ASX Announcement

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SCENESSE® IN DNA REPAIR

CLINUVEL to confirm cellular DNA repair in rare disease xeroderma pigmentosum (XP)

A separate media release – *in simple non-technical terms* – has been lodged outlining the aims and objectives of the DNA Repair Program. CLINUVEL will post background information on XP to its social media channels: Twitter | Facebook | Instagram | LinkedIn

EXECUTIVE SUMMARY

- CLINUVEL to confirm in clinical trials the role of SCENESSE® in cellular UV-induced DNA repair
- XP is a rare genetic life-threatening and mutilating disorder making patients susceptible to 10,000-fold risk of skin cancers throughout their lives (median survival of 30 years - prevalence 1:450,000)
- Clinical objectives for SCENESSE®:
  1. systemic photoprotection to skin cells;
  2. optimisation of the response of skin cells to UV radiation;
  3. anti-oxidative capacity;
  4. elimination of photoproducts (chemical damage to DNA);
  5. increased activity of DNA repair genes (as part of NER and/or BER); and
  6. reduction of cell death (apoptosis) following UV exposure.

Melbourne, Australia, 10 September 2020

CLINUVEL (UK) LTD, a wholly owned subsidiary of CLINUVEL PHARMACEUTICALS LTD, today announced it is evaluating SCENESSE® (afamelanotide 16mg) in patients with the rare disorder xeroderma pigmentosum (XP)[1] to progress its novel DNA Repair Development Program.[1] SCENESSE® is understood to protect and repair DNA, a concept that will now be confirmed in the clinic.

DNA DAMAGE AND REPAIR

Ultraviolet (UVB of wavelengths 290-320 nm and UVA of 320-400 nm) and high energy visible (HEV, 400-600 nm) light penetrate human skin leading to cellular oxidative stress and damage to DNA within the nucleus of skin cells. This damage consists of changes to the DNA structure (photoproducts)[2] which, if left unrepaired, can replicate and increase the risk of skin cancers, such as melanoma.

Under normal conditions, human biology is capable of repairing DNA damage through nucleotide excision repair and/or base excision repair (NER and BER, respectively), in which defective strands of DNA are "snipped" and removed, and replaced by the correct DNA sequences. XP patients, organ transplant recipients and people of Anglo-Saxon origin with red hair, blue eyes and fair skin are at the highest risk of developing skin cancers because they have either insufficient or defective NER and BER, i.e. a reduced capacity to repair damaged DNA.

STAGED DEVELOPMENT PROGRAM: SCENESSE® IN DNA DAMAGE REPAIR

Scientific evidence supports the use of afamelanotide, the active ingredient in SCENESSE®, for photoprotection and repair of UV-induced DNA damage.

During the development of SCENESSE®, a number of categories of scientific evidence have been accumulated:

1. systemic photoprotection to skin cells;
2. optimisation of the response of skin cells to UV radiation;
3. anti-oxidative capacity;
4. elimination of photoproducts (chemical damage to DNA);
5. increased activity of DNA repair genes (as part of NER and/or BER); and
6. reduction of cell death (apoptosis) following UV exposure.

Figure 1 illustrates how the DNA Repair Program has placed emphasis on the safety of patients and volunteers exposed to afamelanotide – more than 10,000 doses in over 1,400 subjects – during 20 years of clinical use, a requisite to being able to complete the clinical use of the hormone as a DNA restorative drug in patients at the highest risk of contracting skin cancers.

FIGURE 1

SCENESSE® (afamelanotide 16mg)
'DNA REPAIR' – STAGED R&D TO DATE

S1. Short-term safety, repeat-dose toxicology

S2. Proof of concept – human subjects
- reduction in apoptosis (cell death) following UV radiation

S3. Long-term safety in clinical trials (20 years)

S4. Mid-term safety commercial use (4 years)

S5. Scientific evidence DNA repair
- in vitro, ex-vivo data
- reduction in apoptosis in humans

S6. Clinical evidence in
- XP (clinical evaluation)
- healthy volunteers (clinical evaluation)

Stages S1 to S5 have been evaluated by the Company and regulatory authorities as satisfactory and complete, enabling Stage 6 of clinical investigation in the scope of SCENESSE® as a DNA-regenerative pharmaceutical therapy. Clinical stage S6 consists first of a Special Access Program in XP to confirm the safety of the drug in this highest-risk population, followed by a pilot study in XP-C (CUV150), and a parallel control study in healthy volunteers (CUV151) who are exposed to UV radiation under standardised conditions.

The exact biochemical and cellular mechanisms of UV-induced cellular damage and repair by SCENESSE® are explained in technical terms in Figure 2, attached below.

