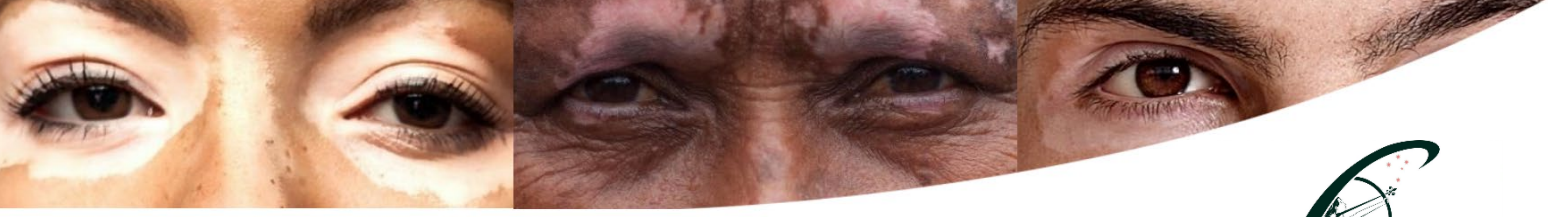


CLINUVEL

Vitiligo Communique III

29 October 2019

In Vitiligo Communiqué I (19 December 2018) and Vitiligo Communiqué II (12 February 2019) essential information and principles on the pathogenesis (the origins of the disease) of vitiligo were provided. In this Vitiligo Communiqué III, we deepen the current understanding of the psychological impact of vitiligo on patients.

Each Vitiligo Communiqué will now feature a global conference calendar where vitiligo will be a focal point of presentations and discussions.

Pigment loss as seen in vitiligo

PSYCHOLOGICAL IMPACT VITILIGO

The psychological impact of vitiligo is still not well understood.

Although vitiligo is a skin disorder with visible characteristics, there are now clinical guidelines, such as the UK guidelines, recommending the assessment of the psychological state during clinical evaluation. While routine psychological evaluation is not yet standard of care for the majority of vitiligo patients, there is a renewed focus on understanding the psychiatric burden of the disease some 40 years since the first studies were published.

In 2015 Ezzedine et al published a review paper in The Lancet, noting the lack of understanding of vitiligo, that its unpredictable prognosis caused fear, insecurity, embarrassment and sadness, and that greater degree of stigmatisation was seen in those patients whose lesions were more visible.[1] Yet the authors also highlighted that there was a clear lack of research into understanding the psychological effect of the disease or its treatment for patients.

Following this high-citation piece, several reviews and meta-analyses studies have sought to focus on the impact of vitiligo beyond depigmentation. In particular, there is a focus on the psychological impact of vitiligo across patient cohorts and its variability alongside co-founding factors, both environmental and genetic.

Amer and Gao conducted a meta-analysis of vitiligo studies which deployed the dermatology life quality index (DLQI), identifying 21 studies with 4,721 vitiligo cases.[2] While not an ideal tool for a pigmentary disorder – it has never been validated for vitiligo and focuses on symptoms, such as itch, which are not present in the disease – the DLQI provides a comparator across cohorts for an extended period of time and shows a marked effect for vitiligo patients, particularly women, younger patients, and those with darker phototypes.

Lai et al published a review of twenty-five studies with 2,708 cases of vitiligo in 2017, where vitiligo patients were found to have a higher rate of depression.[3] Although this was a reasonably subjective study – since self-reported questionnaires were determining the tendency to

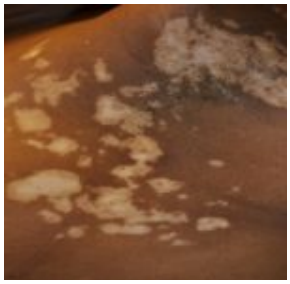
depression – up to 2017 there had been no studies which had performed a full psychiatric evaluation in vitiligo. The authors found in the statistical analyses through the pooled odds ratios a significant difference in the ratio of depression among vitiligo patients compared to controls (95%, $P < 0.001$). The large sample size provided some comfort on the consistency of these findings, although a more objective measure would have been more conclusive.

