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	Börse Frankfurt:	**UR9**
	ADR Level 1:	**CLVLY**

Note to readers: this Technical Note on CLINUVEL's DNA Repair Program accompanies the release of results from CLINUVEL's CUV151 study on 15 August 2023 and assumes knowledge of the Technical Note release on 2 February 2023.

In this technical note, five brief chapters are discussed

i. Executive Summary
ii. DNA Damage and Repair
iii. Use of Melanocortins
iv. Early Clinical Results
v. DNA Repair Program – First Results

i. Executive Summary

Through a program of studies to date, CLINUVEL has generated data on the ability of its drug SCENESSE® (afamelanotide 16mg) to protect skin from the damaging effects of ultraviolet (UV) and visible light. The DNA Repair Program has been designed to focus on understanding the therapeutic potential of SCENESSE® treatment for those individuals who are at highest risk of light-induced DNA skin damage (photodamage), built on the understanding that melanocortins – a family of hormones and their analogues which includes afamelanotide – have been shown in-vitro to not only protect skin, but to repair photodamage. This prevention and repair of photodamage may have considerable implications for the use of melanocortins in the long-term reduction of photoageing and skin cancer rates.

This Technical Note explores the data generated to date from the clinical evaluation of afamelanotide in fair-skinned healthy volunteers (Fitzpatrick Skin Types I-III) and patients with xeroderma pigmentosum (XP), following the release of results from the CUV151 study.

ii. DNA Damage and Repair

UV radiation is a potent mutagen, reacting with DNA in skin cells and damaging the structure of the DNA helix. These DNA lesions, known as "photoproducts", occur at the rate of several hundred thousand per hour of UV exposure and, if left unrepaired, can ultimately lead to the formation of skin cancer. The human body has developed mechanisms to repair or eliminate this damage in order to protect from photocarcinogenesis. Yet, due to genetic variance, many of us have some form of inefficiency or defect in DNA repair (or indeed, in the

case of most XP patients, a near-total lack of capacity), leading to an increased risk of skin cancer from photoproducts.

The most common photoproducts, cyclobutane pyrimidine dimers (CPDs) and 6-4 pyrimidine-pyrimidone photoproducts (6-4PPs), are generally repaired through the nucleotide excision repair (NER) pathway, which enables the removal and replacement of the defective segment of the DNA helix, restoring the cell to a stable state and maintaining a healthy balance in the skin.

For a more in-depth look at DNA damage and repair, and the use of melanocortins, please see Scientific Communique VIII – DNA Repair Mechanisms, published in December 2020, and Scientific Communique IX – Beyond Pigment, the Melanocortin 1 Receptor (MC1R) in DNA Repair, published in March 2021.

Histopathological techniques (using biopsied skin) allow us to evaluate the rates of CPDs in cells, giving an objective measure of DNA damage at a certain point in time. By controlling UV exposure in a clinical setting, and evaluating CPDs over time, we are able to understand the impact of UV radiation, and the function of NER pathways, giving rise to an understanding of the DNA damage and repair mechanisms. When combined with further indicators of skin and DNA damage, such as minimal erythema dose (MED), melanin density, and other markers, one begins to develop a more complete picture of photodamage and the potential of an interventional therapy in high-risk individuals.

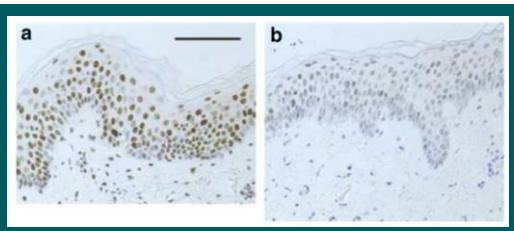
iii. Use of Melanocortins

Afamelanotide is an analogue of the naturally occurring alpha-melanocyte stimulating hormone (alpha-MSH), with both belonging to the family of melanocortins. The natural hormone alpha-MSH is produced by a number of cells across the body, including skin cells as a protective response to UV insult. While its best recognised mechanism in skin is melanogenesis – known commonly as the "tanning response" – is itself photoprotective, it is the more intricate cellular responses which are now better understood and may unlock even greater potential for the development of melanocortin-based therapeutics. Afamelanotide, which has been structurally adapted from alpha-MSH to increase its potency and efficacy to be administered as a drug, is the first melanocortin to be fully evaluated for these cellular responses, with the challenge accepted by CLINUVEL's scientific teams.

