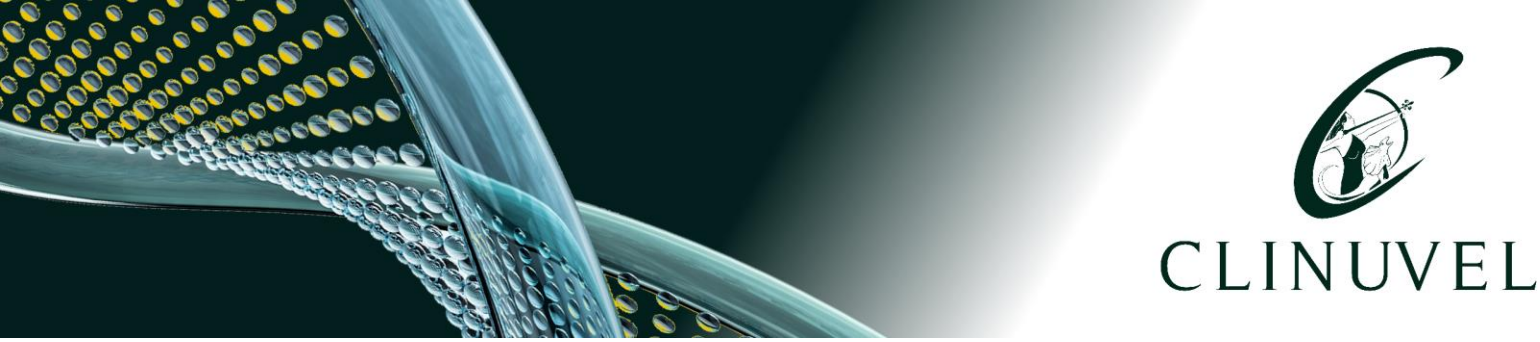

ASX Announcement

ASX: CUV
Nasdaq International Designation: CLVLY
XETRA-DAX: UR9

CLINUVEL STRATEGIC UPDATE

Dual strategy for melanocortins

Melbourne, Australia, 29 October 2020

CLINUVEL PHARMACEUTICALS LTD today released a strategic update on its business. An extensive version (31 slide illustrations) and executive summary (13 slide illustrations) have both been lodged with the ASX.

CLINUVEL is focussing on the commercialisation of the medicinal product SCENESSE® (afamelanotide controlled-release) for the treatment of erythropoietic protoporphyria (EPP) in the European Union, United States and – since 26 October – Australia.

The Update reveals CLINUVEL's strategic intentions are described as dual: ongoing work to scientifically translate melanocortins as prescription medicines for further life-threatening disorders as well as making the technology available for healthcare solutions as non-prescription products. The focus of the latter product category is to provide DNA protection and repair of the skin in individuals at highest risk of solar skin damage from UV exposure.

– End –

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Notes to editors:
CLINUVEL's Strategic Update has been issued to the Australian Securities Exchange and is available on CLINUVEL's website www.clinuvel.com.

[1] SCENESSE® (afamelanotide 16mg) is approved in the European Union and Australia as an orphan medicinal product and the world's first systemic photoprotective pharmaceutical 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.

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 and diversified biopharmaceutical company focused on developing and commercialising treatments for patients with genetic, metabolic, and life-threatening disorders, as well as healthcare solutions for the general population. As pioneers in photomedicine and understanding the interaction of light and human biology, CLINUVEL's research and development has led to innovative treatments for patient populations with a clinical need for systemic photoprotection, DNA repair and acute or life threatening conditions. 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, the US Food and Drug Administration in 2019 and the Australian Therapeutic Goods Administration in 2020 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. 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 two of several registered trademarks 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 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 2020 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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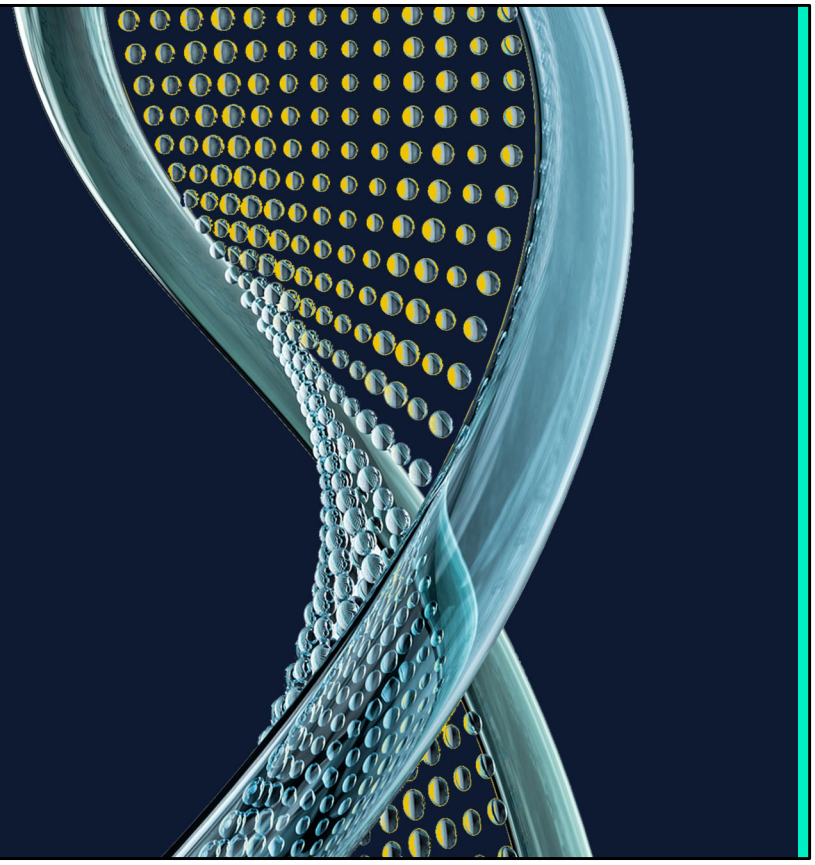
Strategic Update

Targeted Technology Translation

CLINUVEL Group
29 October 2020

ASX:	CUV
Level 1 ADR (Nasdaq International Designation):	CLVLY
XETRA-DAX:	UR9

www.clinuvel.com



Today we share CLINUVEL's strategy, its planning and execution which started in November 2005 and which concluded in June 2006.
In order to communicate to all readers coming from varying backgrounds, the language and definitions used in these illustrations are balanced with a mix of technical and simple expressions so that a non-technical audience is able to understand the concepts and thought processes underlying the successfully executed strategy, while an executive summary is also announced and published on CLINUVEL's website (clinuvel.com) provided for faster reading.

While any navigating crew needs to adjust continuously to unexpected events, adverse conditions, and unforeseen hazards, nearly all objectives set in 2006 have been realised.

The time it took to overturn regulatory objections, scepticism and adversities has been long and has required much patience and incalculable persistence from the same CLINUVEL team which had started the journey exactly 15 years ago.

Now today, the next chapter in the use of melanocortins is unveiled as data, scientific progress, safety and an environment of acceptance of the technology has been established. The strategy is unfolding as had been designed and desired a long time ago with some variations allowing for changes to the business plan when needed; flexibility is imperative when executing complexities.

At these uncertain times of global viral threat, one is required to look ahead and imagine how the world will look, a new world order, new internatonal economic relationships, a digital era and a high level of individualism, requiring one to take responsibility for one's own life.

All of the Group's staff, employees and Board share one common trait:
At CLINUVEL, we realise each day that it is a privilege to work for our common causes and to build a company from its ashes to its current remarkable success, while staying humble to the fact that success can vanish overnight when one becomes complacent. Too big to fail does not exist in our minds nor to small to succeed where others ceased, we manage uncertainty and build in contingency scenarios where we can.

Today, will focus on the expansion of the Pharmaceutical Division as well as the revelation of the Healthcare

Solutions Division, making CLINUVEL a unique hybrid among its peers, but with good reason.

Whereas it has taken decades of innovation, research and development to bring to market(s) a truly unique pharmaceutical product - SCENESSE® (afamelanotide 16mg) - the derivatives and further application should be finding its way to the markets in significantly less time; and that anticipation is owing to the fact that knowledge, IP, data and scientific observations are all transportable to CLINUVEL's downstream applications, products and target markets.

Whereas in pharmaceuticals and medicine one frequently speaks of *translational science*, when using one technology for wider medicinal use, in contrast it is rare to find highly specialised medical technology which can be rendered into a *non-medical application for universal use*. At CLINUVEL we had identified this differential pathway in 2006, but were required – for the protection of patients and our own – *to prove safety of the melanocortin beyond any reasonable doubt*.
The Group has have arrived at a point where the scientific breakthrough of melanocortins will be made available for wider societal utility, benefit for all at risk, all of us who self-identify a need.

With considerable humility, the CLINUVEL staff summarises the execution of this strategy as the completion of a trilogy, the third chapter of a planned CLINUVEL journey, Targeted Technology Translation.

The reader will come away with answers to the questions, WHAT – WHY – HOW – WHERE – and WHEN.

Legal Notice

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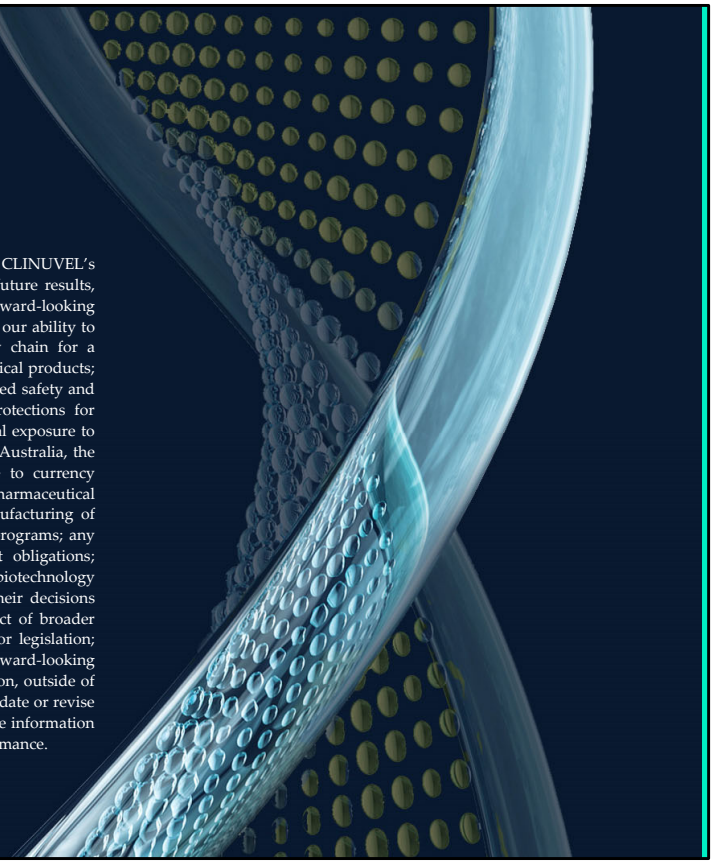


We share with you CLINUVEL's legal notice forewarning any reader from speculating and interpreting future planning in the illustrations and explanatory notes as certain events.
CLINUVEL lists to the reader some of the possible risks which may affect the Group, business and its performance.

Targeted Technology Translation **

**Explanatory notes provided to each illustration

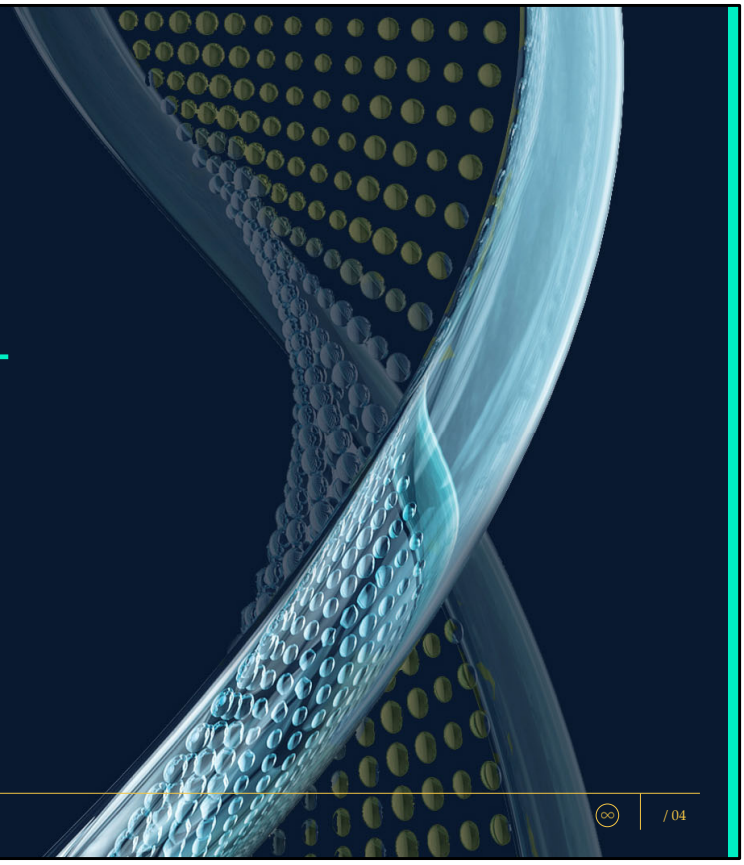
To be able to read individual sections of interest and skip subjects in random order, the index provides for the main themes of the Strategic Update - 29 October 2020.

Strategic Objectives

After 40 years of use of a specific family of hormones (melanocortins) as medicinal products, CLINUVEL universally translated these prescriptive hormones for the benefit of:

i
patients diagnosed with life threatening diseases, and

ii
the general population.