In a 2018 study conducted by Wang et al, progress was made in understanding the prevalence of depression versus clinical depression.[4] A meta-analysis of 1,965 patients identified from 20 eligible cohorts was conducted. The prevalence of clinical depression was 8% (95% CI, 2%-14%) and depressive symptoms 33% (95% CI, 23%-44%) using the Diagnostic and Statistical Manual of Mental Disorders IV or International Classification of Diseases codes-10.

Wang et al found that a patient with vitiligo was 4.96 times more likely to display depression compared with controls. Importantly, in addition, subgroup analysis showed that the prevalence of depression in Asian and female patients with vitiligo was significantly higher than in Caucasian and male ones. Using a Hamilton Depression Rating Scale, the pooled prevalence of depressive symptoms was higher, and the heterogeneity was lower.

In 29 studies evaluating 2,530 patients found from using various databases, Osinobi and co-authors found a wide range of psychological outcomes to be common in patients with vitiligo.[5] It was also found in this 2018 study that there was a need for validation of the psychological outcome screening tools in the field of dermatology. This finding mirrors that of CLINUVEL's teams when working in this particular field of regenerative medicine.

40 YEARS OF UNDERSTANDING



Pigment loss seen in vitiligo (upper torso).

An author with ground-breaking research is without doubt Dr Judith Porter, whose publications in the seventies, eighties and nineties has been fundamental to understanding stigmatisation and the degree of handicap of vitiligo patients. It was in 1978 that she published the first piece – co-authored with sociology professor Ann Hill Beuf and two of the fathers of modern dermatology, James Nordlund and Aaron Lerner – recognising the "considerable sociological and psychological effect [of vitiligo] on many of its victims" that "can, in effect, disable some patients".[6]

In 1991 Porter and Beuf wrote a report on 158 patients diagnosed with vitiligo to investigate the degree of disturbance due to self-esteem and stigmatisation.[7] They had been particularly interested in the differential effects of stigma on vitiligo patients. Essential in their report was the understanding of race in response to physical stigmatisation in the disfiguring disease; this was the first time stigmatisation was ever described in the disorder.

Suggesting that cosmetic disfigurement was a stigmatising handicap putting up barriers to privileges and societal opportunities because of prejudices toward atypical appearance was a novel hypothesis at the time. Indeed, Porter and Beuf went as far as suggesting that vitiligo impaired appearance, equalling or exceeding other body afflictions, and provokes negative emotions of bystanders. Expectedly, Porter and Beuf found that females experienced more stigma due to vitiligo, and in general from appearance related disorders.

"*Turning White may have severe implications for Black identity*." – Porter & Beuf, 1991

Clearly, coping mechanisms differ between patients, but the overall ability to manage depends on the coping resources a patient has at their disposal. The importance that we place on appearance – individually – is part of a major coping resource which can either avert or exacerbate the psychological threat posed by vitiligo.

Other authors have gone as far as identifying that social resources are interpersonal networks to which people belong and serve as essential support.

Porter became interested in the notion that "Master Status" such as race, gender and age was significantly determining how an individual would react to a label. Master Status and societal role broadly determine an individual's experiences with stigma and what resources they have to cope with stigma.

The framework described by the two authors led to the suggestion that appearance-impairing physical stigmas such as vitiligo would affect patients of darker skin complexion more than those with lighter skin.

In Porter and Beuf's view, there is a compounding effect of having both a Master Status and a handicap, while not having sufficient economic and social resources to cope with the disease. Naturally, in darker skinned individuals any vitiligo on exposed skin creates a dramatic contrast in comparison to patients with lighter skin types.

"*Because of racial discrimination, Blacks are subject to more externally imposed sources of strain than are Whites.*"- Porter & Beuf, 1991

The difference in perception of disease among patients of different skin phototypes has been essential to CLINUVEL's work with vitiligo. The differentiation of the impact of vitiligo between skin types is accentuated in Porter and Beuf's evaluation that for people of a lighter skin type "vitiligo is experienced primarily as an appearance impairment" whereas for people of darker skin types it can have a more significant impact upon their fundamental identity.

