CLINUVEL

VITILIGO COMMUNIQUÉ II

12 February 2019

In the second Communiqué we look closer at the role of narrowband UVB (NB-UVB) as the only standard of care at present in vitiligo, both the segmental and generalised form of the disease. Although it is widely accepted in photodermatology that NB-UVB is not a reliable and effective therapy for vitiligo, due to a lack of better available treatment it is offered to patients who show some signs of repigmentation.

In 1903, Professor Niels Ryberg Finsen won the Nobel Prize for medicine for his work treating lupus vulgaris (skin lesions associated with tuberculosis) using "light therapy". Finsen – who himself suffered from the rare Niemann-Pick disease (membranous disease of spleen, liver and heart) and who had become invalid in the latter stages of his life – theorised that additional exposure to light would help treat certain diseases, either in the form of sunlight or artificial exposure. In 1893 Finsen published "Om Lysets Indvirkninger paa Huden" (*A discourse on the effects of light on the skin*) and three years later "Om Anvendelse i Medicinen af koncentrerede kemiske Lysstraaler" (*The use of concentrated chemical light rays in medicine*). He laid the foundation of today's discipline of **photomedicine** and the Society of Photomedicine. His dissertations focused initially on smallpox and lupus vulgaris using different wavelengths of light.

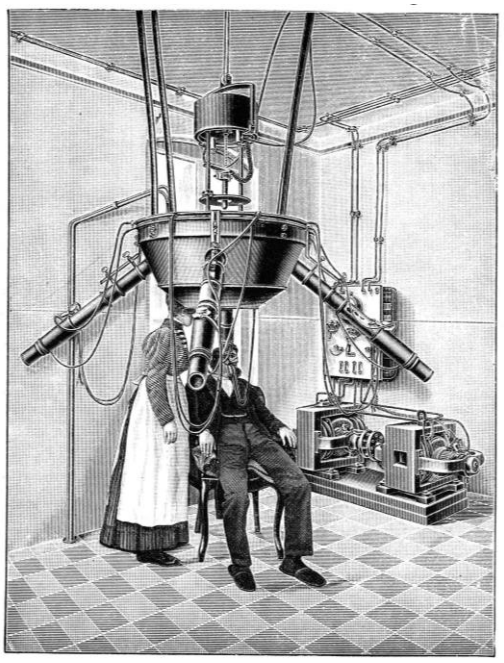

Figure 1. Illustration of an early Finsen phototherapy unit

Two larger organisations originated from Finsen's groundwork. The European Society for Photodermatology very much aims to advance clinical practice by issuing guidelines for therapeutic and diagnostic photodermatologic procedures. In North-America the counterpart gathers annually; on the 28 February the Society of Photomedicine will hold its annual meeting in Washington DC and announce its new name *The Society for Phototherapy and Photoprotection*. Its members and president have decided that the time has come to focus on a new era of research and products under development which provide phototherapy and photoprotection. In August, the European Society of Photobiology will hold its biannual conference in Barcelona. Over the years, it has become apparent that CLINUVEL's work features frequently during these scientific meetings and is a leading pharmaceutical company in this discipline. The community is well aware that CLINUVEL has taken the first systemic photoprotective drug to market.

Figure 2. UV forecast for Australian capital cities, 12 February 2019

NARROWBAND UVB

The American Society of Cancer and the Australian Cancer Council are two of the prominent organisations providing information on the effects of ultraviolet light on human biology. Sun safe campaigns and increasing awareness of the role of UVA and UVB are some of the activities the organisations engage in to forewarn the general public against sun exposure.

The WHO has published its guidelines on UV and outdoors exposure at the hours of highest risk and initiated the UV Index worldwide (http://developer.epa.gov/envirofacts-uv-index-widget/).

Figure 3. An upright phototherapy unit

The controlled use of UV is a different, albeit related, subject which falls under the auspices of the photomedicine societies and photodermatology specialists worldwide. Whereas light along different wavelengths was used at the start of the 20th century, it was not until the 1990s that clinical progress was made on the role of ultraviolet light. The "supra-blue" spectrum of electromagnetic wavelengths was subject to much research in vitro. The bactericidal effects of light had been long known, but the ability to address photodermatoses and other dermatological disorders had become the focus of specialised centres such as Dundee, Scotland.

Initially, broadband UVB **(BB-UVB)** – 280 to 320 nanometres wavelengths – had been used in psoriasis and photodermatoses such as uremic pruritus (itching), idiopathic pruritus, eosinophilic folliculitis and other inflammatory pruritic conditions. **NB-UVB** was introduced later, using light 311 to 313 nanometres in wavelength, to address treatment-resistant psoriasis. Nowadays we know that some forms of psoriasis respond to BB-UVB and others to NB-UVB only. Controlled, fractionated, pulsated and clinical use of NB-UVB became part of the arsenal of dermatologists since the publications by Honigsmann and Ferguson, two prominent photodermatology senior academics, in the early nineties.