In seeking the answer to **WHY** CLINUVEL's dual strategy is appropriate and timely, we start by making an inventory of core technology, IP and skills.

CLINUVEL is unique from many other pharmaceutical companies as **its core technology lends itself to address both clinical (patients') needs and those of individuals, part of the general population at risk.** In other words, core technology to be available for pharmaceutical and non-pharmaceutical markets.

CLINUVEL has long observed that **the selected melanocortins provide five key properties**

(i) **systemic photoprotective** (preventing, reducing photo toxicity caused by UV and HEV light and increasing melanin density- skin pigmentation),
(ii) **anti-oxidative** (quenching free radicals),
(iii) **anti-oncotic** (counteracting oedema, fluid),
(iv) **vaso-active** (acting on blood vessels), and
(v) **DNA-reparative** (regeneration of UV-induced DNA damage).

The CLINUVEL scientific team zoomed in on a number of these characteristics and sought evidence in effectiveness and strength, but most of all significance in treating a variety of medical conditions.
In parallel, it was part of our strategy to keep both an open mind and critical eye on the aspects of scientific evidence which might be of benefit to a wider populations other than the initial patients selected.

In many ways, the patients diagnosed with life threatening and severe diseases and treated by CLINUVEL stood model for scientific evaluation under extreme conditions.
Once the evidence was received and practical benefit observed from the use of CLINUVEL's melanocortin technology in acute circumstances, it was appropriate to start thinking which technology attributes would provide meaningful to benefit wider populations.

In our thinking, Targeted Technology Translation means exactly that: the use of highly specialised technology as prescription medicines which will **in time** benefit those downstream who are at risk of hazard and contracting future disease. In other words, most of us.

Finance

Financial management is a key factor of the Group's current success allowing for operational flexibility to:

I. build countercyclical buffers in economic downturns,

II. minimise equity dilution,

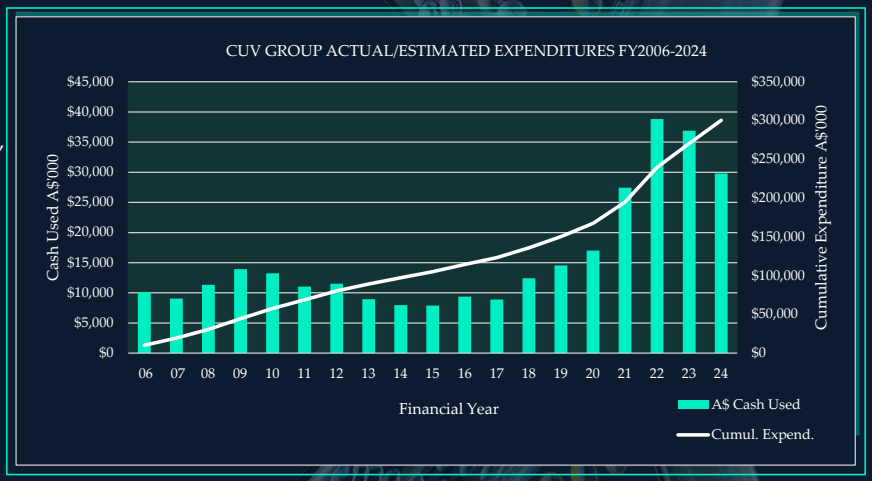
III. maintain profitability,

IV. manage costs,

V. retain and attract talent,

VI. expand the Group, and

VII. vertically integrate all business functions

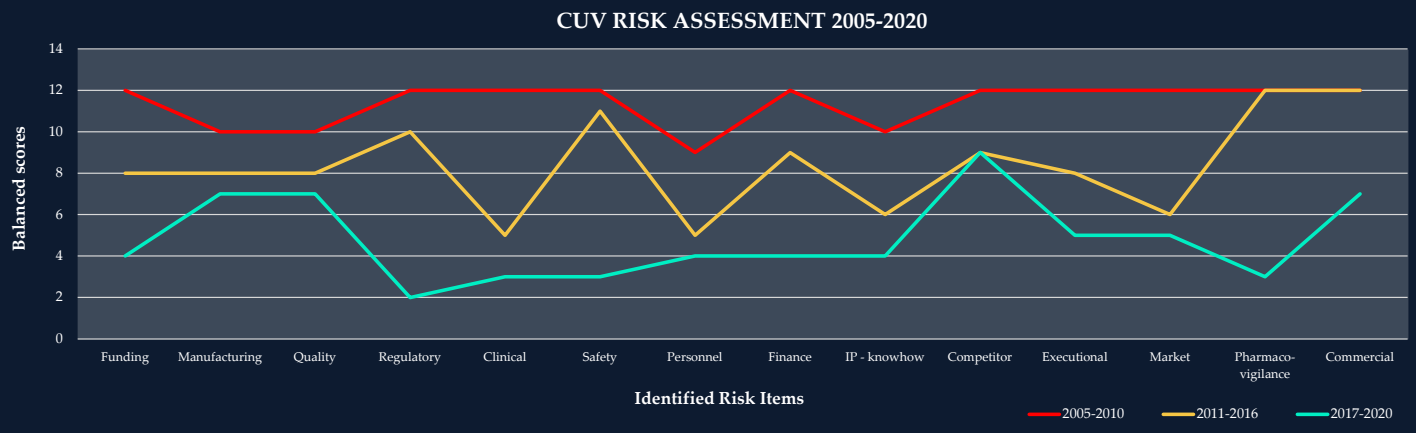


CLINUVEL's aim is to control performance of the group of companies, to being able to navigate adverse economic conditions which periodically occur as history of economics and capital markets has shown .
The challenge taken up by the current management team is – and has been – to minimise risks, maximise main objectives and make new technology available against the backdrop of the previous 25 years of failing to formulate and execute a viable strategy.
Unfortunately, the history of the previous attempts – from 1989 to 2005 – to establish a viable business or strategy naturally had to weigh heavily on the choices made by CLINUVEL along the trajectory.
However, the CLINUVEL Board had set its objectives to expand into a diversified group, providing *products, services and healthcare solutions* to patients and the wider general population.
CLINUVEL's deliberate and gradual expansion captures the Targeted Technology Translation, whereby a main goal is to vertically integrate all skills and functions within the Group.
CLINUVEL does not provide financial guidance at this stage of its operations.
The graphics illustrate planned expenditures for Financial Year 2021-2022-2023 to realise all its programs and expand the group of companies and vertically integrate further functions.
In this planning and intended level of expenditures, at present time CLINUVEL aims to develop and launch multiple prescriptive drugs and at least three products (non-prescription products) under the division Healthcare Solutions.

Business Model

I. the Group had identified 14 risks from 2005-2020
II. 3 time intervals evaluated (from 2005 to 2020)
III. significant reduction in risk per time interval

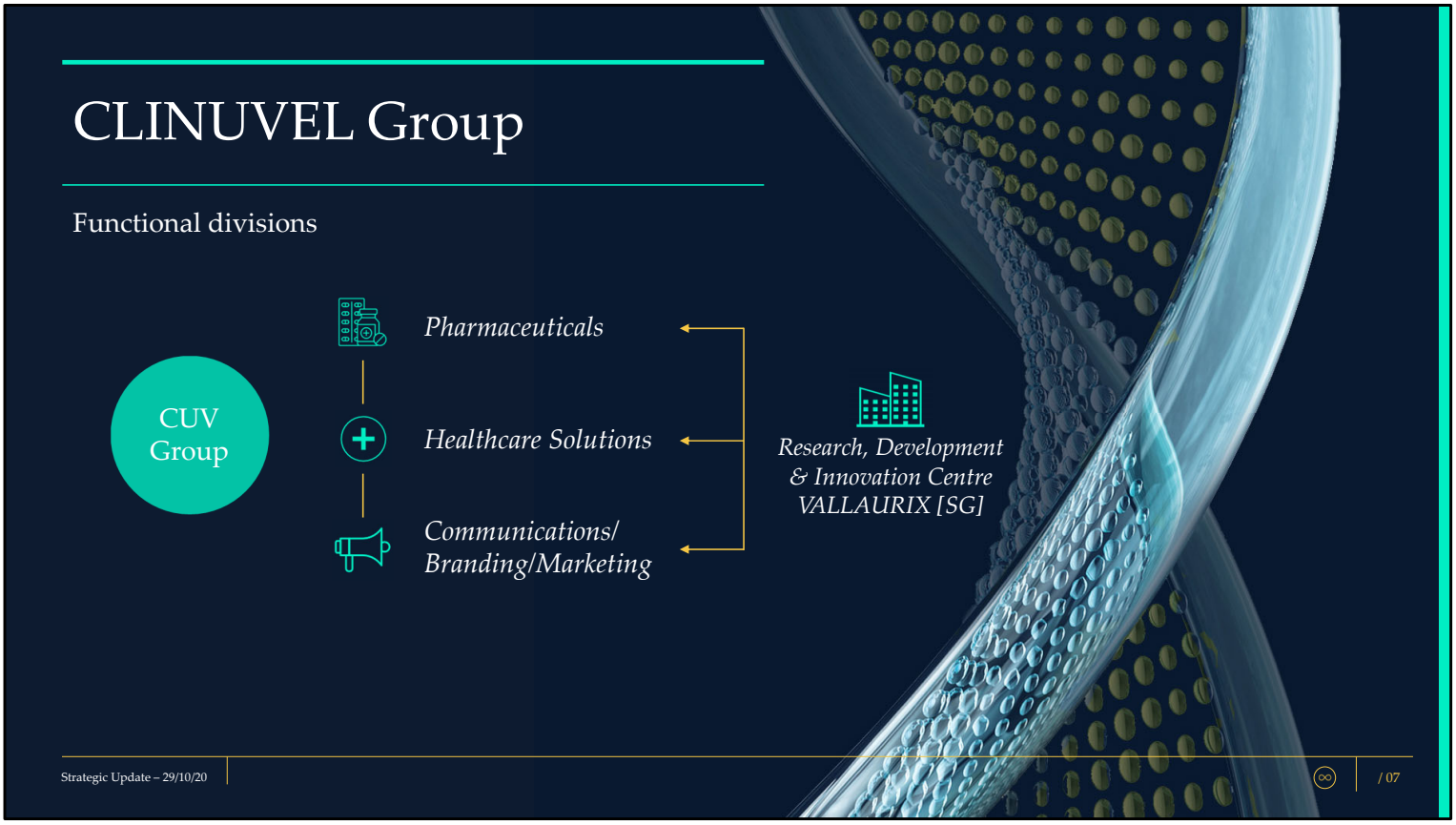
Comparison	Difference in mean risk score	p-value
2011-2016 vs 2005-2010	-3.0	0.0001
2017-2020 vs 2011-2016	**-3.6**	**<0.0001**
2017-2020 vs 2005-2010	-6.6	<0.0001



As widely published, the pharmaceutical sector is generally known to herald high risk in pursuit of new medicinal solutions.
Armed with this knowledge, CLINUVEL's starting point was to list all foreseeable and unlikely risks to the business.
In our undertakings, we monitor year on year the addressable risks as a collective attempt within the group of companies to think about and face these potential business hazards, to be able to reduce each single one.

The illustration shows the 14 most important identified risks to CLINUVEL which required systematic confrontation. Whereas the scores have come down significantly ($p<0.0001$) during the three time-intervals, there remains ample work to be done to reduce the risks further. Risk management in our world is a continuous process. The turquoise line in the graph depicts the current status.

In summary, by focussing on reducing risks, CLINUVEL's business model was executed to advance the Group to its current advanced position.

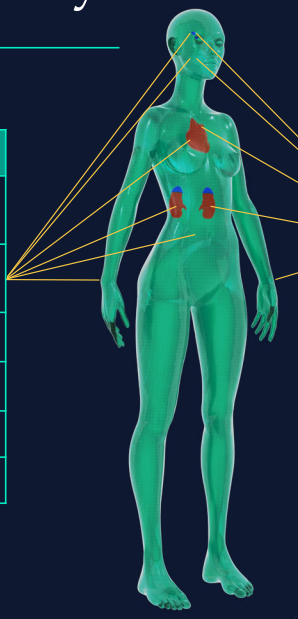


The core strength of CLINUVEL started from a pharmaceutical team which gradually expanded over more than a decade.
With CLINUVEL's clinical success, the focus incrementally widened to the use of melanocortin technology to other fields of medicine, but also to its applicability day to day, *healthcare solutions* or *universal care*.
As part of the strategy pursuing 'Targeted Technology Translation' a separate division and teams are established who are required to work on healthcare solutions, non-prescriptive products: The Healthcare Solutions Division.
Linking the pharmaceutical and healthcare solutions is the Research, Development & Innovation (RDI) Centre in Singapore, known as VALLAURIX SG, which is set up as a technology innovation centre. The VALLAURIX activities link the three main divisions within the Group.
The Communications-Branding-Marketing Division delineates which product strategies need to be implemented to ensure close alignment between disciplines but most of all to be successful in both the pharmaceutical market and the B2C market which will be addressed by the Group.

Imperative for future success is cross-linking all divisions, alignment, coordination of information on technology and communications within and externally.