XERODERMA PIGMENTOSUM

XP is a group of disorders expressing eight different genes (XP-A to G, and V) involved in the NER process, with a collective prevalence of approximately 1:450,000 in the European population. Due to these genetic deficiencies in DNA repair proteins, XP patients are 10,000-fold more susceptible to skin cancers including melanoma, necessitating them to shield from ambient and outdoor light from birth onwards. The consequences of exposure to non-ionising radiation (UV) are severe as many XP patients suffer loss of extremities, facial anatomy such as ears, and eye-sight due to the lack of fully functional DNA repair. The median age of survival for XP patients is approximately 30 years.

SCENESSE® will first be evaluated in XP-C patients – carrying a defect in gene 3p25.1 – since it is the most prevalent form of XP in Europe and the United States. XP-C is characterised by an insufficiency of the damage recognition protein XP-C required for efficient DNA repair of skin cells.

CLINUVEL will publish when the first XP-C patient has been administered with SCENESSE®.

COMMENTARY

"*We are delighted to be able to proceed with the landmark evaluation of SCENESSE® in XP and putting the final piece of evidence together for the melanocortin product as a DNA-regenerative pharmaceutical solution,"* CLINUVEL's Chief Scientific Officer, Dr Dennis Wright said.

"Worldwide, there is no therapy available in XP and we are compelled to help these patients since they lead a compromised and short life.

"The clinical challenge is enormous as we aim to confirm defined effects from SCENESSE® in XP patients which will need to lead to the conclusion that DNA regeneration is assisted and accelerated. I can only applaud our team who have been remarkably patient, working over many years to meet regulatory and ethics requirements," Dr Wright said.

"As we progress through the two clinical studies we will be evaluating available assays needed to validate positive effects on DNA repair in XP patients," CLINUVEL's Clinical Operations Manager, Dr Pilar Bilbao said. *"It is an exciting time as we are already starting from a positive base knowing that SCENESSE® reduces apoptotic cells following UV exposure; now the next objective is to demonstrate this very effect in XP patients.*

"We expect the first results in 2021 and will monitor the safety of the XP patients receiving SCENESSE® day to day. It is of high relevance to confirm the role of SCENESSE® in UV radiation damage regeneration and will improve the general understanding how to reduce skin cancer risk for many of us," Dr Bilbao said.

- END -

[1] SCENESSE® (afamelanotide 16mg) is approved in the European Union as an orphan medicinal product for the prevention of phototoxicity in adult patients with erythropoietic protoporphyria (EPP). SCENESSE® is approved in the USA to increase "pain-free" light exposure in adult EPP patients with a history of phototoxicity. Information on the product can be found on CLINUVEL's website at www.clinuvel.com.

[2] Cyclobutane pyrimidine dimers (CPDs), 6-4 pyrimidine pyrimidone dimers (6-4 PPs) and Dewars isomers are formed within seconds of exposure of unprotected skin to radiation, causing breaks in the strands of DNA.

Authorised for ASX release by the Board of Directors of CLINUVEL PHARMACEUTICALS LTD

About CLINUVEL PHARMACEUTICALS LIMITED
CLINUVEL PHARMACEUTICALS LTD (ASX: CUV; NASDAQ INTERNATIONAL DESIGNATION ADR: CLVLY; XETRA-DAX: UR9) is a global biopharmaceutical company focused on developing and delivering treatments for patients with a range of severe genetic, skin, and systemic disorders. As pioneers in photomedicine and understanding the interaction of light and human biology, CLINUVEL's research and development initially has led to innovative treatments for patient populations with a clinical need for photoprotection and repigmentation. These patient groups range in size from 5,000 to 45 million worldwide. CLINUVEL's lead compound, SCENESSE® (afamelanotide 16mg), was approved by the European Commission in 2014 and the US Food and Drug Administration in 2019 for the prevention of phototoxicity (anaphylactoid reactions and burns) in adult patients with erythropoietic protoporphyria (EPP). More information on EPP can be found at http://www.epp.care. CLINUVEL is advancing its portfolio of melanocortins, among which is PRÉNUMBRA® for the treatment of several critical disorders. Headquartered in Melbourne, Australia, CLINUVEL has operations in Europe, Singapore, and the USA. For more information please go to http://www.clinuvel.com.

SCENESSE® and PRÉNUMBRA® are registered trademarks 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 2019 Annual Report and 2020 Preliminary Final 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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Figure 2: The exact biochemical and cellular mechanisms of UV-induced cellular damage and repair by SCENESSE® are explained in technical terms.