CLINUVEL

The mechanism of SCENESSE® in vitiligo

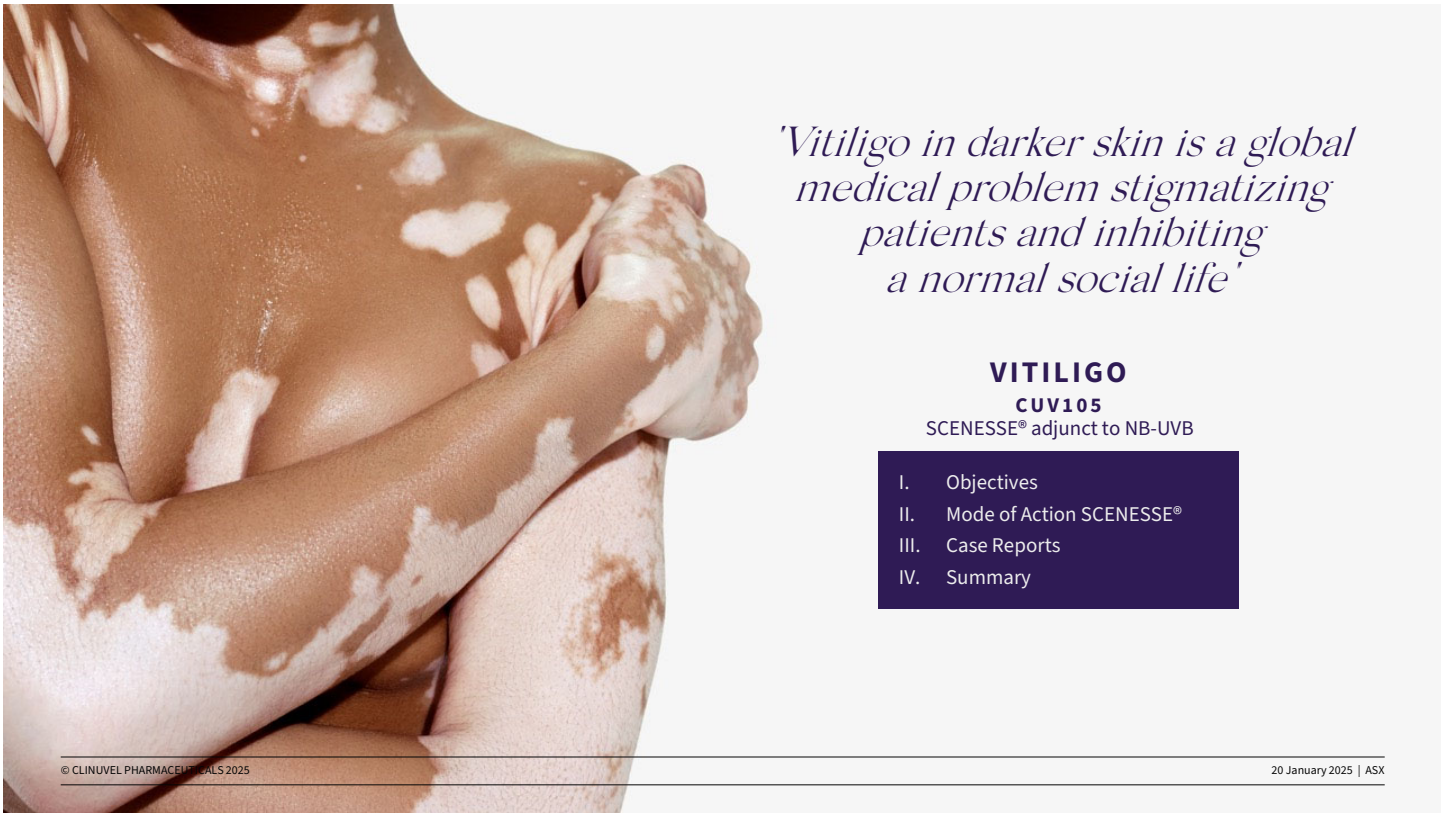
As the randomised study CUV105 progresses, first observations are being shared by physicians and patients.

Given the novelty of the proposed therapy in non-segmental vitiligo, a pattern of skin repigmentation follows a number of stages, shown in this publication.

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 and/or other world, regional or national events affecting the supply chain for a protracted period of time, including our ability to develop, manufacture, market and sell biopharmaceutical and PhotoCosmetic products; competition for our products, especially SCENESSE® (afamelanotide 16mg), CYACÊLLE, PRÉNUMBRA®, NEURACTHEL® or products developed and characterised by us as PhotoCosmetics; our ability to achieve expected safety and efficacy results in a timely manner 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, the UK, Israel, China, Japan, and/or LATAM regions 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®, CYACÊLLE, PRÉNUMBRA®, NEURACTHEL® or products developed as PhotoCosmetics which may lead to the Company being unable to launch, supply or serve its commercial markets, special access programs and/or clinical trial programs; any failures to comply with any government payment system (i.e. Medicare, Medicaid, and U.S. Department of Veteran's Affairs) reporting and payment obligations; uncertainties surrounding the legislative and regulatory pathways for the registration and approval of biotechnology, cosmetic and consumer based products; decisions by regulatory authorities regarding approval of our products as well as their decisions regarding label claims; our ability to retain or attract key personnel and managerial talent; the impact of broader change within the pharmaceutical industry, cosmetic industry and related industries; potential changes to tax liabilities or legislation; environmental risks; and other factors that have been discussed in our 2024 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 preliminary and uncertain forecasts and estimates is available on request, whereby it is stated that past performance is not an indicator of future performance.