The Melanocortin Story

MOLECULE	RECEPTOR	TARGET ORIGIN
ACTH 1-24[1]	MC2, MC1, MC3, MC4, MC5	CNS[11] HYPOTHALAMUS[12] PITUITARY GLAND
ACTH 1-39[2]	MC2, MC1, MC3, MC4, MC5	ANT. PITUITARY GLAND ADRENAL CORTEX
BREMELANOTIDE[3]	MC4, MC1, MC3, MC5	HYPOTHALAMUS, SKIN
SETMELANOTIDE[4]	MC4, MC1, MC5	HYPOTHALAMUS, SKIN[13]
CZEN001/002[5]	MC3, MC1	GI TRACT[14]
KPV[6]	MC1, MC4	GI TRACT, SKIN



MOLECULE	RECEPTOR	TARGET ORIGIN
AFAMELANOTIDE[7]	MC1,MC4, MC3, MC5	SKIN, BLOOD VESSELS[15], CNS, HEART[16], KIDNEY[17]
CUV9900[8]		
PHIMELANOTIDE[9]		
PARVYSMELANOTIDE[10]		

The melanocortin story started well before 1952, when an American rheumatologist, Dr Philip S. Hench, used an extract of ACTH from porcine pituitary glands in the search of an immune related answer to rheumatoid arthritis. In 1949, the first arthritis patient was injected with ACTH and in 1950, Dr Hench and two others were awarded the Nobel Prize in Medicine. In 1952, the FDA approved H.P. Acthar Gel, or "highly purified" ACTH mixed with gelatin to make it last longer in the body and require fewer injections. ACTH was introduced on the US market before the clinical trial programs (Phase I, II and II) became mandatory under the 1962 Kefauver-Harris Amendments to the US Food, Drug and Cosmetic Act (1938).

The melanocortin story is illustrated here to provide a broad overview of main melanocortin molecules on the market , i.e. ACTH, bremelanotide, and afamelanotide SCENESSE®).
Bremelanotide was developed for the treatment of female sexual dysfunction, while setmelanotide is in clinical development to activate and promote weight loss in specific rare disorders. Both molecules are synthetic cyclic peptides.

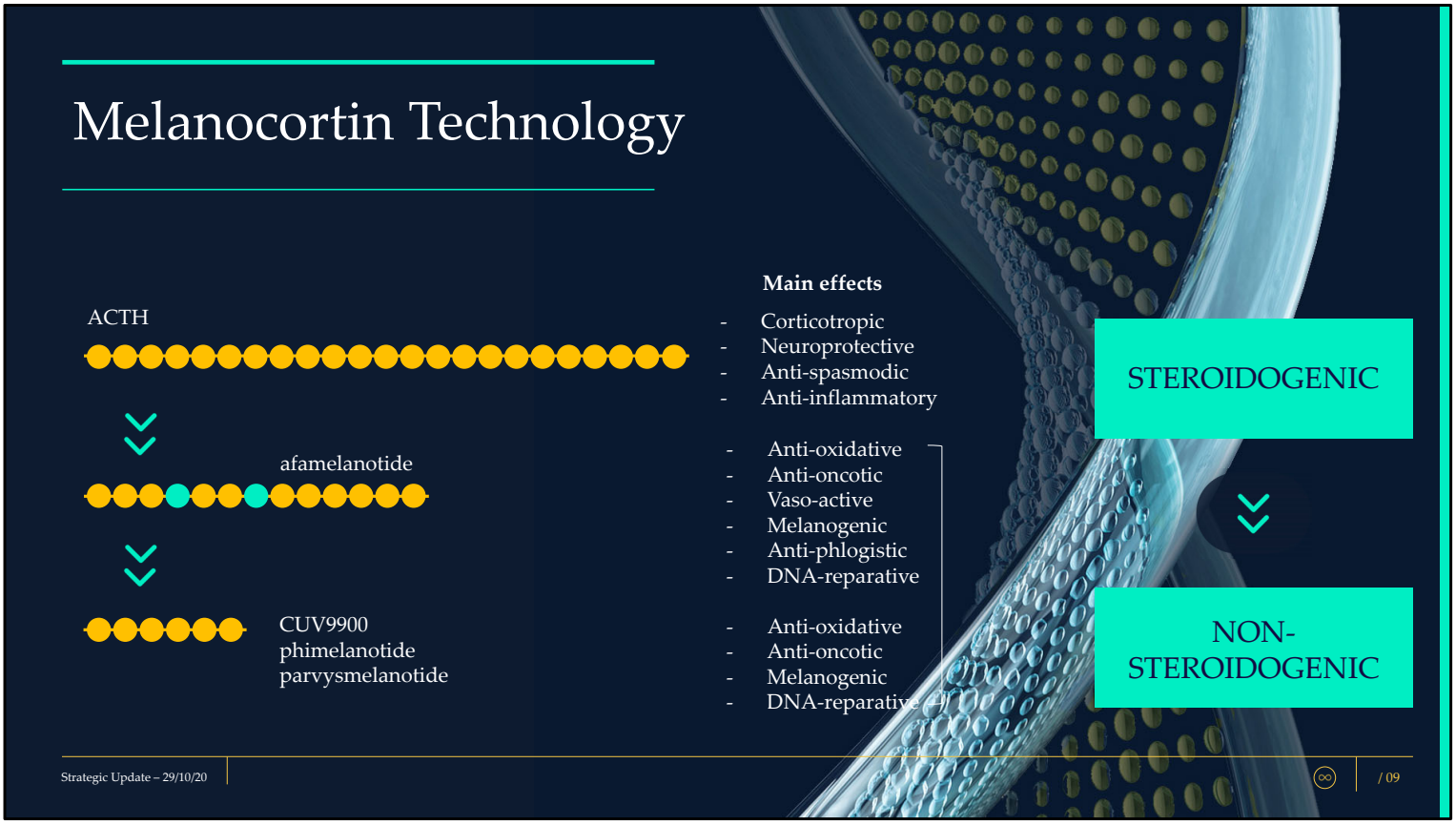
Agonists of melanocortin receptor 4 were discontinued by a number of pharmaceutical companies, while the development of KPV, a melanocortin tripeptide, failed in clinical trials. Discontinuation of CZEN001/002 also was reported due to lack of sufficient and convincing clinical response.

A number of reasons led to the discontinuation and cessation of various businesses developing melanocortins, while at present a larger US pharmaceutical which had been distributing ACTH analogues has now filed for bankruptcy, owing to its involvement in the US opioid scandal.
All in all, just one or two successes have been booked to date with the development and commercialisation of melanocortins. CLINUVEL is one of the companies who have managed to successfully commercialise melanocortins, while it is expected that in the future a number of companies will focus on specific melanocortin molecules.

CLINUVEL is expanding its pharmaceutical pipeline of melanocortins with CUV9900, phimelanotide and parvysmelanotide for systemic and topical use, the next generation of melanocortins. The use of these molecules will be illustrated further.

Interest in melanocortins has increased the past years, and for good reasons.

[1]ACTH is marketed as a 24 amino acid hormone targeting structures in the central nervous system (brain).
[2]ACTH is also synthesised as the original 39 amino acid molecule.
[3]Bremelanotide was approved in 2019 in the United States for the treatment of female sexual dysfunction.
[4]Setmelanotide is in development for the treatment of Bardet-Biedl syndrome marked by obesity.
[5]Development of CZEN001/002 was discontinued due to the inability to show efficacy.
[6]The tripeptide KPV did not pass Phase I clinical trials and was discontinued.
[7]CLINUVEL's afamelanotide obtained marketing authorisation in 2014 in the European Union, 2019 in the United
States and 2020 in Australia, as the world's first systemic photoprotective drug for the treatment of erythropoietic protoporphyria (absolute light intolerance).
[8]CLINUVEL is evaluating the use of CUV9900 as the next generation melanocortin derivative in development.
[9'10]As part of the development program the small molecules phimelanotide and parvysmelanotide are being evaluated for safety and efficacy.
[11]Central Nervous System.
[12]The hypothalamus is home to various centres which respond to melanocortins through the MC4 receptor.
[13]The skin expresses at least two melanocortin receptors: MC1 and MC4, but more evidence is being sought for other G-coupled receptors.
[14]The gastro-intestinal tract expresses MC1, MC4, MC5 and MC3.
[15]The vascular system is regulated locally and centrally in the brain stem, mainly expressing MC4, MC3 and MC5.
[16]Cardiac tissue expresses MC3, MC4 and MC5.
[17]Kidneys are known to express melanocortin receptors, mainly MC3, MC4, MC5.



In the fifties, the hormone ACTH was the first synthetic molecule to be researched for human therapy.
It was soon found that ACTH acted via the hypothalamic-pituitary-adrenal axis (HPA) and exerted an effect on the adrenal glands.

Cleaved from proopiomelanocortin (POMC), derivatives such as ACTH and other smaller peptide fragments are agonists to five melanocortin receptors, however the potency of each molecule depends on a number of factors within the host.

The image illustrates that some of the active sites within the ACTH molecule provide activity to afamelanotide, an alpha-melanocyte stimulating hormone analogue of the physiological (body own's hormone) tridecapeptide.

In simple terms, fragments of ACTH hormone can be cut to arrive at active smaller peptides. Each smaller hormone has different modes of action. CLINUVEL's Research, Development & Innovation Centre focuses on this scientific work.

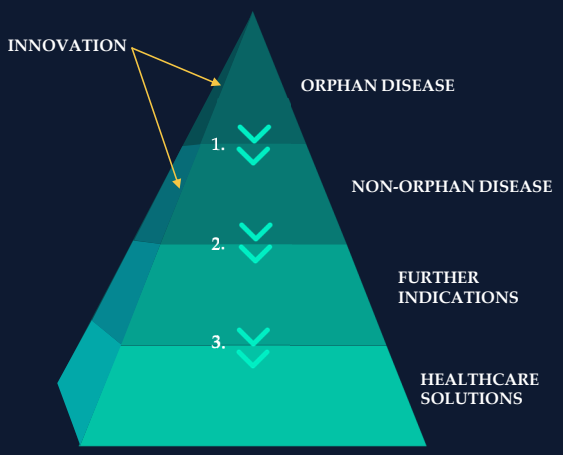
It is important to distinguish the afamelanotide hormone from the ACTH hormone in that the former has not no corticotropic effects, meaning it does not act on the adrenal glands. This provides a number of clinical advantages.

All melanocortins share that their half-life in the human body is relatively short, measured in minutes, meaning that length of time for the starting dose to drop to half the concentration is extremely fast.

In the illustration, the various main effects of the hormones are listed.
Importantly, the hormones with strong affinity for the MC1 receptors in the skin exert a number of effects depending on doses, strength and other pharmacological factors.

Controlled Strategy

Differentiated in medical need and distribution



TRANSLATION INNOVATIVE TECHNOLOGY			
Active Ingredient	Botulinum toxin	Bimatoprost	Afamelanotide
Product	Botox®	Latisse®	SCENESSE®
Primary Efficacy	blepharospasm/ bladder spasms	ocular hypertension / glaucoma	phototoxicity DNA damage (UV)
Need for Primary Efficacy	HIGH	HIGH	HIGH
Secondary Efficacy	facial relaxation	growth of eyelashes	DNA repair
Need for Secondary Efficacy	LOW	LOW	HIGH
Product Differentiation	2 product	1 products	2 products
Distribution	Uncontrolled	Uncontrolled	Controlled

Scientific translation is not new, some examples exist in the pharmaceutical sector, however there are important differences to achieve long-term success.

CLINUVEL's controlled strategy is contemporary and befits the changing environment and perception by regulatory authorities, practitioners, patients and the general public.
In answering further the **WHY** of the chosen strategy of **Targeted Technology Translation**, we expand our narrative to two examples which demonstrate small but important differences. Each technology is taken on its own merits with its own set of limitations.

In the past, companies have pursued a dual strategy of translating and repositioning drugs for a new set of users, new populations.
Some conspicuous examples are provided in the table illustrated to point to parallels and key differentiation points, two business cases which have shown how, and where, successes and errors can be made and which have led to recurrent confrontations with regulatory authorities and consumers.

Botulinum toxin was first developed to treat blepharospasms (spasms of the eye muscle) and bladder spasms, and second became widely sold for its observed side effect of improving facial grooves and wrinkles (providing a younger appearance in those seeking beauty). The medical need in blepharospasm is low to moderate, while in bladder dysfunction the medical need is higher. The absolute non-medical need in cosmesis is deemed low, while the desire to beautify has grown in the Western world.

While botulinum toxin is arguably a successful product in terms of revenues and innovation, the off-label strategy has caused much corporate anguish and resulted in hefty fines paid by Allergan, reported to be north of US$1B in total. The botulinum toxin was formulated as an aqueous solution as the final sterile injectable product being promoted downstream as a product for facial beautification and aesthetic enhancement. The distribution of botulinum toxin is uncontrolled and widely promoted among non-healthcare providers, shopping malls, tattoo parlours and organised during so-called "botox-parties".

The second example of technology translation is quite similar where bimatoprost, a PGE2 agonist, was formulated as an aqueous and implant formulation to lower intra-ocular pressure and improve glaucoma. The absolute medical need is high. However, it was observed that bimatoprost was able to cause a positive effect on

hair follicles, leading to growth of eyelashes. Allergan has been reprimanded and fined by the FDA on several occasions for inappropriate promotion and advertising of bimatoprost. The absolute need for the secondary efficacy of eyelash growth is deemed low. The use of bimatoprost is relatively uncontrolled through healthcare practitioners, healthcare spas and beauty parlours, and non-medical personnel.

CLINUVEL's strategy is quite different in making its melanocortin technology available first for healthcare practitioners, and second by reformulating derivatives at various concentrations as products benefiting the general population, i.e. those at risk of DNA damage caused by UV and high energy visible (HEV) radiation. CLINUVEL's differential approach is found by retaining control of its products at all times and using controlled distribution channels for its prescriptive products. The need for DNA reparative products is high among patients and individuals at risk of developing skin cancers.