The evaluation of 158 respondents taught Porter and Beuf that visibility is indirectly associated with the degree of disturbance in vitiligo through its effect on perceived stigmatisation and self-esteem. In the study findings, many of the hypotheses of the authors could not be confirmed. It may well be that the social and psychological resources of patients with darker skin types enable and mitigate against stigmatisation due to vitiligo.

An author who has been prominent in the development vitiligo treatments is Dr Pearl Grimes, who observed that a multitude of global cultures and societies emphasise the significance on appearance, aesthetics, and pigmentation. Therefore, in these cultures, any condition which affects appearance may be fraught with loss of privilege, opportunities, and often upward societal mobility. In vitiligo, self-esteem is compromised given the inherent visibility of the depigmentation.

Now, 41 years after Porter first discussed the psychological impact of vitiligo, numerous studies and meta-analyses of large cohorts have demonstrated that the disease is affecting all skin types with a perceived burden due to the visibility of vitiligo.

Finally, as one can expect, the more body surface area affected by vitiligo, the more severe the impact on patients' self-reported quality of life.[8] The loss of pigmentation on the head and neck is perceived as most disfiguring irrespective of race, gender and age. Many patients are also found to be embarrassed by the loss of pigmentation in unexposed genitals for fear of being stigmatised, as in some cultures the loss of pigmentation around the genitalia is associated with sexually transmittable diseases. At CLINUVEL we focus on specific cases of vitiligo, whereby lesions affecting more prominent visible areas such as the head and neck, and more sensitive areas, such as the genitalia, are understood to have a more severe impact on patients' self-esteem and quality of life.

In CLINUVEL's studies, we anecdotally found female patients to suffer from loss of pigmentation more than male patients of colour, confirming the findings of various groups. The gain in pigmentation on larger body surfaces was perceived as a major clinical event for patients affected, since many patients had undergone earlier treatment attempts with corticosteroids and narrowband UVB alone.

Much attention is given to psychological impact and factors as self-esteem by CLINUVEL's teams in making decisions on the development of SCENESSE® (afamelanotide 16mg) for vitiligo patients.[9]

CONFERENCE CALENDAR

VITILIGO CONFERENCES 2020

Date	Location	Conference
19 Mar	Denver, USA	Annual Meeting of the Photomedicine Society
19 Mar	Denver, USA	Annual Skin of Color Society Symposium
20-24 Mar	Denver, USA	American Academy of Dermatology (AAD) Annual Meeting
13-14 Apr	Tokyo, Japan	3rd World Congress on Dermatology and Aesthetic Medicine
30 Apr-2 May	Porto, Portugal	16th European Academy of Dermatology and Venereology Symposium
13-16 May	Scottsdale, USA	77th Annual Society of Investigative Dermatology (SID) Meeting
11-13 Jun	Vienna, Austria	20th European Society for Paediatric Dermatology Annual Meeting
18-21 Jun	Yamagata, Japan	23rd International Pigment Cell Conference (IPPC)
7-9 Jul	Manchester, UK	100th Annual Meeting of the British Association of Dermatologists
23-27 Sept	Vienna, Austria	European Academy of Dermatology and Venereology Annual Meeting

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7. Porter & Beuf (1991). Racial Variation in Reaction to Physical Stigma: a Study of Degree of Disturbance by Vitiligo Among Black and White Patients. *J Health Soc Beh*. 32(2):192-204.

8. Silverberg & Silverberg (2014). Quality of life impairment in children and adolescents with vitiligo. *Pediatr Dermatol*. 31(3):309-18. Epub 2013 Oct 18.
9. SCENESSE® (afamelanotide 16mg) is approved in the European Union as an orphan medicinal product for the prevention of phototoxicity in adult patients with 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 clinuvel.com.

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 and the US Food and Drug Administration in 2019 for the prevention of phototoxicity (anaphylactoid reactions and burns) in adult patients with erythropoietic protoporphyria (EPP). More information on EPP can be found at http://www.epp.care. Headquartered in Melbourne, Australia, CLINUVEL has operations in Europe, Singapore and the USA. For more information please go to http://www.clinuvel.com.

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, 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 2019 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.

www.clinuvel.com

Level 11 T +61 3 9660 4900

535 Bourke Street F +61 3 9660 4999

Melbourne

Victoria, Australia, 3000