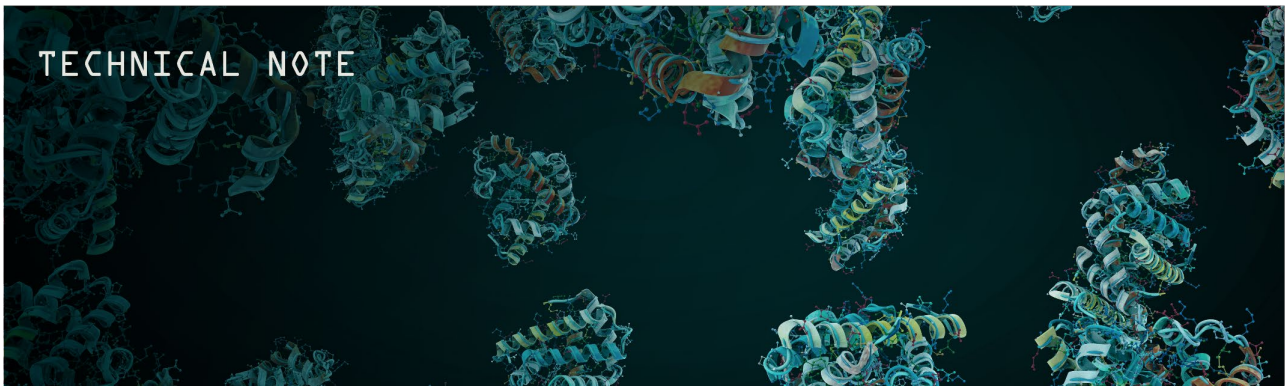
Adrenocorticotropic hormone (ACTH)

CLINUVEL



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Developing a melanocortin pipeline

On 23 January 2023 CLINUVEL announced an update on its portfolio of melanocortin molecules, having completed critical analytical method development work for its adrenocorticotropic hormone (**ACTH**) product lines, to be commercialised as *NEURACTHEL® Instant* and *NEURACTHEL® Modified-release*. ACTH is the latest melanocortin announced in CLINUVEL's pipeline, but its development is grounded in many years of expertise working with this family of hormones and their analogues and understanding how a greater clinical potential could be realised for ACTH and other molecules. **This technical note** explores some of the foundational knowledge underpinning the use of melanocortins in the clinic, as well as looking at their potential future use.

Clinical use of melanocortins – now and the future

Melanocortin research has been ongoing for several decades. A number of melanocortins molecules have been synthesised to maximise their binding to a target receptor and subsequently developed for clinical use, targeting a range of melanocortin receptors.

A number of clinical programs have been initiated by industry to evaluate the potential of melanocortins as therapeutics. To date, only five molecules targeting melanocortin receptors have been approved for clinical use by at least one regulatory agency, while around a dozen are in various stages of clinical development. The rates of melanocortin development program discontinuation, however, are high, with a number of high-profile products failing at various stages of clinical development, from preclinical to Phase III clinical trials.

CLINUVEL's clinical program is focusing on several melanocortins, while the Company has disclosed programs to evaluate the therapeutic potential of six key properties for use in severe unmet medical needs:

- Systemic photoprotection – preventing and reducing phototoxicity and damage caused by ultraviolet (UV) and high energy visible (HEV) light
- Anti-oxidant activity – quenching free radicals
- Anti-oncotic activity – counteracting oedema and fluid
- Vasoactive activity – acting on blood vessels
- DNA repair – regeneration of UV-induced DNA damage
- Repigmentation – activating melanin in skin

CLINUVEL has already commercialised SCENESSE® (afamelanotide 16mg) for the prevention of phototoxicity in adult patients with erythropoietic protoporphyria (EPP) and is now seeking to extend the use of this product to adolescent EPP patients, with a label extension currently under review by the European Medicines Agency. In EPP, afamelanotide is understood to provide both systemic photoprotection – preventing damage to patients' skin by providing a biological barrier of eumelanin – as well as activating strong anti-oxidant activity to scavenge free radicals and reduce oxidative stress.

Current clinical trial programs are focused on the potential of afamelanotide as a DNA repair therapy (see the recent technical note accompanying the release of results from the CUV156 study in xeroderma pigmentosum), as a vasoactive and anti-oncotic therapy in arterial ischaemic stroke, and a repigmentation therapy in vitiligo. Broader programs are planned in undisclosed severe disorders with unmet medical need. Table 1, below, provides a summary of CLINUVEL's melanocortins in development.