NB-UVB exerts its biological effect in a number of ways. First, it acts as an immune modulator to T-cells (T-lymphocytes, white blood cells). Specifically, T-helper cells Th1/Th2 and Th17 play an important role in the expression of the inflammatory response seen in photodermatoses and psoriasis. In psoriasis for instance, dendritic and macrophage cells present antigens which lead to the activation of the T-helper cells and their differentiation into Th1 and Th17. In general, one can say that Th1 cells selectively produce a range of cytokines such IL-2, IFN-γ, LT-α, LT-β and TNF-α, whereas Th2 cells produce IL-4, IL-5, IL-6, IL-9, IL-10 and IL-13. The subsequent release of these cytokines leads to activation of the inflammation and epidermal thickening (hyperplasia).

In psoriasis, the mechanism of NB-UVB phototherapy is to down-regulate Th1/Th17 pro-inflammatory cytokines and up-regulate the Th2 pathway, a counter-regulatory response. Interleukin-17 (IL-17) is one key effector of the Th17 pathway in psoriasis, and IL-22 and IL-23 play a role in the pathogenesis. Phototherapy with NB-UVB aims to provide targeted light emission along relatively short wavelengths to achieve penetration of the skin (dermis). Various research groups have demonstrated that NB-UVB administered twice weekly provides a decrease in serum IL-17, and other cytokines. The anti-inflammatory effect of NB-UVB is well known among photobiologists and photodermatologists.

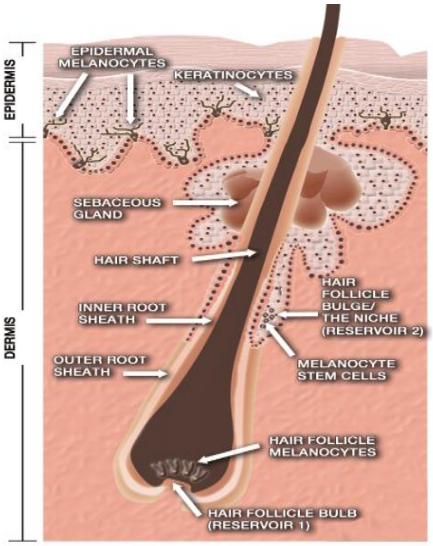

Figure 4. A cross section of skin showing the niche

The precise mechanism of light therapy on cytokines is not fully understood yet, although it has been demonstrated that light of 311 nanometres wavelengths suppresses the IL-23/IL-17 axis in psoriasis and other inflammatory diseases of the skin. Light of 312 nanometres wavelengths suppresses interferon-γ and IL-12, while other cytokines can be upregulated as a reactive mechanism.

NB-UVB is delivered through light sources emitting non-ionising light at the specific wavelengths 308nm or 311nm (+/- 2nm), coming in the form of either stand-up booths, or hand-held devices for domestic use. Each hospital unit or private office determines a treatment regimen for patients initially based on their tolerance to first reddening or "burning" from UV exposure ("the minimal erythemal dose or MED" – see Scientific Communiqué III), measured in J/cm2 surface area. Typically, doses are increased at each clinical visit (often in 10-20% increments) according to the individual response seen and number of sessions, with patients attending 5 to 10 minute sessions at clinics 2 or 3 times weekly for up to 18 months. The variance in dose and treatment times is a point of much professional debate, whereby a patients' constitution and response to therapy dominate the clinical decisions in NB-UVB.

NB-UVB IN VITILIGO

Melanocytes reside at the base of the epidermis, the top layer of skin, surrounded by cells known as keratinocytes. In non-affected healthy skin there are about 36 keratinocytes to each melanocyte. While keratinocytes turn over rapidly, melanocytes live for many years and the body is less capable of regenerating these cells once lost. The aim of the current vitiligo therapy with NB-UVB is to both arrest the loss of melanocytic output and stimulate repigmentation from the defective, or new melanocytes.

While the precise mechanism of NB-UVB is still being researched, clinical sessions are known to trigger a clinical response seen as localised follicular or peripheral repigmentation in some patients. Additionally, NB-UVB stimulates the production of alpha-melanocyte stimulating hormone (α-MSH) by melanocytes and keratinocytes (auto-/paracrine) aiming to signal to their neighbouring melanocytes. This natural hormone binds to the melanocortin-1 receptor (MC1R) on the melanocyte to produce melanin, returning colour to the skin (see Scientific Communiqué II).

