS).[1]

"Afamelanotide has the potential to reduce the impact of stroke and prevent further brain damage," CLINUVEL's Head of Clinical Operations, Dr Pilar Bilbao said. *"We advance some key learnings from the first study and try to explore the clinical benefits of a flexible dose of afamelanotide in CUV803.*

"Given the paucity of available therapies for the majority of stroke patients, the opportunity to provide a new treatment option is great. By being diligent and vigilant, we advance clinical management of stroke."

Afamelanotide in arterial ischaemic stroke

AIS is caused by an arterial clot blocking blood supply to the brain. The resulting lack of oxygen and glucose causes immediate tissue death, with a larger area of the surrounding brain – known as the *penumbra* – at risk of further damage, due to fluid formation and inflammation. Patients suffer irreversible damage which, if not fatal, often leads to the permanent loss of mobility and/or speech. AIS accounts for around 85% of the 15 million

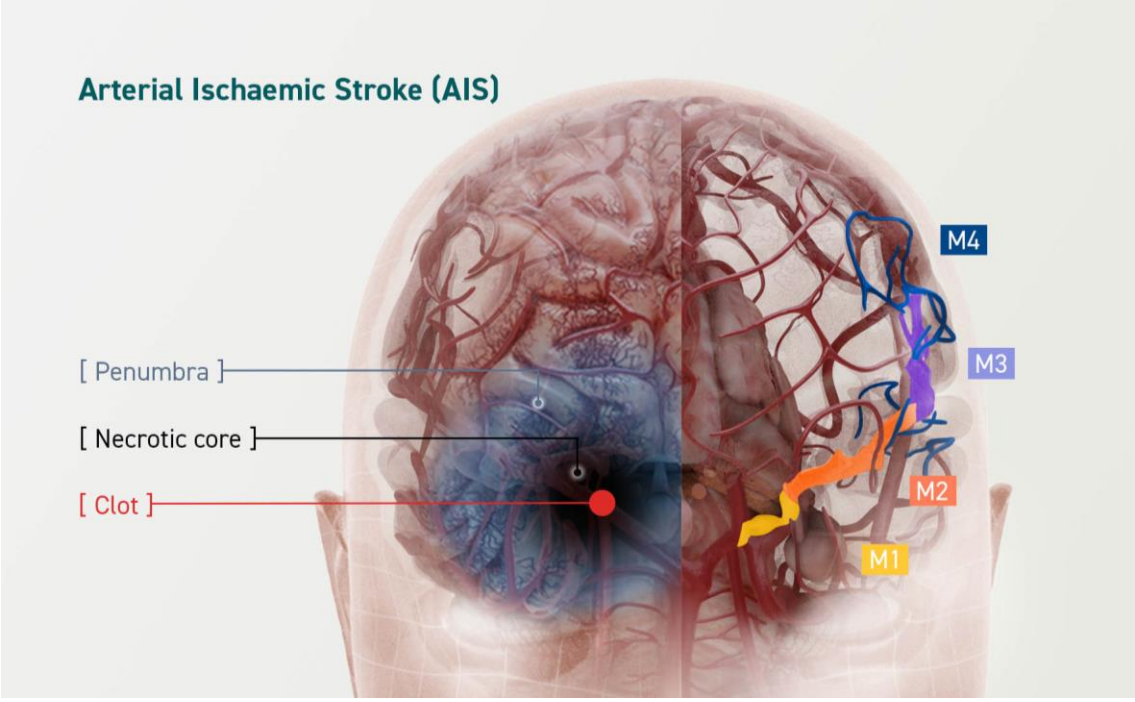

Figure 1 *A clot lodged in a brain vessel causes a central zone of dead brain tissue, known as the necrotic core. The area surrounding the core, called the penumbra, is at immediate risk of tissue death: this brain tissue can be returned to normal function if immediate intervention with a drug or clot removal can be offered. The right side of the image shows the middle cerebral artery (MCA), branches from M1–M4.*

strokes incurred globally each year, with an estimated 70–80% ineligible for treatment with IVT or EVT.