Product/s	Active ingredient/s	Formulation(s)	Patient/user populations	Indications / targeted use
SCENESSE®	Afamelanotide	Controlled-release	Adults, adolescents	Erythropoietic protoporphyria (EPP), xeroderma pigmentosum (XP), vitiligo
PRÉNUMBRA®	Afamelanotide	Instant & Modified-release	Adults, children	Stroke, undisclosed vascular disorders
NEURACTHEL®	ACTH	Instant & Modified-release	Adults, children	Infantile spasms, multiple sclerosis, undisclosed
Next generation melanocortins	CUV9900 Phimelanotide Parvysmelanotide	Topical, leave on	Adults	Anti-oxidative, DNA repair, repigmentation

***Table 1** summary of CLINUVEL's melanocortins under development as pharmaceutical or healthcare solutions products*

Formulating melanocortin products

Like most drugs, to obtain the desired therapeutic effect from a melanocortin it must be delivered at the right dose to the right patient at the right time. Large molecule melanocortin products pose particular challenges: they need to be able to reach the melanocortin receptor in the target cell at a level sufficient to elicit the desired effect without causing unwanted side effects or being destroyed by the body before they reach their target.

The first generation melanocortin pharmaceutical products were all injectable formulations, administered either subcutaneously or as an intramuscular presentation. CLINUVEL introduced an innovative implant (SCENESSE®), providing controlled-release delivery in optimal bioavailability. The appropriate interaction of afamelanotide with the melanocortin-1 receptor in the target cells, facilitated by the release from the implant, resulted in the desired therapeutic effect. This clinical benefit could not have been achieved by a simple subcutaneous or intramuscular injection because these methods of administration would have delivered too much drug too quickly. While some drugs are best administered in a way that achieves high blood levels, and this may be required in some clinical indications, others require careful administration such as SCENESSE® in EPP.

Newer technologies have been developed or are under investigation for less invasive administration of melanocortins. To date, none have been approved by a global regulatory body. The challenge remains to administer the drug with minimal side effects while achieving a therapeutic effect.

CLINUVEL is working on a next generation melanocortin products within the pipeline in both pharmaceutical and healthcare solutions (see Table 1). The products in development include new injectable approaches/formulations which are intended to expand the therapeutic arsenal available to physicians and provide more personalised dosing.

The melanocortin system and physiological role of melanocortins

Melanocortins are a family of structurally related peptides derived from a 31- to 36-kDa precursor peptide, pro-opiomelanocortin (POMC), produced in the pituitary gland with post-translational modifications of the peptide fragments. They share significant structural similarity and are named because their diverse physiological effects that include melanotropic and corticotropic activities. The melanocortin system consists of melanocortin peptides derived from the pro-opiomelanocortin gene, five melanocortin receptors (MCRs: MC1R to MC5R), two endogenous antagonists, and two ancillary proteins. Examples of the melanocortin peptides include α-MSH, β-MSH, γ-MSH, and ACTH. The endogenous melanocortin antagonists include agouti signal protein (ASP) and agouti-related protein (AgRP). In addition, two ancillary proteins, mahogany and syndecan-3, have been found that modulate the activity of the melanocortins.