CLINUVEL has made it publicly clear and reemphasises that it cannot support an off-label strategy for SCENESSE®; an off-label strategy is incompatible to the Company's ethos, strategy and vision, while Board, management and regulators cannot bear the responsibility for unauthorised use due to off-label promotion. CLINUVEL's consistent approach to the business will need to translate in time to **brand confidence and trust** for all other product categories downstream.
Scrutiny of CLINUVEL's melanocortin products will always remain high due to selective melanogenic (activating skin's pigmentation) properties of our melanocortins. These factors have shaped CLINUVEL's strategy and have resulted in the pathway which has generated results at present day. These collective results are now translated to products for larger audiences.

Corporate leadership is built on a foundation of trust, a confidence which will translate in **brand equity** for all its products in time. This adherence to one direction runs throughout the Group of companies and is built over decades of innovation, research & development, and commercialisation.

In a pyramidal model, innovative pharmaceutical technology can enter the markets as medication for an orphan or non-orphan diseases [1], and subsequently translated into therapies for further indications and larger audiences [2].
However, seldom does a pharmaceutical technology **lend itself to wider use** to general populations [3]. In CLINUVEL's case however the selected melanocortins – our core technology – do seem to provide wider benefit to general populations [3]. Today we will expand on this notion and further answer the **WHY** of this Targeted Technology Translation.

Vitiligo Program

SCENESSE® in combination with NB-UVB:

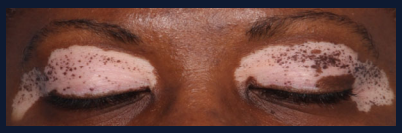
1. acceleration of repigmentation
2. darker skin most responsive to treatment
3. North-America first target market

Day 0

At start of the study
CUV102

Day 35

After 1 implant – 15 NB-UVB
CUV102



Day 66

After 2 implants – 29 NB-UVB
CUV102

Day 171

After 4 implants – 62 NB-UVB
CUV102

SCENESSE® in combination with NB-UVB provided
80% repigmentation of head & neck [CUV102] in darker skin

The vitiligo program is aimed at using SCENESSE® in combination with narrow-band UVB (NB-UVB) in darker skin patients since they are most responsible to the hormone.
CLINUVEL intends to first market SCENESSE® in generalised vitiligo in North-America.

Vitiligo Results

SCENESSE® in combination with narrowband UVB [NB-UVB][1]

Clinical results thus far from CUV102 and CUV103 studies, show SCENESSE®:

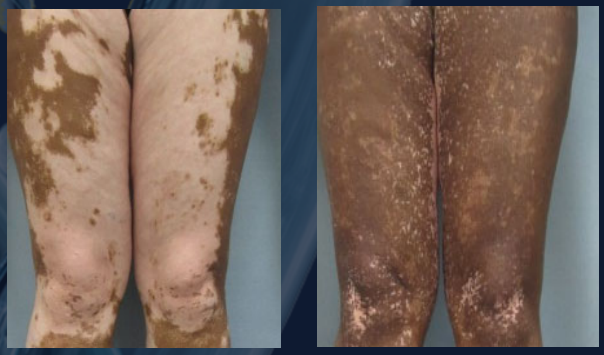
1. repigments vitiligo patients with skin type IV-V-VI:
   - most responsive: arms, legs, breast, back, head and neck (>80%)
   - least responsive: hands and feet (structure/lack of hair follicles)
2. causes dramatic emotional reaction in patients of skin type V-VI
3. reduces radiation burden of NB-UVB
4. reduces exposure time of NB-UVB from 18 to 7 months and NB-UVB
5. optimises skin stem cell response.

Day 0

Before the start of treatment [CUV102]

Day 140

4 implants and 32 NB-UVB sessions [CUV102]



SCENESSE® dosed every 4 weeks
in combination with NB-UVB three times per week

Afamelanotide controlled-release injectable formulation (SCENESSE®) has been used in three clinical trials (CUV101-CUV102-CUV103) in generalised vitiligo, of which two (CUV102-CUV103) were in patients of darker skin complexion (Fitzpatrick IV-V-VI). Vitiligo is a disease causing progressive and widespread (from head to toe) loss of skin pigmentation.
Since vitiligo is a disease which rapidly and visibly reveals the loss of skin colour, an effective therapy is easily visible too as the skin starts to repigment day by day.

In both studies it was quite apparent for the treating physicians that afamelanotide in combination with narrowband UVB provided repigmentation in patients suffering from generalised vitiligo.
However, the most prominent results of repigmentation in the CUV102 study were observed in American patients of Fitzpatrick skin type V and VI (darker skin complexion).

In the illustration, the patient presented loss of more than 60% loss of pigmentation of the entire skin, whereby the upper leg shows the extent of depigmentation: the depigmented skin dominates the patient's own native colour and caused much distress for this female patient.
After four implants and 32 doses of narrowband UVB (regarded by dermatologists as only available treatment modality for extensive vitiligo) more than 80% of repigmentation was already achieved.
In the published results from the CUV102 study (reference: Lim et al., *JAMA Dermatol.* 2015), therapy with SCENESSE®, the radiation with NB-UVB therapy was reduced by a median of eight months, and additionally saved patients considerable time off work and travel time to the clinic. The most important gain was not only the pigmentation achieved but also the reduction of NB-UVB exposure (UVB radiation) to the overall body surface of patients.

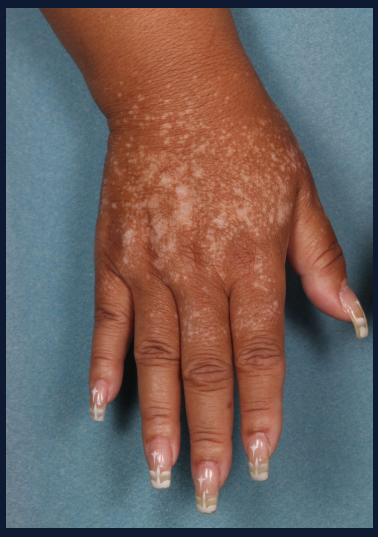
An important finding in the CUV103 study was that, despite the observed regeneration of skin pigmentation, some Asian patients of different ethnic and cultural background would not tolerate a temporary darkening of the surrounding skin as a result of the effectiveness of afamelanotide, since this was socially not acceptable.

In the next vitiligo study (CUV104), the clinical target proposed is to achieve 75% repigmentation compared to baseline recordings of extent of loss of pigmentation, so called vitiligo lesions.

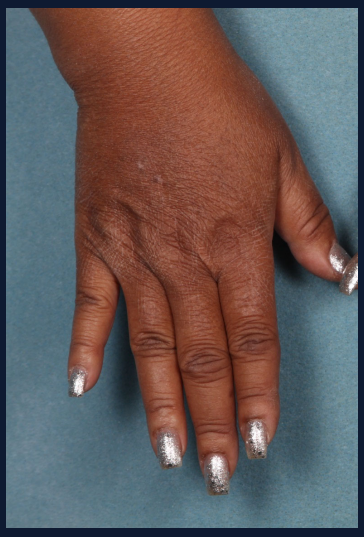
Vitiligo CUV104

SCENESSE® in combination with NB-UVB:

1. Reduction of radiation dose NB-UVB
2. Determination optimal number of implants [6, 7 or 8] to repigment >0.5% of BSA[1] of head/neck
3. Darker skin complexion Type IV-V-VI[2]
4. 3 months follow up of stability pigmentation
5. Consensus on protocol by global vitiligo experts
4. Final agreement to be reached with FDA on study protocol.



Day 0 – before treatment



Day 102 – 4 implants, 34 NB-UVB sessions

The next CUV104 trial design awaits FDA agreement, while global experts have consented on its form. CLINUVEL's systemic drug SCENESSE® seeks to repigment patients with the highest need.

Additionally, it is necessary to emphasise repigmentation of patients' head and neck since this part of the body is in many cultures our first port of communication. Various vitiligo clinicians state that vitiligo patients care much more about their face, therefore it is a first anatomical site to assess early treatment outcomes.

[1] Body surface area.
[2] Fitzpatrick skin types IV-V-VI.

Vitiligo Addressable Market

SCENESSE® in combination with NB-UVB

The phototherapy market in the US is growing at a CGAR of 6% per year

Phototherapy is used mainly for psoriasis, acne and vitiligo (NB-UVB).

For generalised vitiligo there is no standard of care, but NB-UVB is the best alternative for treatment [range 6 – 18 months].

Highest need: dark skin patients suffer from the strongest contrast between pigmented and depigmented skin.

USA addressable market for vitiligo skin type IV-V-VI: est. 2,749 to 5,498 patients (depigmentation of ≥40% body surface area).

UNITED STATES	POPULATION 328,239,523[1]	
Dark skin, African-Americans (IV-V-VI)	13.4% [1]	43,984,096
Vitiligo prevalence	1% [2]	439,840
≥40% depigmentation	10-20%	10,996–21,992
Seeking initial treatment	25%	2,749–5,498
Compounded Annual Growth Rate	5%	137–274

PHOTOTHERAPY EQUIPMENT (USA)	% OF TOTAL CARE FACILITIES	
Hospitals	>5,000	81.3%
Dermatology clinics	3,900	50%

CLINUVEL's focus in vitiligo is on patients with the highest unmet medical need and most likely to respond to the combination therapy of afamelanotide with NB-UVB.

With a lack of standard of care in vitiligo, treatment approaches vary. NB-UVB is considered the best alternative treatment. It is widely adopted in clinical practice within the USA as a treatment for vitiligo, but also other dermatological disorders (such as psoriasis and acne), with use of phototherapy growing at a CGAR of 6% per annum.

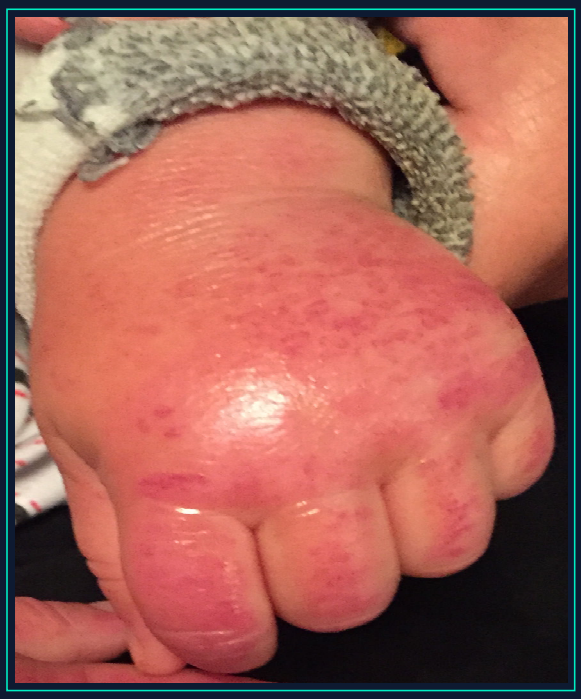
Vitiligo often affects the face, chest and extremities and may gradually spread to the limbs and other body surfaces. Patients are most affected psychologically when exposed parts of the body show extensive loss of pigmentation, quantified as greater or equal to 40% of total body surface area, as US expert physicians state. It is not the case that patients with smaller body surface do not suffer equally or more, however in patients of dark skin
Although vitiligo is seen in all skin types (Fitzpatrick types I-VI), the highest psychological and societal impact is reported in darker skin complexions (types IV-VI). Based on the prevalence of vitiligo in the USA, it is estimated that 10,996-21,992 individuals (all ages) meet the definition of widespread depigmentation in skin type IV-VI. The estimated addressable market is 25% of these patients, reflecting the broader vitiligo population who seek treatment for their condition.

[1] US population 2019, United States Census Bureau.
[2] Ezzedine et. al., (2015). Vitiligo. *Lancet*. 386(9988):74-84.

EPP Program

SCENESSE® systemic photoprotection 2005 -2020

1. Erythropoietic protoporphyria patients request continuous treatment >94% [data 2019].
2. CLINUVEL first entrant, growing market YOY.
3. 5,000 to 10,000 patients worldwide.
4. Dramatic treatment effect: able to engage in normal daily activities exposing to HEV light and UV.



CLINUVEL is marketing afamelanotide (SCENESSE®) in the European Union and United States for the treatment of patients suffering from erythropoietic protoporphyria (EPP) and it has recently received the same status to distribute the product in Australia (26 October 2020).

In summarising the symptoms of EPP patients, they are absolute intolerant to light to due to their lifelong risk to incur phototoxicity, that is the severe burning reactions caused by HEV and UV light, triggering a chemical reaction within the skin of these patients. EPP is a genetic disorder rendering these patients at high risk since birth.

The illustration shows the immediate reaction leading to swelling (fluid accumulation) in skin and underlying tissues, which makes patients ill for weeks. As a reaction, patients are forced to live indoors and shield from light. Many of the EPP patients lead a nocturnal existence and sleep during day, depriving them of normal social activities and contacts.

SCENESSE® is approved for the prevention of phototoxicity in adult erythropoietic protoporphyria (EPP) patients in Europe, the USA and Australia. CLINUVEL has developed and commercialised the drug for EPP, pioneering the concept of systemic photoprotection. There are no alternative treatments which have proven safe and effective in a completed clinical trial program, or subject to regulatory review.

EPP is a poorly characterised rare metabolic disorder causing lifelong absolute light intolerance. Due to a genetic defect, EPP patients suffer debilitating acute phototoxic reactions (anaphylactoid reactions and second-degree burns) after just a few minutes of exposure to visible light (including sun and artificial light). Burns and reactions may last days to weeks. Without treatment patients must withdraw from light exposure to prevent phototoxicity, leading to lifelong social isolation. SCENESSE® has been shown to reduce the incidence and severity of phototoxic reactions and increase the amount of time patients can expose to light without incurring phototoxicity. Most satisfying for the CLINUVEL team, patients report being able to expose to light and sun for the first time without phototoxicity or the fear of incapacitating burns following SCENESSE® treatment.