Melanocortins and afamelanotide are known to offer neuroprotection, providing potent antioxidative effects. Afamelanotide is suggested to increase blood flow and nutrients to the affected areas, as it is active on blood vessels and reduces fluid formation. It thereby protects tissue and restores the blood brain barrier.

The flexible PRÉNUMBRA® Instant formulation allows physicians to make faster dosing decisions, taking into account each individual patient's clinical need. The new afamelanotide formulation is expected to provide a faster clinical response. In stroke, the speed of intervention is associated with an improved chance of recovery.

In 2022, the first study in AIS, CUV801, five of six patients diagnosed with a mild to moderate stroke showed improved neurological function following afamelanotide, administered as a controlled-release implant. The treatment was well tolerated.

CUV803 study

Patients enrolled in the CUV803 study will receive an individually determined dose of PRÉNUMBRA® Instant for up to five consecutive days following a stroke. The study is conducted in acute neurological units in European expert centres. The study's objective is to evaluate the interventional drug as a possible option in AIS, evaluating its safety and efficacy. The NIHSS will be used to assess overall disease severity. Cognitive functions will be measured using the Mini Mental State Examination (MMSE), and activities of daily living will be evaluated using the Activities of Daily Living questionnaire. Standardised neuroimaging tools (MRI/CT) will assess the volume and blood flow of the brain areas, affected by the stroke comparing imaging on Day of admission, Day 3, and Day 42. Patients will be followed up for 42 days.

"The CUV803 study has been designed to maximise the information and data captured, engaging experts and regulators ahead of a larger pivotal trial.," Dr Bilbao said. *"We are particularly keen to understand the safety and effects of a new dosage form in more severely affected patients, who currently have a very poor prognosis. The chance to make a considerable clinical impact drives all of us."*

First results from CUV803 are expected in late 2023.

– END –

[1] The National Institutes of Health Stroke Scale (NIHSS) consists of 15 tests to evaluate neurologic functioning and impairment caused by a stroke. A clinical assessment is made on the basis of consciousness, language, neglect, visual-field loss, extraocular movement, motor strength, muscle control, speech, and sensory loss. A trained clinician assesses the patient's ability to answer questions and perform specific activities. In general, the evaluation is made in less than 10 minutes. The scale categorises severity according to mild (score 1-4), moderate (5-15), moderate-severe (16-20) and severe (≥21).

Annex I: Following ASX Best Practice

Name of trial
A Phase IIa, Open Label, Proof of Concept Study to Evaluate the Safety of Aqueous Afamelanotide Solution in Patients with acute Arterial Ischaemic Stroke (AIS) who are ineligible for Intravenous Thrombolysis (IVT) or Endovascular Thrombectomy (EVT)

Primary endpoint
To evaluate the safety of afamelanotide in AIS patients.

Secondary endpoints
Evaluate the impact of afamelanotide on neurological functions in patients with AIS

Identify changes in reperfusion of the ischaemic penumbra in AIS patients, specifically the ischaemic core and/ or the penumbral ischaemic zone (salvageable tissue)

Assess cognitive functions and activities of daily living in AIS patients.

Blinding status
Open label.

Product development status
Good Manufacturing Practice (GMP) Standard.

Treatment method and dose levels
PRÉNUMBRA® Instant

Number of trial subjects
Up to twelve AIS patients.

Subject selection criteria
To be eligible to enter the study, patients must meet the following inclusion criteria:

- Male or female subjects with a diagnosis of Arterial Ischaemic Stroke (AIS)
- No severe disability prior to stroke
- Written informed consent obtained from patient and or immediate family or carer(s) prior to study-start.

Further safety related exclusion criteria apply.

Trial location
Specialist stroke centres in Europe.

Duration of trial
42 days

Trial standard
In compliance with Good Clinical Practice (GCP) and ICH guidelines.

About CLINUVEL PHARMACEUTICALS LIMITED

CLINUVEL (ASX: CUV; ADR LEVEL 1: CLVLY; XETRA-DAX: 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 specialized 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 2022 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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