CLINUVEL

COMPANY ANNOUNCEMENT

# AFAMELANOTIDE REDUCES DNA PHOTODAMAGE IN XERODERMA PIGMENTOSUM

***First Phase II results show decrease in UV-induced skin damage***

**Melbourne, Australia, 16 January 2023**

| | |
|---|---|
| ASX: | CUV |
| XETRA-DAX: | UR9 |
| ADR LEVEL 1: | CLVLY |

**A TECHNICAL EXPLANATION TO THIS ANNOUNCEMENT HAS BEEN RELEASED SEPARATELY:**

**TECHNICAL NOTE**


**EXECUTIVE SUMMARY**

Analyses following afamelanotide administration demonstrate:

1. Reduction of CPDs, photodamage
2. Increase in p53, tumour suppressor gene (variable)
3. Increase in gamma-H2AX expression
4. Increase in UV tolerance (reduced erythema)
5. Increase in melanin density
6. Drug substance well tolerated by XPC patients.


CLINUVEL today shared the first results of a phase II study (CUV156) evaluating afamelanotide in patients with xeroderma pigmentosum (XP), a genetic disease characterised by a defect in DNA skin repair (NER[1] defect). Analyses showed a decrease in ultraviolet (UV) light-induced DNA skin damage following treatment. This study constitutes the first time globally that permission was granted to expose XPC patients to a novel systemic therapy. Despite living in fully shielded and isolated conditions, this population suffers from frequent skin cancer(s), resulting in a median life expectancy of 30 years.

## INTERIM RESULTS CUV156

The CUV156 study is conducted over ten weeks, with a six month follow up. Patients are administered six doses of afamelanotide as well as controlled UVB radiation on unexposed areas of the skin (buttocks), with DNA markers evaluated. UVB serves to evaluate tolerance (MED[2]) to the point of inducing DNA skin lesions, cyclobutane pyrimidine dimers (CPDs[3]), characteristic for photodamage*. Skin biopsies are taken of UVB irradiated and non-irradiated anatomical sites before and after treatment and analysed through immunohistochemical staining (IHC; microscopic analyses).

In the three patients, a reduction of CPDs was found (**Table 1**), most specifically in the deeper layer of the skin (basal layer of epidermis).

In two patients, the skin specimens showed an increase in p53 expression[4], indicating activation of natural defence mechanisms. P53 serves as a biological marker in man for suppressing tumour formation.

In three patients, γH2AX (a DNA marker[5]) showed an increase, indicative of the activation of cellular repair mechanisms of the skin.

All three patients showed reduced erythema when increasing UVB dosing, whereby two showed an increase in MED[24], indicating the ability to tolerate higher UV doses without incurring 'skin burns'.

| CUV156 | CPDs[3] | p53[4] | γH2AX[5] | MED[2] | MD[6] |
|---|---|---|---|---|---|
| **Patient 1** | -48.0% | -15.2% | +17.1% | Decrease | Increase |
| **Patient 2** | -17.1% | +36% | +1.65% | Increase | Increase |
| **Patient 3** | -4.5% | +16.5% | +15.47% | Increase | Increase |
| **Overall clinical assessment** | **Positive results** | **Variable results, increase** | **Positive results** | **Variable results, positive** | **Positive results** |

**Table 1: First results of CUV156, evaluating afamelanotide in three XPC patients.**

In all patients, an increase in melanin density (MD[6]) was seen, suggestive for the formation of skin pigmentation acting as a physical UV barrier.

Overall, clinical assessment by the treating physicians was that afamelanotide provided effective systemic photoprotection in XPC patients. These first positive results justify further progression of the CUV156 study in XPC and the ongoing CUV152 study in XPV patients.

## CLINICAL RELEVANCE OF THE FIRST RESULTS

Due to inherited defects in the DNA repair process, the XP population is globally known to experience the *highest risk* of skin cancer development. A therapy providing systemic photoprotection, reducing photodamage, and assisting DNA skin repair – nucleotide excision repair (NER) and base excision repair (BER) – would be of high value to these patients. This therapeutic approach bears relevance for a wider population at higher risk of skin cancers. Melanocortin therapy would potentially benefit those affected by medical conditions, active in high-risk environments (reflective surfaces, high altitude, high UV intensity), or whose genetic make-up (those with non-pigmented skin, blue eyes, and fair hair colour) places them at higher risk of incurring solar damage.

## COMMENTARY

"*With great enthusiasm, and most of all to the satisfaction of XPC patients, we have learned for the first time that afamelanotide provides assisted DNA repair by reducing photoproducts and decreasing the risk factors of skin cancer development*," CLINUVEL's expert genomic scientist, Dr Jessica Nucci said.

"*Although, a small sample for now, in many ways this is an immense clinical step forward in systemic photoprotection and addressing photodamage of the skin. We are all very much looking forward to the data from other XP patients to speed up the extension of commercial use of this drug for untreated patients,*" Dr Nucci concluded.

## MODE OF ACTION AFAMELANOTIDE

Afamelanotide belongs to the family of proopiomelanocortins which exhibit a number of documented and published properties, such as the activation of melanin, the optimisation of cellular response (signalling) to UV skin damage, the assistance in DNA damage, the reduction of oxidative damage, reduction in oncosis (swelling), and decrease in inflammatory processes.

**– End –**

[1] *nucleotide excision repair*

[2] *Minimal Erythemal Dose is the dose administered by UVB to provoke the first visible reddening, erythema, of the radiated skin surface, representing the first DNA skin damage incurred.*

[3] *cyclobutane pyrimidine dimers, photodamage expressed as single strand DNA adducts*

[4] *p53 is a protein in the nucleus of the cell which controls cell division and cell death*

[5] γ2HAX is the phosphorylated form H2AX, which is formed as a response to the induction of double strand breaks

[6] *melanin density was measured at 6 anatomical sites following the administration of afamelanotide, representing a physical barrier providing photoprotection against UV and HEV radiation of the skin.*

[*] *photodamage is known to present as photoproducts within a DNA strand within skin cells, expressed as CPDs, 6-4-PPs, Dewar isomers, pyrimidine hydrate, thymine glycols, dipurine adducts.*

**For more in-depth information, the reader is referred to the technical explanation and note attached:**

**TECHNICAL NOTE**

**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 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); 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, 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® 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 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 the forecasts and estimates is available on request. Past performance is not an indicator of future performance.

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