Data from the real-world use of the drug in Europe since launch in 2016 shows strong patient demand year on year, with over 94% of patients returning for treatment (2019 post-authorisation safety study data). Treatment access continues to grow year on year, with the drug launched in the USA in April 2020.

Over 7,500 doses of SCENESSE® have been administered to over 1,000 EPP patients globally since the first clinical trials in 2006. A growing cohort of patients have received continuous treatment for five years, with a number of Swiss and Italian patients treated continuously for more than ten years.

Image courtesy of the K family.

Arterial Ischaemic Stroke Program (AIS)

Afamelanotide in patients with stroke of large vessels at M2 level and higher

Stroke occurs most frequently (>50%) in the middle cerebral artery (MCA).

Blockages (clots) occur at various segments (levels), M1-M2-M3-M4.

High unmet need: minimal to no chance of treating stroke at M2 and higher.

Afamelanotide to
- improve blood flow,
- reduce oxidative damage, and
- reduce fluid formation in brain.

Ischaemic stroke is characterised by either a bleeding or clot formed inside the brain artery.
CLINUVEL focuses on the ischaemic strokes, which forms the lion's share of all strokes (85%).

CLINUVEL focuses on those patients who do not receive any therapy, those with blockages at M2 levels and higher.

Scientific progress has shown melanocortins to exert a positive effect on the central nervous system, including the brain.

Arterial Ischaemic Stroke (AIS) Program

Afamelanotide in patients with stroke of large vessels higher in the brain

CUV801 (6 stroke patients) who cannot be treated by:

I. thrombolytic therapy (IVT; dissolution of the clot), and

II. endovascular therapy (clot removal), and

who have a clot (occlusion) in a cerebral artery

III. at M2 level and higher [*see image previous page*].

Afamelanotide assessed on its safety in acute ischaemic stroke patients.

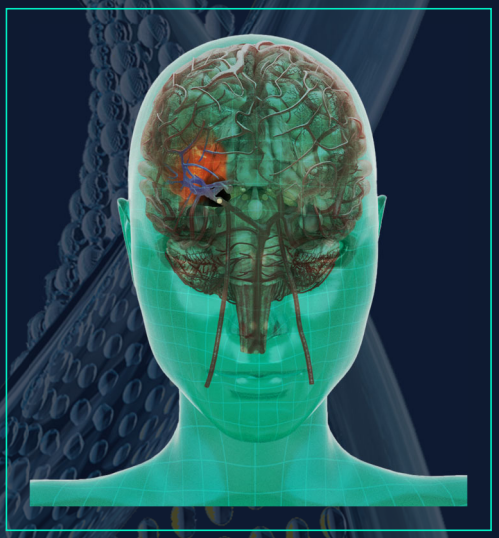
Afamelanotide evaluated on the therapeutic effect on blood flow to the:

A. ischaemic penumbra (salvageable brain tissue), and

B. ischaemic core (centre of the stroke, dead brain tissue).

Afamelantotide evaluated after 42 days by comparing

- CT angiogram (day of stroke)
- MRI scans during therapy
- Neurological functions (mRS, NIHSS)



In ischaemic stroke (AIS), the standard of care is intravenous thrombolysis (IVT) and endovascular thrombectomy (EVT) to be administered within 4.5 hours (neuroprotective international guidelines) after the stroke has occurred.

There are various reasons why clots form in arteries causing a stroke, but without expanding on multiple reasons, all arterial blockages result in dead brain tissue forming around and behind the blocked artery. A part of the brain deprived from blood and oxygen dies off swiftly (core) while wider peripheral brain tissue is at immediate risk of becoming hypoxic (penumbra) due to the blocked artery.

The CUV801 study will intensely monitor patients receiving afamelanotide for its safety, while the further objectives are to assess the size of the infarction (dead tissue) and brain tissue at risk of becoming necrotic too.

Patients will be assessed by comparing images of the brain and in their neurological functions, ability to move the affected side of their body, speech and cognitive functions.

AIS Addressable Market

Afamelanotide in occlusion of brain artery at M2 level and higher

Addressable market of stroke M2 and higher, not receiving IVT or EVT.

Acute arterial ischaemic stroke (AIS)

- arterial clot accounts for 85% of all acute strokes (ischaemic)
- 15% of acute strokes are caused by an acute bleeding (haemorrhage).

ISCHEMIC STROKE	UK	USA
Annual stroke incidence	113,000	795,000
Haemorrhagic stroke : Ischaemic Stroke	15% : 85%	
Arterial ischaemic stroke (LVO)[1]	46%	
AIS eligible for IVT	<20%	<20%
AIS contra-indications for IVT[2]	38.3%	
AIS eligible for EVT[2]	12%	11%
AIS patients untreated,	>35%–60%	

Strokes occur frequently in western societies: in the England there are more than 113,000 cases per year and close to 800,000 in the USA.

The majority of strokes are those caused by blockage of a brain artery, whereby the middle cerebral artery (MCA) is the most frequently affected.

The table illustrates that most patients are not receiving IVT or EVT due to underlying diseases, delay in time of hospital admission and location of the clot within the brain.

The range in percentage of untreated AIS patients remains alarmingly high, and the condition poses a true unmet medical need.

[1] Large vessel occlusion.
[2] See illustration on slide 17.

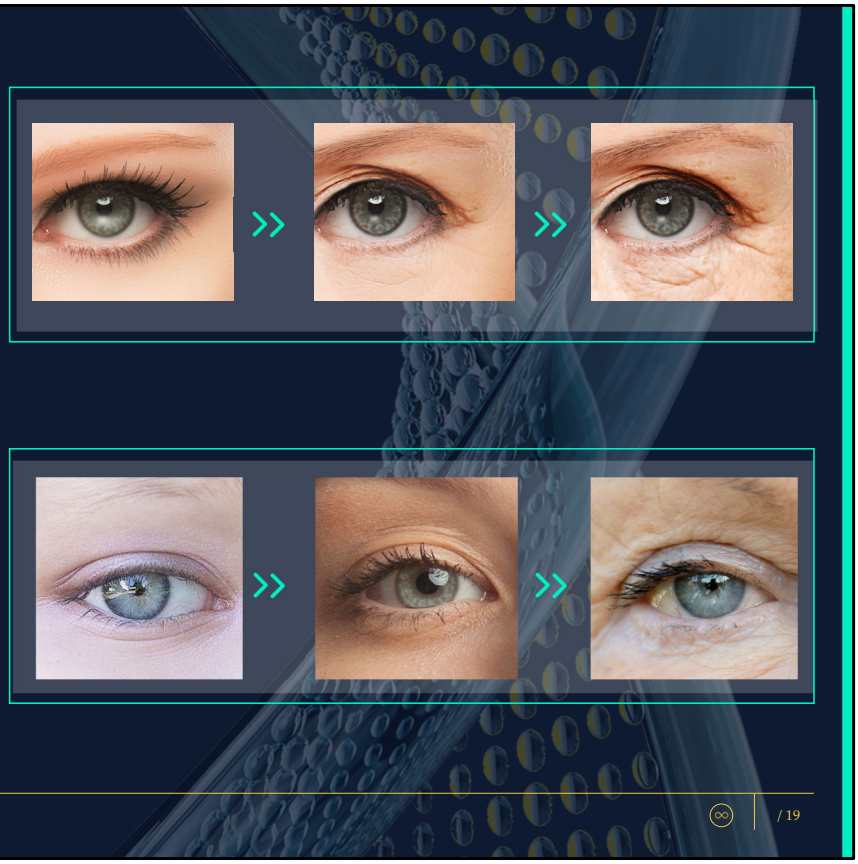
DNA Repair Program

Afamelanotide repairs DNA skin damage caused by UV radiation

Drug safely used in humans since 1996.

Afamelanotide to confirm DNA-damage response following UV skin damage in three studies.

Afamelanotide in genetic disease XP serves as model for assisting DNA repair in all populations affected and at risk of solar damage.



DNA repair is relevant to every human, since all of us expose to High Energy Visible light and UV radiation. Among the general population, there is a hierarchy of most susceptible groups to least susceptible individuals to photoageing and premature ageing due to UV exposure.

CLINUVEL has frequently reported on its scientific and clinical work to evaluate melanocortin(s) in various populations susceptible to various forms of photodamage.
Short studies were conducted in a number of diseases either initiated by CLINUVEL or individual clinical centres evaluating the effect of afamelanotide in polymorphous light eruption (PLE), Solar Urticaria (SU), Hailey-Hailey Disease (HHD), Erythropoietic Protoporphyria (EPP), Congenital Porphyria (CEP).
In all these diseases, patients are still able to respond and recover in some manner from DNA damage, but they express severe reactions to light. These patients have a sufficient DNA damage response.

However, various groups carry genetic traits or lack the efficient mechanisms of DNA skin repair and are at high or highest risk of developing skin cancers.
Some examples of patent populations who deserve CLINUVEL's highest attention are to people of Anglo-Saxon origin with blue eyes, ginger colour hair, tendency to develop freckles and sunspots fast (RHC type). Typically, these individuals burn fast under solar radiation, and are prone to develop first signs of sun damage and precancerous (before mature cancer stage) wounds of the skin. Chronic exposure to sun is not recommended for these patients since the DNA reparative process in these patients is shown to be suboptimal.

Another example of individuals in society at high risk of photodamage, are those patients who receive immune-suppressive therapy for longer time due to chronic disease. These patients are known to develop a higher rate of skin cancers, among other.

In summary, DNA regeneration of skin damage caused by solar exposure is a topic which affects us all, and the interest to address and find healthcare solutions for photodamage or solar damage is growing. The older we become, the more our DNA repair systems of the skin risk failure, and following previous periods of long exposure to sun we become prone to skin cancers - as the global statistics show.

With the scientific progress and understanding of the role of afamelanotide and other melanocortin molecules (drugs in development), the use of molecules to prevent and restore DNA damage of the skin can be expected

and follows a trail of evidence.

CLINUVEL's attention is owed to these highly susceptible individuals mentioned above.

The recently announced clinical program of afamelanotide in xeroderma pigmentosum (XP) serves as a clinical model to demonstrate the drug's ability to positively affect patients who suffer greatly from a genetic disease, which leads to the highest frequency of skin cancers and melanoma due to a defective DNA repair system.

In parallel, the Company is collecting final data confirming the ability of melanocortins to assist DNA-regeneration in randomly selected (non-diseased) individuals.

Naturally, various formulations and products have been planned to address DNA-restoration since the need remains high.

Xeroderma Pigmentosum [XP]

Afamelanotide in genetic disease XP: deficiency DNA Repair of skin

In XP, UV causes damage to DNA of skin/eyes since patients lack sufficient NER[1] repair capacity.

Lack of sufficient DNA repair capacity leads to skin cancers in XP.

XP patients have up to 10,000-fold risk of developing skin cancers, all are treated for multiple skin cancers and melanoma.

Afamelanotide has been shown to repair DNA in healthy patients, now it is evaluated in XP and repeat studies.

A young girl diagnosed with XP-C showing poikiloderma (disintegration of skin), leathery appearance, several wounds below the eyes and around the nose, persistent fluid of lower lip.

Eight variants of XP are known, CLINUVEL's initial focus is on patients diagnosed with XP-C. The C variant is expressed in patients who have an extreme high rate of skin cancer development and melanoma since they are deficient in the DNA repair process known as nucleotide excision repair (NER)[1.] The changes of the skin in these patients occur at infancy, when the skin starts to change in texture becoming leathery and easily develops wounds upon any solar exposure. As time passes, in early childhood their skin starts to break, disintegrate (poikiloderma) and first superficial skin cancers are reported. Needles to state how painful, distressing and traumatic this is for a growing child and their parents.
While there are three main causes of skin cancers (basal cell and squamous cell carcinoma, and melanoma), in XP patients the consequences are grave and mutilating; frequent surgeries leave scars on all exposed areas, while wound healing is compromised.
In XP-C, patients frequently live to the third decade while eventually passing away due to spread of the cancers (metastases).
The quality of life in these patients is unfortunately – despite advances in modern medicine – very low.

CLINUVEL had planned to treat these patients 15 years ago at the start of the scientific work on afamelanotide, but needed to generate sufficient data to be able and allowed to treat these patients, due to the high risk of disease and death in these patients.
It is most gratifying and somewhat emotional after more than a decade for the CLINUVEL team to seek a treatment for this forgotten group of affected patients, being able to contribute is a force which bonds all staff at CLINUVEL.

