Melbourne, Australia, 2 February 2023	**ASX:**	**CUV**
	Börse Frankfurt:	**UR9**
	ADR Level 1:	**CLVLY**

In this technical note, four brief chapters are discussed

i. Executive summary
ii. Relevance of CUV151 results
iii. Erythema and Minimal Erythema Dose (MED)
iv. How does UV cause solar damage?

i. Executive summary

Ultraviolet radiation (UVR) exposure leads to erythema, which is the first indication of DNA skin damage, known as photodamage. Cumulative photodamage can lead to (photo-)ageing and skin cancer. Non-invasive techniques like spectrophotometry are able to quantify erythema as an objective sign of DNA damage.

Research had shown how afamelanotide can assist in the reduction of photoproducts following UVR. For the first time, it was observed in the CUV151 study that the 16mg afamelanotide implant can reduce erythema following the dosing of one implant in fair-skinned volunteers.

Likewise, melanin density was shown to be increased, very much confirming many previous studies on afamelanotide.

The reduction of DNA damage, expressed as erythema as a first sign, lowers DNA mutations, and the risk of skin cancers.

ii. Relevance of CUV151 results

CLINUVEL today released first results in of nine healthy volunteers from the CUV151 study, part of the Company's DNA Repair Program. Analyses showed that there was a significant decrease in UV-erythema dose response and an increase in minimal erythemal dose (MED) when skin was irradiated with different doses of UV after one 16mg afamelanotide implant.

It was also shown that melanin density increased in all subjects six days after the administration of one afamelanotide implant. It is known that afamelanotide stimulates the production of melanin in the epidermis (top layer of the skin), which works as a mechanical protective barrier which also has antioxidative properties. This is one possible mechanism by which afamelanotide increases the amount of UVR needed to generate erythema. Melanin density starts increasing progressively following drug administration, and it may be not visible to the naked eye after just six days, but non-invasive techniques such as spectrophotometry allowed it to be precisely measured, showing a statistically significant increase in melanin density.

An increase in melanin density is of high relevance to daily living, as approximately a 1% increase in melanin density has been associated with 40% increase of skin melanin levels, leading to a reduction of UVR skin damage of approximately 50%.

The combination of significant reduction in UV-erythema dose response and melanin increase - following one implant of afamelanotide - is clinically meaningful, as this correlates to a decrease in solar DNA damage and risk of skin cancer. These results are in agreement with all the peer reviewed research published to this point, which shows that melanocortin hormones can activate the production of melanin, optimise cellular response to UV damage, assist in the repair of DNA damage, and reduce oxidative damage, as well as decrease inflammation.

iii. Erythema and Minimal Erythema Dose (MED)

Sunburn, otherwise known as solar erythema, is an acute dermal response to UVR, in particular to UVB (290-320 nm). The artificial provocation of erythema is a long-standing objective method to quantify photodamage and develop methods of photoprotection, looking at both the dose of UVB required and the overall extent of damage from incremental dosing.

Minimal Erythema Dose (MED) is a measurement used regularly to examine skin tolerance to UV in the clinic and within experimental studies. Specifically, MED is a quantification of the threshold dose required to stimulate the signs of solar erythema, reddening of the skin, and first indication of DNA damage, following UVB exposure. It is used primarily to determine sun protection factor (SPF), calculate suitable doses for light therapy, and during the diagnosis of photoreactive disorders (phototesting).

Importantly, and relevant to CLINUVEL's focus, MED has also had a suggestive role as a minimally-invasive alternative to other common clinical approaches to evaluate UV-induced DNA damage.

A baseline MED on unprotected skin depends mainly on skin types (Fitzpatrick skin type or phototype), with darker complexions conveying greater natural protection. It is now well described that MED increases by steady increments between each sequential Fitzpatrick phototype and thus MED and melanin density are correlated. Lower MED is consistently associated with lighter skin.

In CLINUVEL's DNA Repair Program, MED is one of several measures used to evaluate overall skin damage and repair following UV insult. Xeroderma pigmentosum (XP) patients, for example, may show different response to MED depending on their complementation group. Generally, XP-A, XP-D and XP-E patients have a delayed and a lower MED compared to healthy volunteers. In contrast XP-C, XP-F and XP-V show normal MED.