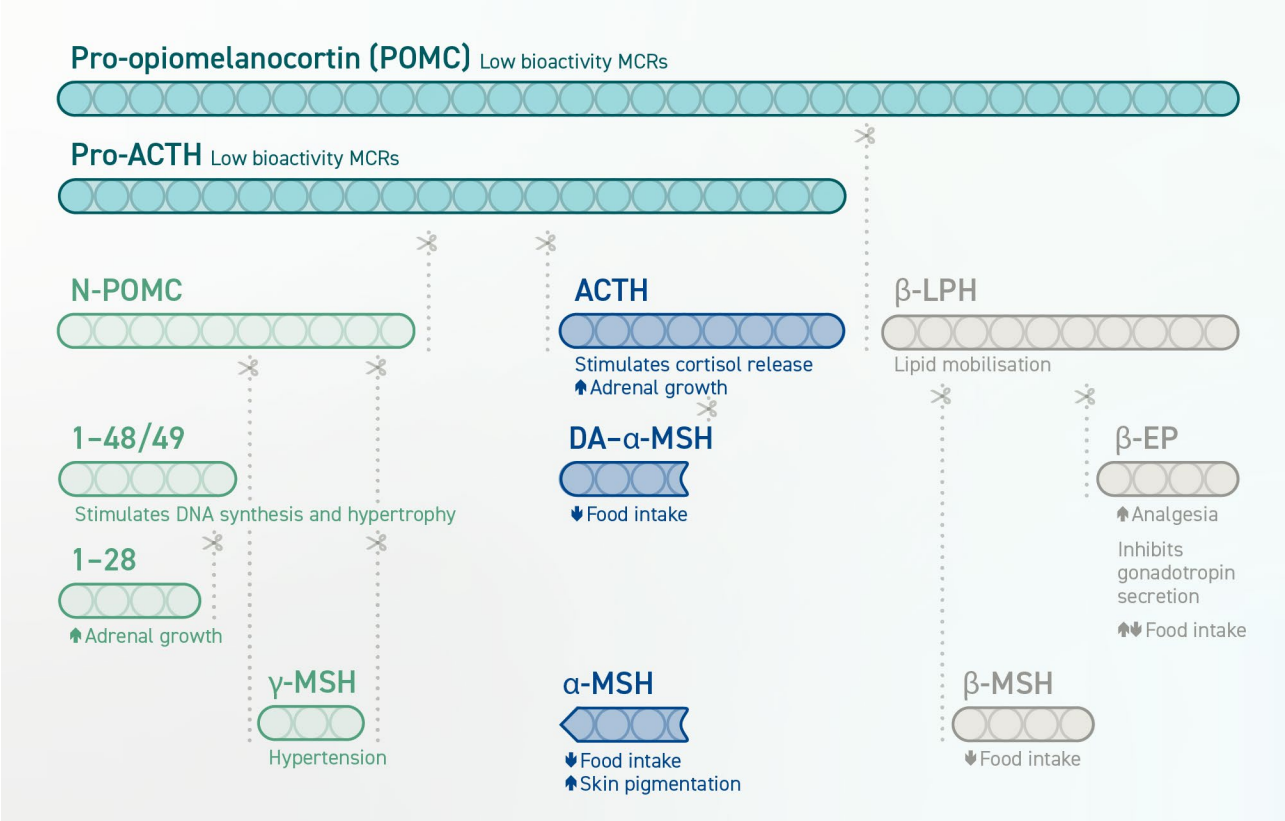

Figure 1 *functional peptides cleaved from POMC with selected roles in the human body*

Biological activities of melanocortins

Melanocortins are synthesised in various sites in the central nervous system and in peripheral tissues, and participate in regulating multiple physiological functions (see Table 2).

MCXR	Agonist / Antagonist Profile	Tissue Expression	Identified Cell Types
MC1R	α-MSH = ACTH > β-MSH > γ-MSH *(Antagonist: ASP)*	Skin, brain, immune system, gut, testis, ovary, placenta, lung, liver, adrenal gland, skeletal muscle, the pituitary, corpus luteum, endothelial cells, glioma cells, GI tract	Melanocytes, keratinocytes, fibroblastic cells, endothelial cells, secretory epithelia, microglia, astrocytes, monocytes/macrophage, lymphocytes, neutrophils, mast cells, intestinal epithelia, Leydig cells, lutein cells, trophoblastic cells, skeletal muscle cells, sebocytes,

			monocytes, mast cells, dendritic cells
MC2R	ACTH	Adrenal glands, testes, skin, adipose tissue, pancreas	Cells of the zona fasciculata and glomerolasa, adipocytes, keratinocytes, lymphocytes, ß pancreas cells
MC3R	α-MSH= β-MSH = γ-MSH = ACTH *(Antagonist: AgRP)*	Hypothalamus, thalamus, hippocampus, anterior amygdala, cortex, placenta, stomach, duodenum, and pancreas; detectable in the testes, ovary, mammary gland, skeletal muscle, kidney, heart, immune system	Macrophages, intestinal epithelial cells, lymphocytes
MC4R	α-MSH = ACTH > β-MSH >> γ-MSH *(Antagonist: ASP, AgRP)*	Brain (widely expressed in CNS, including the cortex, thalamus, hypothalamus and brain stem), skin, skeletal muscle	Dermal papilla cells, skeletal muscle cells, lymphocytes
MC5R	α-MSH > ACTH = β-MSH >> γ-MSH *(Antagonist: AgRP)*	Skeletal muscle, brain, skin, exocrine glands, lung, heart, spleen, immune system, kidney, adipose tissue, adrenal gland, uterus, ovary, placenta, bone marrow, skeletal muscle; presence in liver, thymus, testes, mammary glands, fat cells	Adipocytes, mast cells, secretory epithelia, macrophages, skeletal muscle cells, intestinal epithelial cells, lymphocytes

***Table 2** melanocortin receptors and their locations*

The effects of melanocortins are mediated by activation of one or more of the MCRs, each of which are seven-transmembrane G protein-coupled receptors. All MCRs are functionally coupled to adenylyl cyclase and mediate their effects primarily by activating the cAMP-dependent signalling pathway. All MCRs differ from each other in their tissue distribution, their binding affinity for the various melanocortins and their antagonists.

Five MCRs have been identified and a specific melanocortin acting on a specific MCR regulates a particular biological response; for example, α-MSH on MC1R increases melanogenesis within melanocytes, ACTH on MC2R increases cortisol production within adrenal zona fasciculata cells. Within the brain melanocortins regulate satiety (through MC4R) amongst other functions.

Other biological activities include:

- Stimulation of eumelanin synthesis in mammalian melanocytes
- steroidogenesis in adrenocortical cells
- regulation of food intake and energy metabolism
- neuronal regeneration
- endogenous antipyretic agents
- systemic as well as peripheral antiinflammatory effects
- sebotrophic effects, induce lipolysis, regulate exocrine glands, cardiac and testicular functions, and natriuresis.

While some of these activities are now subject to clinical programs (see above), opportunities exist to develop melanocortin therapies to assist patients. Throughout the course of 2023, CLINUVEL anticipates providing updates across its melanocortin development programs, including new applications of its technology.

– End –

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 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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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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