DNA Repair Studies

Afamelanotide in genetic disease XP: deficiency DNA Repair of skin

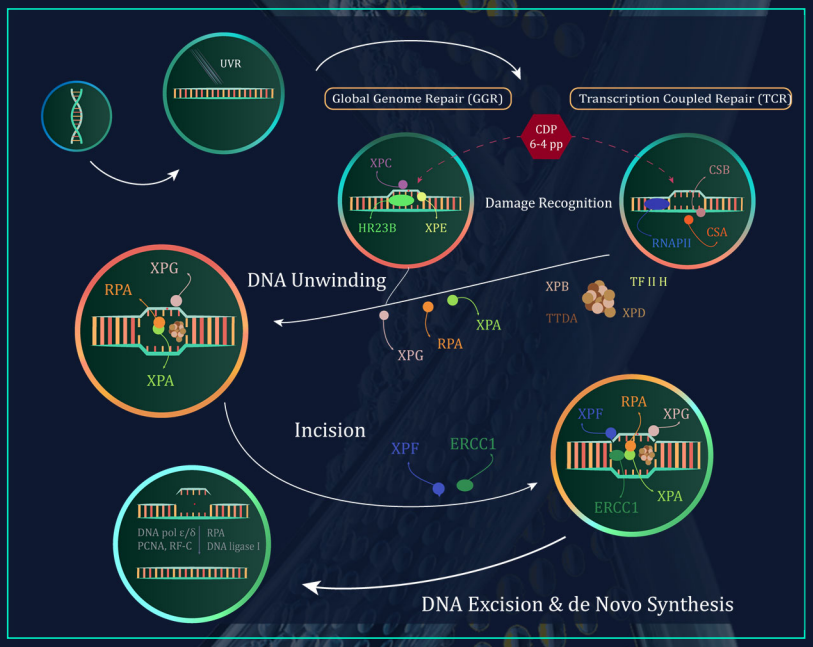
DNA Repair Program 2020-2021

I. repeat preclinical study

II. XP-C – 6 adult patients (CUV150)

III. Control group of 10 Caucasian volunteers (CUV151)

Results 2021.[1]

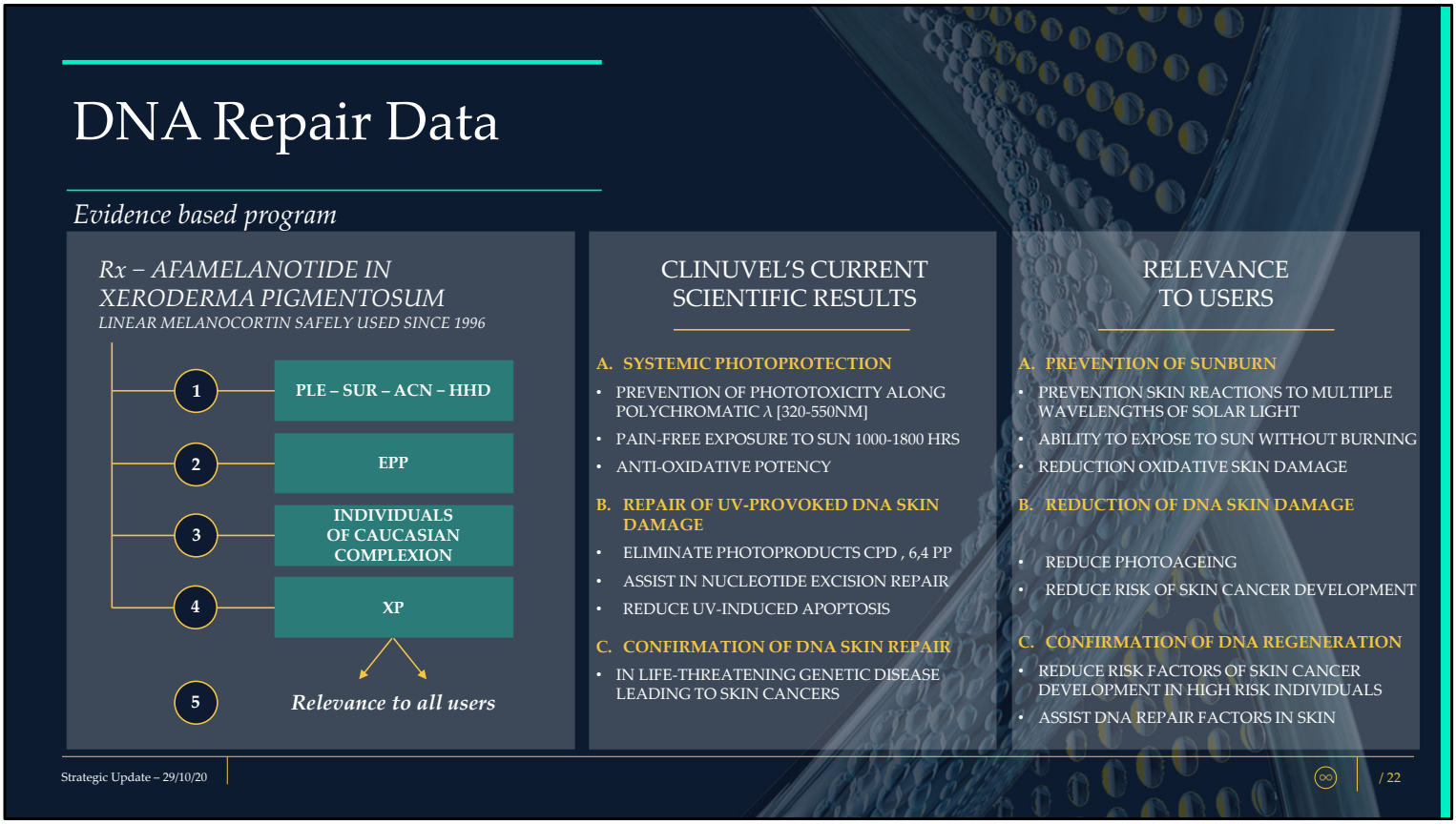


The nucleotide excise repair (NER) pathway and its role in DNA repair in all humans.

The three studies listed aim to show the benefit of afamelanotide and further melanocortins in a preclinical model, XP and healthy fair-skinned individuals. Skin samples will be collected at high frequency to determine the skin changes at the start and during treatment.
Approximately 60 skin samples in total will be evaluated to confirm the effects of the melanocortin therapy on DNA restoration.

The confirmatory evidence from the three studies assist CLINUVEL further in its launch of DNA reparative products since these contain the active ingredients as evaluated the past years and in these current studies.

[1]The three studies are expected to provide first results in 2021, however COVID restrictions may impact the ability of hospitals to treat patents and therefore analyses could be delayed.



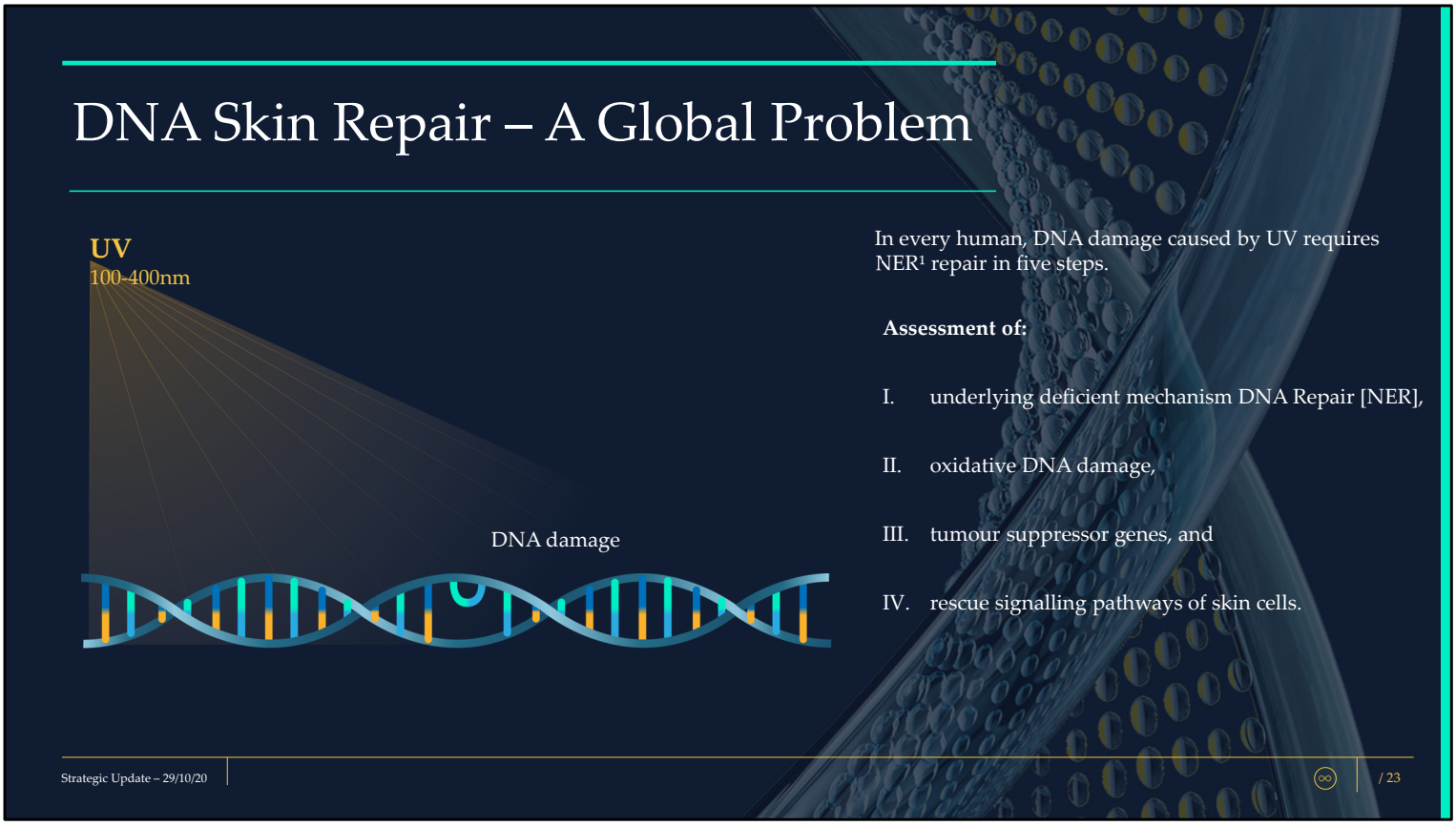
In the illustration, scientific findings in the middle column are translated to common terminology of relevance to general users.

The path to a successful DNA repair program was established during the development, use afamelanotide as well as other melanocortins in scientific experiments, preclinical studies and human trials.
A number of studies provided evidence from phototesting, photoprovocation under standardised conditions. During these experiments diseased patients, as well as healthy individuals, were exposed to controlled doses of NB-UVB, NB-UVA and HEV light. In measuring recovery under influence of afamelanotide treatment, many datasets were collected.
Key to the successful path of DNA protection and repair were the consistent safety data of the novel pharmaceutical ingredient and product. Without this emphasis and outcomes on safety, a further translation of technology would not have been feasible, and today's strategic direction would not have been possible.
It is infrequent that a planned course, vision and wish to make novel drugs available in a specific manner hold during decades, since many unexpected changes often are necessary to change the original plan.

Key CLINUVEL's current position has always been the question: **"How do we make the innovation relevant to general audiences, in other words how does the chemistry translate to benefit people at risk and those who were not part of CLINUVEL's clinical trials or patients with erythropoietic protoporphyria?"**

The first part of the answer was found in 2006, when we analysed the results of healthy individuals who had been administered frequent does of afamelanotide, these results had shown the first evidence of DNA protection and repair by a reduction of skin cells affected and damaged by solar radiation.

From then onwards, the scientific team at CLINUVEL kept its focus to follow DNA repair where all evidence came together, while the scientific community worldwide was providing further proof on afamelanotide and melanocortins as future agents in DNA-restoration of the skin.



UV radiation leads per se to DNA damage as fast as minutes exposed to solar rays, whereby the first demonstration is erythema (redness) of the skin. At that moment a number of processes within the skin are activated to reduce the results of the solar insult. As part of the domain of CLINUVEL, we deepened the subject of "tanning" caused by the sun, as a local SOS reaction sent out by the underlying cells.
In reality tanning is a reaction of the upper layers of the skin to produce "brown-ish" (eumelanin) pigmentation to protect our largest organ, the skin, from further burning.

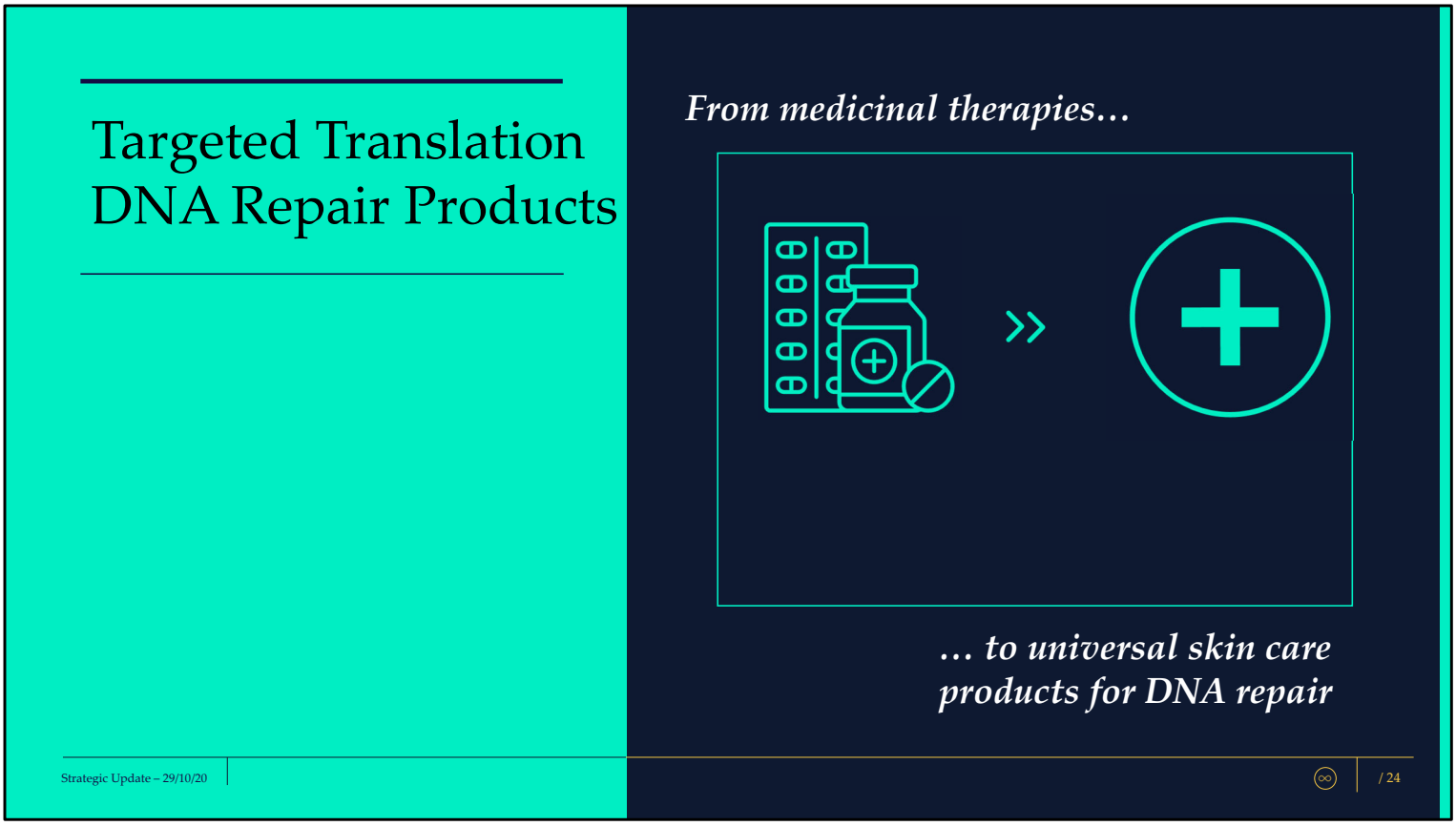
At cellular level DNA damage occurs in all of us, even in darker skin (although not visible).