CLINUVEL's DNA Repair Program builds upon existing expertise, based on both pre-clinical and clinical work, as well as two decades of safety data from the use of the controlled-release injectable SCENESSE® formulation. The approach recognises that photodamage is multifaceted and seeks to explore the effects of afamelanotide treatment across a range of markers, with the ultimate goal that melanocortins form part of the photoprotective and reparative regimens for both patients and high-risk consumers.

iv. Early Clinical Results

Relevant to the release of the CUV151 results are the findings from an early photoprotective program conducted in healthy volunteers which looked at the induction of sunburn cells (apoptotic cells), MED, and DNA damage following the administration of an aqueous injectable solution of afamelanotide and, later, an early implant formulation. The earlier study (EP002) published as *Barnetson et al (2006)* showed that MED significantly increased after two months of discontinuous treatment for those individuals receiving afamelanotide compared to untreated volunteers, and a significant reduction of sunburn cells as well as reduction in thymine dimers (a form of CPD) after 90 days (with a greater reduction seen in fair skin types).



Taken from *Barnetson et al (2006)*, photomicrographs of a single subject show a reduction in thymine dimers (brown staining) from baseline (a, 83% of cells positive) and day 90 (b, 14% of cells positive) following afamelanotide treatment.

The later study, EP008, with a similar placebo-controlled model showed a significant difference in the erythema dose response 28 days after afamelanotide treatment, indicating a better photoprotective response following treatment. In both early studies, subjects administered afamelanotide saw a significant increase in melanin density.

v. DNA Repair Program – First Results

Since the conduct of the early volunteer studies, the understanding of the role of melanocortins, the melanocortin-1 receptor (MC1R) and skin cells in photoprotection and DNA repair has advanced, adding weight to their findings, as well as enabling greater evidence capture in clinical studies. In parallel, the 16mg afamelanotide implant (SCENESSE®) has enabled a controlled-release of afamelanotide to patients, considerably reducing the amount of drug required to achieve melanogenesis, while utilising a more convenient injectable implant.

This has led to study designs which seek to better evaluate the impact of treatment during the acute phases of UV insult, while ensuring a photoprotective and DNA repair response is achieved at lower dosing. Preliminary results from the first study of the program – CUV156 in XP patients with the "C" complementation group – have so far shown that afamelanotide decreased CPDs in three patients, two of whom also showed an increase in MED and γH2AX (a further marker of DNA damage). A variable impact was also shown on p53, the so-called guardian of the genome, which controls cell division and cell death (apoptosis). For XP patients, who are at extreme risk of skin cancer, these results are encouraging, requiring verification, while the drug was well tolerated.

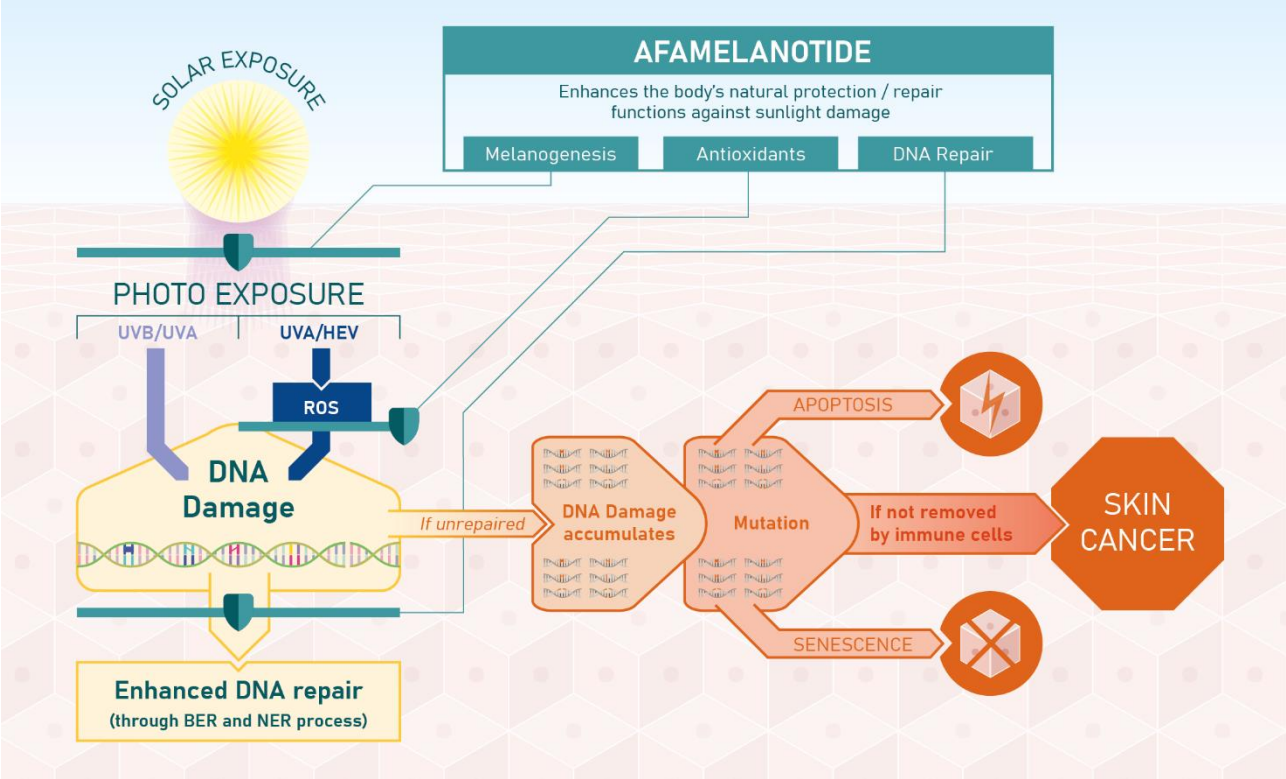
Two sets of results from CUV151 have now been released, reinforcing data seen across the program to date. Results released in February 2023 showed that UV-erythema ("provoked sunburn damage") was significantly reduced, while MED increased. Today's announcement gives rise to new findings, showing that a single dose of afamelanotide significantly reduces DNA damage (CPDs) both immediately after UV exposure (15 minutes) and 24 and 48 hours thereafter, indicating a lasting protective and reparative effect of treatment in healthy volunteers. Further analyses of skin biopsies are ongoing to assess the impact on other markers (including p53 and γH2AX) which, if confirmed, will only strengthen the justification for the ongoing development and use of melanocortins in individuals at the highest risk of photodamage. A summary of select data relevant to the DNA repair program is provided below.