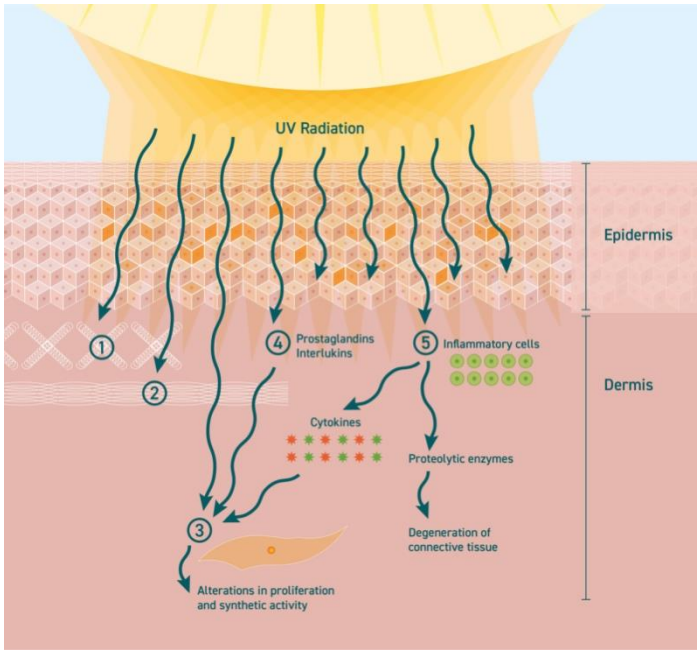

Figure 1 *The possible effects of UV radiation on skin photoageing. UVA can directly affect collagen (1), and elastin fibres (2) and fibroblasts or endothelial cells (3), leading to wrinkling and skin sagging. UVR has been shown to liberate various mediators from the epidermis such as prostaglandins and interleukins (4) which may affect fibroblasts or endothelial cells. In addition, there is accumulation of inflammatory cells (5) which can also affect cellular functions or by liberating various enzymes to degrade connective tissue.*

iv. How does UV cause solar damage?

Actinic damage (also referred to as solar or photodamage, or photoageing) is progressive, chronic skin damage resulting from repeated and intensive UVR exposure. The damage can present as wrinkling, elastosis, actinic keratosis,

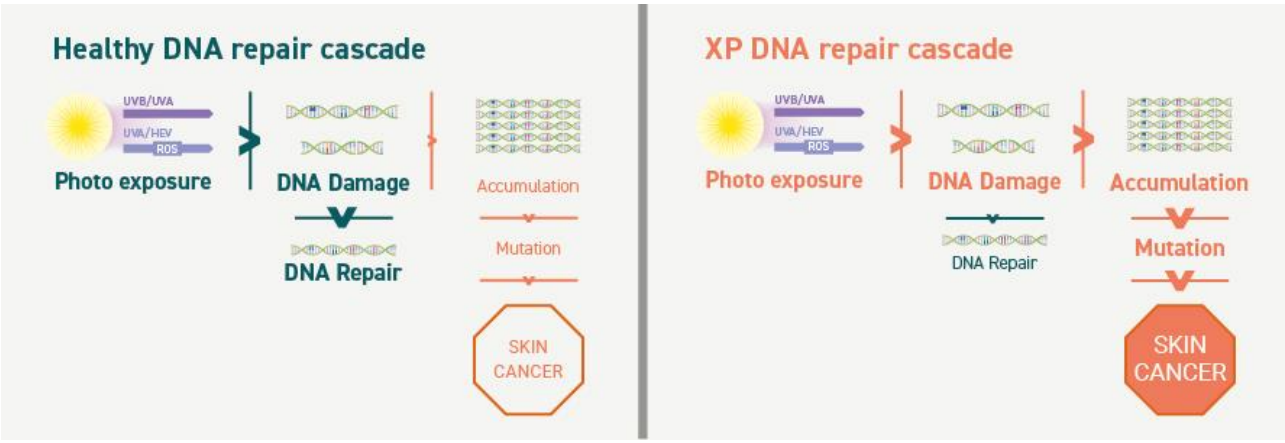

Figure 2 *DNA repair cascade*

irregular pigmentation, telangiectasia, and the development of malignant skin tumours, typically arising on chronically sun-exposed skin surfaces such as face, nape, and arms.