The repair processes within skin cells required to protect from longer solar exposure are relevant to all of us. Specific focus is required for the nucleotide excision repair (NER) of DNA.

Associated themes which attract global attention are photodamage, photoageing and premature ageing of the skin due to sun. Large consumer-focussed companies have long focused on this popular theme of DNA repair, however originating from a cosmetic viewpoint.

It is now understandable that photoprotection, locally or systemically, melanogenesis (tanning as a response), photoexposure and damage leading to DNA damage are all closely associated.
In using the analogue of a natural hormone in human skin – alpha-MSH – which aims to protect us from solar damage, it is logical to further the field in DNA repair, since evidence has pointed in that direction.
CLINUVEL aims to be the first company globally using melanocortins in assisting the repair of genomic skin damage.

Assessment of underlying mechanism of damage, radical oxygen species, expression of protective tumour genes and cellular function will provide further evidence in 2021.



The third part of CLINUVEL's enduring strategy is to translate both its proprietary technology and intrinsic knowhow to medicinal products and healthcare solutions which would benefit DNA protection and repair of the skin for populations at risk.

CLINUVEL - A Phased Approach

From medicinal products diseases to healthcare solutions for all

Product Availability	Character Target Population	Phase 1 (2005-2020)		Phase 2 (2020-2023)			
Rx (prescription)	Life threatening		Skin cancer	XP/DNA Repair - 2nd indication			
	Severe		EPP	EPP (commercial)			
	Moderate		Photoderm.[1]	Vitiligo			
	Non-severe	Healthy Vol.[2]					
Healthcare Solutions (no prescription)	Specific target groups				Affected populations with a history photodamage		
	General population				Caucasians at risk of DNA damage		
		T0	T1	T2	T3	T4	T5
		1980	2005	2020	2021	2022	2023

Strategic Update – 29/10/20 / 25

As the title of the strategic update suggests, Targeted Technology Translation is a course along decades. However, the lapse of time provides ample reason to test hypotheses and assumptions, since novel technology requires time to become accepted, time to mature and a logical pathway to arrive at its final destination.

In this sense, many global experts have always proclaimed: "*If alpha-MSH and melanocortins had not been important in the evolution of man, why are these released and sitting on the surface of our skin as regulators for environmental damage?*"

In less simple terms, the significance of the family of hormones is nowadays well acknowledged by decision makers globally and CLINUVEL is benefiting from this authentication.

[1] Photodermatoses.
[2] Healthy volunteers.

Foundation for Branding DNA-Repair

PUBLICATIONS ON AFAMELANOTIDE – MELANOCORTINS 2005 - 2020

PUBLICATIONS	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	TOTAL
ASX announcements	73	55	54	43	45	56	47	38	39	59	36	52	32	54	72	54	
Media	198	80	80	66	305	242	132	109	66	119	124	98	121	113	439	408	
Publications – melanocortins	994	1073	1026	954	969	987	891	884	947	813	854	777	782	667	619	307	
Publications – Afamelanotide	1	5	0	4	9	12	5	3	9	5	15	6	15	36	43	68	
Total	1266	1213	1160	1067	1328	1297	1075	1034	1061	996	1029	933	950	870	1173	837	**17,289**

Afamelanotide: Heightened awareness global medical community

essential step to ensure first adoption of technology

Global regulatory recognition & validation: EMA - FDA - TGA

essential step to ensure first adoption of technology

Long term clinical value to patients at risk[1]

essential step to ensure first adoption of technology

Translation into DNA Repair products – universal care for all

STAGE 1: MEDICAL COMMUNITY

- AWARENESS: ESTABLISHED
- RELEVANCE MELANOCORTINS: LOW- SPECIFIC TO PATIENTS

STAGE 2: GENERAL PUBLIC AT RISK

- AWARENESS: VERY HIGH
- RELEVANCE: HIGH TO ALL

Longevity and consistency in communicating a theme, a product and service generally leads to raised awareness among a target audience.

In thinking about CLINUVEL's main focus on the validity of claims of safely using melanocortins for medical purposes, an audience consisting of a targeted medical community had been established over two decades. The table illustrates the number of announcements to the Australian Securities Exchange, media releases and peer review publications on melanocortins and afamelanotide over the past decennia confirming frequent and systematic communication around the technology.

From here onwards, a heightened awareness has been seen among the medical community, expert physicians, researchers, target medical specialists, patient associations and patients as end users. A desired halo effect was being created during this time as wider audiences consisting of patients' families, national authorities, insurers and stakeholders in general became aware of the innovation in melanocortin technology as it became more widely used by hospitals globally.

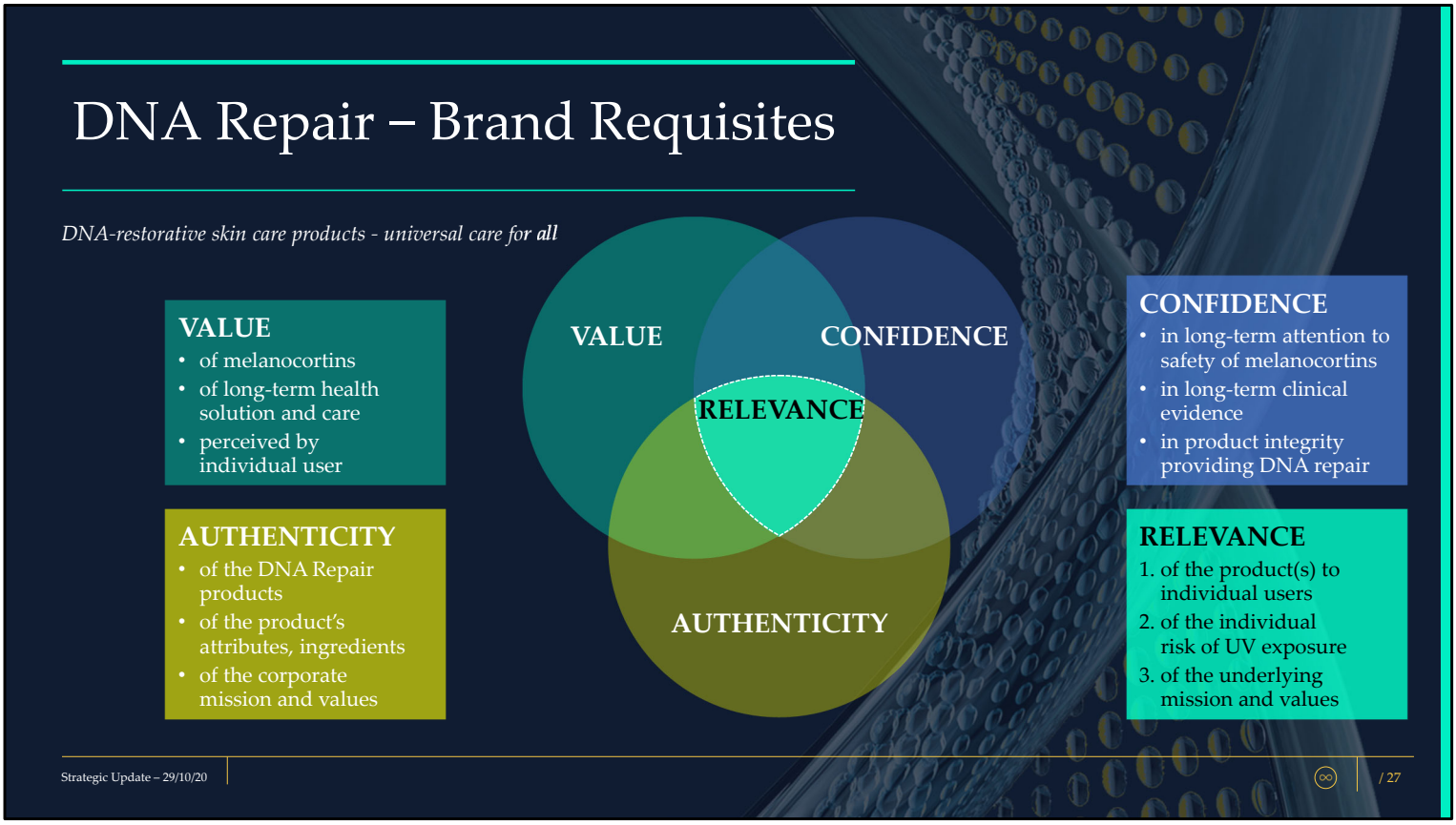
Industry and general press heeded the relevance of the technology with more attentiveness, once the European Medicines Agency (EMA) and US Food and Drug Administration (FDA) formally acknowledged the technology in 2014 and 2019, respectively. To put the position of CLINUVEL's branding, relative to the timetable, in the innovation curve one finds itself just at the beginning of adoption of a DNA-reparative technology.

Awareness of a fledgling product brand in pharmaceuticals is heightened once the safety of a product becomes widely known among its users and medical community validating the status of the drug for a much larger group of users.

[1]For instance, among others, the peer review publications by Biolcati et al (2015) in the *British Journal of Dermatology*, Langendonk et al (2015) in the *New England Journal of Medicine*, Barman-Aksoezen et al (2020) in *Orphanet Journal of Rare Diseases* and Wensink et al (2020) in *JAMA Dermatology*, confirmed the safety of the melanocortin product long term. These are landmark events in the life cycle of new technology and underpin the initiation of broader awareness surrounding the themes relating to DNA-restoration, systemic photoprotection and risk of skin cancers over time. Effectively linking these themes along a path of evidence will be one of CLINUVEL's objectives the coming years.

In a staged manner, a final trajectory in confirming the utility of the melanocortin technology, in casu SCENESSE® (afamelanotide controlled-release formulation), is found in its use as a DNA-reparative agent, its benefits derived from scientific data in vitro, ex vivo and from human use.

Thus the preceding journey spanning decades took CLINUVEL along pharmaceutical branding markers such as consistent communication, safety, acceptance in peer reviews, wide acceptance by the medical community, validation by the two main global regulators and long term safety under real-world-conditions. In essence, the foundation was laid to be in the position ***to brand the concept of DNA repair by melanocortins for patients and universal use****.*



In making melanocortins available for general use, target groups have been identified first to raise the awareness of the technology and theme of DNA-repair of the skin following UV provoked damage.

However, awareness alone of the effects of DNA-damage is not sufficient to successfully introduce a novel concept of DNA repair and CLINUVEL's brand.
Three factors play a role, first *the users' perception of value* proposed by the product and technology.
Second, the confidence of the product and team behind the valued technology, therefore longevity and safety are integral parts.
Third, the authenticity of the proposed products will need to be established swiftly by users not to lose attention and revert or continue with habitual behaviour.
All these factors come together in *the ultimate requirement of relevance of the product, its message and problem it addresses.*

Surely, the awareness of the need to regenerate, rejuvenate, restore the skin is already relatively high among the general public seen from the consumption of leave-on and topical (skin care consumables as lotions, cremes, emulsions) products which have been made available for large audiences.

The specific theme of DNA skin damage which CLINUVEL is now addressing finds an increased awareness, an established subject and popular concern among many globally as environmental awareness has taken hold of us.

In searching for CLINUVEL's position among many actors in the field of DNA repair, rejuvenation, regeneration and personal care, one finds that the Group *differentiates itself from any other peer or company globally in that it originates its authority and knowhow from decades of safe use of specific pharmaceutical technology for medicinal use,* melanocortins.

From here onwards, *Targeted Technology Translation as part of* CLINUVEL's long held strategy may becomes more understandable and logic.

At present, CLINUVEL stands out from the majority of its peers in that it possess and focusses on technology with dual application, for both specific medical purposes as well as for the benefit of individuals at risk, many in the population.

It a is relatively rare phenomenon in pharmaceuticals to possess technology which has applications for targeted medical communities as well benefiting general populations. This dual structure requires a different approach than used in mainstream pharmaceutical companies, which solely target diseased populations.

CLINUVEL's focus on technology and knowhow surrounding melanocortins **lends itself uniquely to serve greater populations following a phased and planned strategy**.
In context, a long-term positive safety profile could in CLINUVEL's plans then be translated to safe *pharmaceumables*, non-prescriptive personal care products for universal use.