Preventing and Repairing DNA Photodamage: Summary of Clinical Evidence

Clinical Indicator	Detail	Clinical Data
Melanin density	Melanogenesis, the "tanning response" is a natural protective response. A 1% increase in melanin density has been associated with 40% increase of skin melanin levels, leading to a reduction of UV-induced skin damage of approximately 50%.	Afamelanotide has been shown to consistently increase melanin density, particularly in high-risk Fitzpatrick skin types I-III, but also in XP.
Minimal erythema dose (MED)	A quantification of the threshold dose required to stimulate the signs of solar erythema (sunburn, reddening of the skin), and first indication of DNA damage, following UV exposure.	MED increase seen following afamelanotide treatment in healthy volunteers & XP patients.
DNA Damage, CPDs*	Photodamage expressed as single strand DNA adducts.	Reduction in CPDs shown following afamelanotide treatment in healthy volunteers & XP patients.
DNA Repair, γH2AX*	The phosphorylated form of H2AX, which is formed as a response to the induction of double strand breaks in DNA.	Increase in γH2AX seen in XP patients (CUV156), analyses in CUV151 ongoing.

P53*	The "guardian of the genome", a protein in the nucleus of the cell which controls cell division and cell death.	Variable results seen in CUV156, analyses in CUV151 ongoing.
Sunburn cells*	Measure of damaged apoptotic cells, evaluated through biopsies of UV-irradiated skin.	Reduction in sunburn cells seen in early healthy volunteer studies.

* Clinical indicator evaluated by analyses of biopsies, generally taken after UV-irradiation of the skin.



The figure above summarises the potential of afamelanotide to prevent and repair photodamage following exposure to UV and high energy visible (HEV) light. CLINUVEL's program is currently focused on those individuals at highest risk of photodamage.

References

Barnetson, R., Ooi T., Zhuang L., Halliday G.M.,Reid C.M., Walker P.C., Humphrey S.M. and Kleinig M.J., [Nle4-D-Phe7]-a-Melanocyte-Stimulating Hormone Significantly Increased Pigmentation and Decreased UV Damage in Fair-Skinned Caucasian Volunteers. Journal of Investigative Dermatology (2006) 126, 1869–1878.

For further references, see CLINUVEL's Technical Note, 2 February 2023.

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CLINUVEL has issued a separate general release on the results from the CUV151 study. Please go to www.clinuvel.com.

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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Head of Investor Relations
Mr Malcolm Bull, CLINUVEL PHARMACEUTICALS LTD

Investor Enquiries
https://www.clinuvel.com/investors/contact-us

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.

Contact


+61 3 9660 4900
+61 3 9660 4909


www.clinuvel.com


Level 11, 535 Bourke St
Melbourne, 3000 Vic, Australia