The NB-UVB treatment, when it shows first signs of clinical response comes in the form of follicular repigmentation – "islands" of colour returning to the skin of vitiliginous lesions around the hair follicle (see *Figure 5*). With repeated NB-UVB doses these islands can become confluent, providing the patient with first signs of repigmentation.
The use of combination therapies – additional drugs known to help the repigmentation process – is common, although regimens vary. In general, vitiligo experts worldwide concur that an effective therapy for vitiligo is still lacking despite some response seen from NB-UVB.

Dermatologists commonly prescribe combination or maintenance therapies – most often topical products – either during or after the completion of a course of NB-UVB to ensure ongoing benefit from the treatment. For instance, topical steroids and calcineurin inhibitors are often used off-label to act on the immune system locally in between NB-UVB sessions and have seen some success in trials when compared to NB-UVB monotherapy.

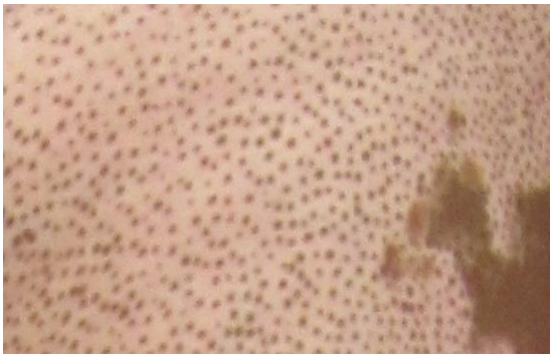

Figure 5. Follicular repigmentation in a vitiligo patient

CLINICAL BURDEN

The burden of NB-UVB treatment is high for patients. Treatment compliance is not a guarantee for achieving satisfactory repigmentation, and physicians often temper expectations. While the return of pigment may provide positive trial results, the effect may not be sufficient for patients who have endured 18 months of twice or thrice weekly visits. Certain body parts are also stubbornly resistant to treatment – particularly the hands and feet.

Due to the lack of understanding of the NB-UVB process, there is no way to provide patients with a prediction of success in treatment, with the standard approach to encourage patients to visit clinics for three to six months before the first assessments are made of therapeutic benefit. The cost of regular dermatology visits, and the time away from work or study needed to facilitate these, remains a substantial financial, as well as psychological, burden.

SAFETY

The logical question to ask is whether accumulated doses of NB-UVB increases the risk of skin cancers in these patients. The impact of UV light is well known, with broadband UV exposure causing both acute (sunburn) and chronic (DNA damage, photoproducts and skin cancer) damage. With narrowband exposure, specifically NB-UVB, our understanding is less detailed, but it is believed to have some long-term effects. While NB-UVB has been recognised as safer than older phototherapies (in particular psoralens and UVA), there are valid clinical concerns around the use of a known carcinogen as a therapy. A 2018 paper reported 15 years of experience with NB-UVB in patients (both vitiligo and other disorders) with an increased risk of non-melanoma skin cancer compared to the general population. This contrasts with other reports rebuking the carcinogenic potential of NB-UVB, but gives pause for concern, and a strong rationale to limit the overall cumulative exposure of patients to UV light.

FURTHER STEPS IN NB-UVB

A recent Cochrane review, a systematic meta-analysis of randomised clinical trials found in the medical literature, determined that the best evidence to date favours the use of NB-UVB with combination therapies for vitiligo, particularly generalised or widespread disease. The review lamented, however the lack of consistency in treatment protocols and high rate of disease recurrence (reported as 40%) after initial success with treatment. In short, more needs to be done to provide physicians and patients with the surety that treatments are safe and effective in the long term.

Experts have sought to address the challenges posed by NB-UVB treatment by first seeking agreement on the best way to treat patients. An international working group recommended that NB-UVB be the first intervention for patients with more than 5-10% of their body surface area affected by vitiligo, with six months of therapy given to determine efficacy and evaluations made at further three-month intervals. The group concludes, however, that new therapies are needed to better address the clinical challenge of vitiligo. CLINUVEL recognised this while monitoring the past decades whether new therapies actually were being developed and is now working towards fulfilling this ambition.

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About CLINUVEL PHARMACEUTICALS LIMITED

CLINUVEL PHARMACEUTICALS LTD (ASX: CUV; NASDAQ INTERNATIONAL DESIGNATION ADR: CLVLY; XETRA-DAX: UR9) is a global biopharmaceutical company focused on developing and delivering treatments for patients with a range of severe genetic and skin disorders. 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 photoprotection and repigmentation. These patient groups range in size from 5,000 to 45 million worldwide. CLINUVEL's lead compound, SCENESSE® (afamelanotide 16mg), was approved by the European Commission in 2014 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, Switzerland, the US and Singapore, with the UK acting as the EU distribution centre.
For more information go to http://www.clinuvel.com.

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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, 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 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 2018 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.