The most critical risk factor associated with the development of actinic damage is cumulative UV exposure. Other risk factors include fair skin and hair (Fitzpatrick skin types I and II), male gender, baldness in men, older age, geographic latitude, and immunosuppression. Countries such as Australia, which have large Caucasian populations and are located close to the equator, have prevalence rates of actinic damage as high as 40–50% in adults 40 years and older.

Histologically, actinic damage can result in several changes in dermal and epidermal connective tissues such as increases in elastin, and collagen damage, and alteration of resident cells in keratinocytes, melanocytes, fibroblasts, and endothelial cells.

Due to numerous contributing factors and its complex nature of developmental process, there have been discrepancies in the duration and dose of UV to induce measurable actinic damage. The dose of UV correlates with the degree of actinic damage (the higher of the UV energy, the more severe the skin damage). Repeated and regular exposure to low dose UV can also trigger the chronic skin transformation.

References

1. Tan, Y. et al. Identification of factors associated with minimal erythema dose variations in a large-scale population study of 22 146 subjects. *Journal of the European Academy of Dermatology and Venereology* 34, 1595–1600 (2020).
2. Bilaç, C., Şahin, M. T. & Öztürkcan, S. Chronic actinic damage of facial skin. *Clinics in Dermatology* **32**, 752–762 (2014).
3. Hashim, P. W., Chen, T., Rigel, D., Bhatia, N. & Kircik, L. H. Actinic Keratosis: Current Therapies and Insights Into New Treatments. *J Drugs Dermatol* **18**, s161-166. (2019).
4. Oikarinen, A., Peltonen, J. & Kallioinen, M. Ultraviolet Radiation in Skin Ageing and Carcinogenesis: The Role of Retinoids for Treatment and Prevention. *null* **23**, 497–505 (1991).
5. Lavker, R. M., Gerberick, G. F., Veres, D., Irwin, C. J. & Kaidbey, K. H. Cumulative effects from repeated exposures to suberythemal doses of UVB and UVA in human skin. *Journal of the American Academy of Dermatology* **32**, 53–62 (1995).
6. Pinto, D., Trink, A., Giuliani, G. & Rinaldi, F. Protective effects of sunscreen (50+) and octatrienoic acid 0.1% in actinic keratosis and UV damages. *J Investig Med* **70**, 92–98 (2022).
7. Ichihashi, M. & Ando, H. The maximal cumulative solar UVB dose allowed to maintain healthy and young skin and prevent premature photoaging. *Experimental Dermatology* **23**, 43–46 (2014).

8. Young, A. R. *et al.* The Similarity of Action Spectra for Thymine Dimers in Human Epidermis and Erythema Suggests that DNA is the Chromophore for Erythema. *Journal of Investigative Dermatology* **111**, 982–988 (1998).
9. Kohli, I. *et al.* The impact of oral Polypodium leucotomos extract on ultraviolet B response: A human clinical study. *Journal of the American Academy of Dermatology* **77**, 33-41.e1 (2017).
10. Wu, S. *et al.* History of Severe Sunburn and Risk of Skin Cancer Among Women and Men in 2 Prospective Cohort Studies. *Am. J. Epidemiol.* **183**, 824–833 (2016).
11. Berg, R. J. W., Ruven, H. J. T., Sands, A. T., de Gruijl, F. R. & Mullenders, L. H. F. Defective Global Genome Repair in XPC Mice Is Associated with Skin Cancer Susceptibility But Not with Sensitivity to UVB Induced Erythema and Edema. *Journal of Investigative Dermatology* **110**, 405–409 (1998).
12. Sugaya, M. *et al.* Whole-exome sequencing and host cell reactivation assay lead to a diagnosis of xeroderma pigmentosum group D with mild ultraviolet radiation sensitivity. *The Journal of Dermatology* **48**, 96–100 (2021)
13. 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

– End –

CLINUVEL has issued a separate general release on the first 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 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

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