With this specific approach comes at the same time a phased and coordinated communication strategy, which is aimed *to explain the translation and therefore relevance of technology, raise awareness among a greater population*.

This perceived relevance is central to today's strategic update.

DNA Repair Addressable Market

	Europe	USA	Australia
Actinic keratoses – prevalence in adult patients[1]	6-29%	10-27%	37-55%
Skin cancer (SCC-BCC) incidence[2]	119-145/100,000	5.3m per annum	2,448/100,000 patient years

Global anti-aging services market (2018)[3]	US$23.45bn
Global facial rejuvenation market (2019)[4]	US$19bn
Projected DNA-based skin care products market, 2025[5]	US$11.7bn

This table gives a broad impression of the market of solar damage, anti-ageing and rejuvenation without a specific subdomain for DNA repair of the skin. The latter is a relatively new field of attention under the premise that it is better to focus on prevention of photodamage and skin cancer.

With CLINUVEL's upcoming products this new subsegment of users will need to grow as awareness will increase.

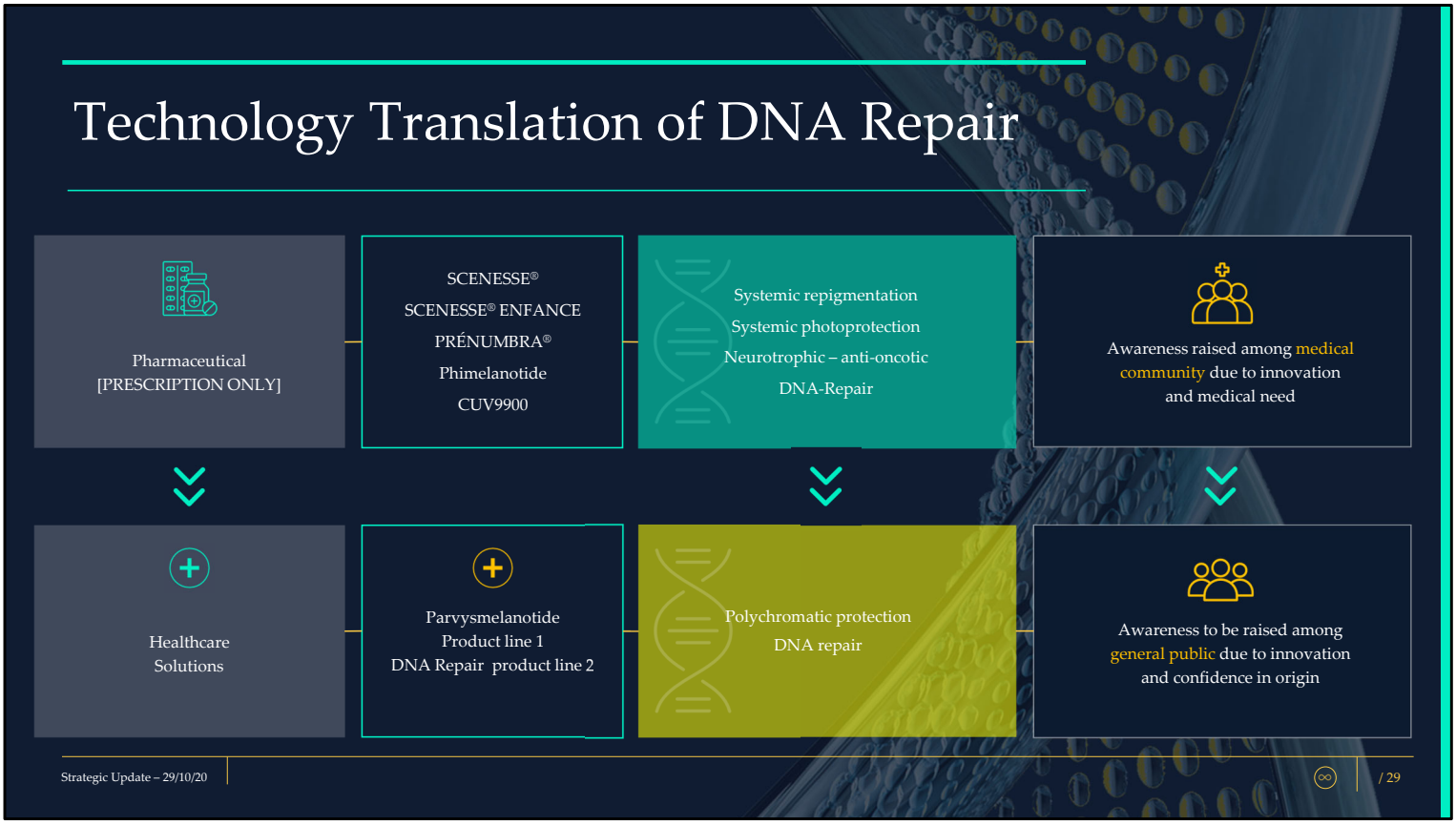
[1] News Medical – Actinic Keratosis Epidemiology, online at https://www.news-medical.net/health/Actinic-Keratosis-Epidemiology.aspx; Ferrandiz et. al., (2016). Prevalence of actinic keratosis among dermatology outpatients in Spain. *Actas Dermo-Sifiliographicas.* 107(8):674-680.

[2] Skin Cancer Foundation – Skin Cancer Facts & Statistics, online at https://www.skincancer.org/skin-cancer-information/skin-cancer-facts/; Perera et. al., (2015) Incidence and prevalence of non-melanoma skin cancer in Australia: A systematic review. *Australas J Dermatol.* 56(4):258-67, Eisemann et. al., (2014). Non-Melanoma Skin Cancer Incidence and Impact of Skin Cancer Screening on Incidence. *J Inv Dermatol.* 134(1):43-50.

[3] Grand View Research - Anti-aging Services Market Size, Share & Trends Analysis Report By Demographics, By Type (Chemical Peel, BOTOX, Microdermabrasion, Breast Augmentation, Liposuction), And Segment Forecasts, 2019 – 2026, abstract online at https://www.grandviewresearch.com/industry-analysis/anti-aging-market.

[4] InsightSlice - Facial Rejuvenation Market size was estimated to be US$ 19 billion in 2019, online at https://www.globenewswire.com/fr/news-release/2020/09/22/2097541/0/en/Facial-Rejuvenation-Market-size-was-estimated-to-be-US-19-billion-in-2019-insightSLICE.html.

[5] Grand View Research - DNA-based Skin Care Products Market Size Worth $11.7 Billion By 2025, abstract online at https://www.grandviewresearch.com/press-release/global-dna-based-skin-care-products-market.



Two cardinal questions will stand out in time:
What makes CLINUVEL special compared to its peers and competitors? And why are CLINUVEL's products relevant to larger audiences beyond a limited patient population it serves now? The company's consistent communication onwards will provide answers to both questions and will attract larger interested readers and users.

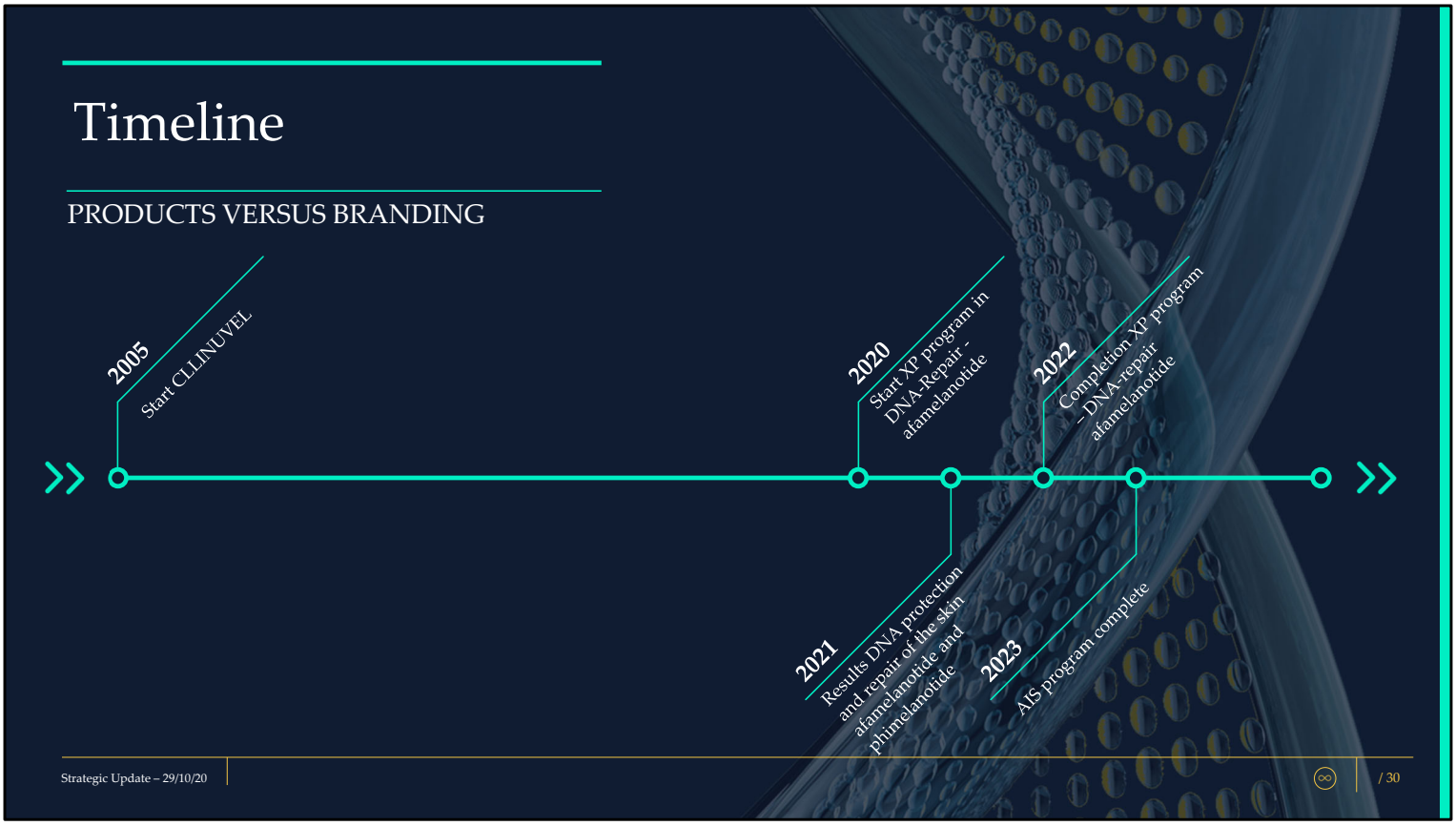
In the illustration, one sees – on the top row – that the five medicinal melanocortin products SCENESSE® - SCENESSE® ENFANCE - PRÉNUMBRA® - and phimelanotide and CUV9900 aim to serve *prescription only demand*. The pharmaceuticals are being developed and marketed to provide systemic repigmentation, systemic photoprotection, neurotrophic properties and DNA repair. The awareness of melanocortins among the wider medical community has been significantly raised the past years due to innovation and medical need for these hormones.

On the bottom row, one sees how the attributes of the medicinal product parvysmelanotide from the top row are translated to *non-prescription products* (pharmaceumables) for universal care aiming to provide healthcare solutions to wider audiences.

The first product line to be released is a product line offering polychromatic protection under extreme conditions and targeting populations at risk of HEV and solar damage. Awareness of the new products will be raised before and during the initial launch of the product line, while larger campaigns are being prepared for the global distribution.
The second product line aims to provide DNA protection and repair of the skin in individuals at risk of solar damage and specific high-risk populations. Awareness of the healthcare risk is relatively high among the users, and modern marketing will assist in raising attributes of the product line and awareness of value proposed.

In launching new products (pharmaceumables) originating from pharmaceutical product(s) and relevant to all future users, consistency is required in communicating to larger audiences. The consistency will be found in messages, approach, technology, healthcare solutions and all broadcasts.

The translation of technology and knowhow *from medicinal use to healthcare solutions* stems from one of the core attributes of melanocortins lending themselves uniquely to universal care benefiting all.



The CLINUVEL team is on a trajectory to complete the majority of the DNA-repair program. This projection much depends on regulatory timelines, turnaround and ability to generate data under current global restrictions.

The first launch of the non-prescription polychromatic protective is foreseen in 2021, from here on further product extensions are being prepared.

In this dense strategic update, a summary has been provided of the Targeted Technology Translation of medicinal products to healthcare solutions benefiting all at risk of HEV and UV and DNA damage of the skin.

As CLINUVEL's journey started with a focus on the medicinal benefits of melanin, it went to systemic repigmentation and systemic photoprotection to finally arrive at DNA protection and repair of the skin. The melanocortin technology used by CLINUVEL lends itself to this specific strategy dictated by the molecular properties of these hormones.

The safe use of afamelanotide has enabled the technology to be evaluated in Xeroderma Pigmentosum (ongoing) and most recently Arterial Ischaemic Stroke (AIS). Translational science is a lateral excursion to other life threatening applications of afamelanotide and melanocortins, while Targeted Technology Translation captures CLINUVEL's strategy from medicine to healthcare solutions for universal use.

The same management team that has taken SCENESSE® to three pharmaceutical markets - EU – US – AU – are completing the triptych strategy of making technology available for DNA repair. It relishes the medical and commercial opportunity and take up the challenge.
As CLINUVEL is growing its funds and qualified personnel, all within the group of companies are aligned to succeed in this enormous challenge. However, it is not a larger challenge than the team faced when it started the journey in 2005.

With humility and health CLINUVEL will also succeed in these objectives and current programs presented.

Thank You

For your support & trust

CLINUVEL Group
29 October 2020

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