The document may contain forward looking statements, readers are advised to review the Company's disclaimers.



Index

Today we share new clinical observations which are relevant to the understanding of therapeutic effects of afamelanotide in non-segmental vitiligo patients.

Four case reports are discussed, and physicians' and patients' responses are provided.

I

Objectives

1. Treatment of skin type III-IV-V-VI
2. Follicular + peripheral melanogenesis
3. Stability of melanogenesis
4. Establish treatment paradigm SCENESSE®

CUV105

INCLUSION CRITERIA

Skin type (FST) III-IV-V-VI
Widespread depigmentation
Face-head-neck involvement

PRIMARY ENDPOINT

T-VASI 50%

SECONDARY ENDPOINTS

F-VASI
VitiQoL, PGIC, PtGA, VNS
Maintenance of pigmentation
Safety

Objectives

The focus of the Company is to develop afamelanotide for patients with the highest medical need. In CUV105, a number of clinical objectives are being evaluated as the study advances.

These objectives are reflected in the inclusion criteria of CUV105:

a. Non-segmental vitiligo patients with darker skin types (Fitzpatrick Skin Type III-IV-V-VI)

b. Widespread disease (T-VASI ≥3 excluding hands and feet)

c. Face, head & neck involvement

The primary endpoint

a. Total Vitiligo Area Scoring Index (T-VASI) improvement 50%

The secondary endpoints

a. Facial Vitiligo Area Scoring Index (F-VASI) improvement

b. VitiQoL, PGIC, PtGA, VNS – measures of quality of life, patient satisfaction and disease noticeability

c. maintenance of pigmentation

d. safety

II

Mode of Action SCENESSE®

1. **2–3 weeks** after afamelanotide and NB-UVB: first follicular response (pink-reddish)
2. **3–4 weeks** persistent follicular response
3. **4–5 weeks** unaffected skin becomes darker
4. **5–8 weeks** confluency follicular islands
5. **9–16 weeks** follicular & epidermal repigmentation vitiliginous lesions
6. **17–26 weeks**, overall darkening, unaffected skin starts to reduce to baseline colour
7. vitiligo trunk-back, arms-legs & face to reduce to less than 50%. Unaffected skin returns to baseline complexion

AFAMELANOTIDE & NB-UVB

CLINICAL RESPONSE IN VITILIGO IN 7 VISIBLE STAGES

Staged repigmentation in non-segmental vitiligo following administration of SCENESSE®

A particular pattern is seen following the use of SCENESSE® in vitiligo, adjunct to NB-UVB, broadly defined in seven stages (approximations from clinical observations):

Stage 1 **2-3 weeks** after administration of narrowband UVB (NB-UVB) and afamelanotide 16mg, some itching and redness can be seen on the white vitiligo patches. Unaffected skin starts to show redness.

Stage 2 **3-4 weeks** after study start, a first follicular response is seen within the white vitiligo patches. This is seen as first pink to reddish dots within vitiligo lesions. The unaffected skin starts to turn darker.

Stage 3 **4-5 weeks** after study start, a persistent follicular response is observed within the vitiligo patches. At this stage the surrounding unaffected skin becomes darker, this may give the appearance of an increased contrast between white vitiligo patches and unaffected skin that has become darker.

Stage 4 **5-8 weeks** after start, the pink follicular islands within the white vitiligo patches become brown, unaffected skin remains darker.

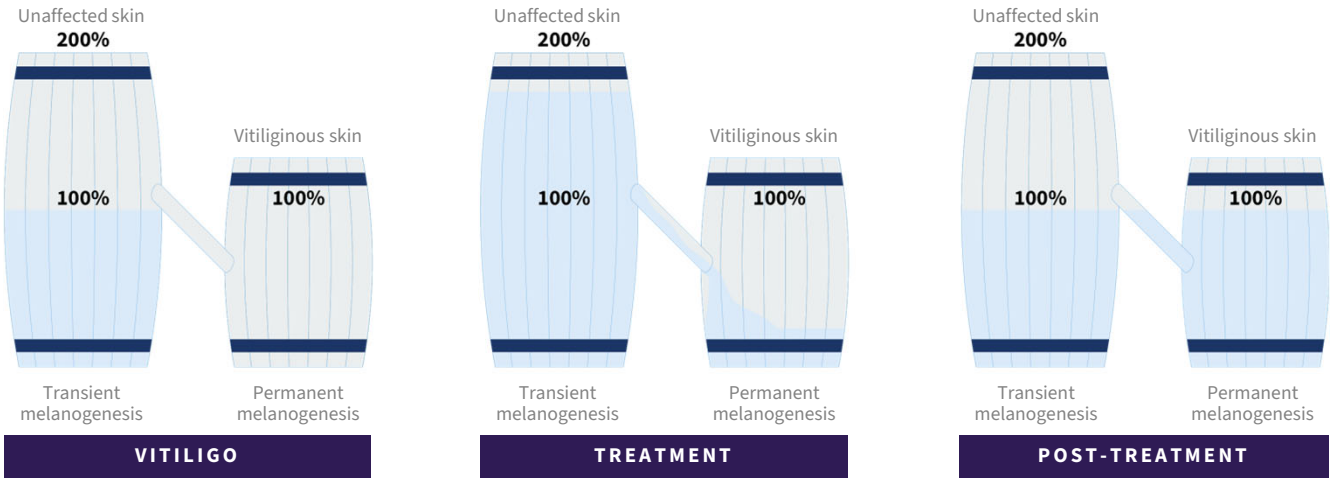
Stage 5 **9-16 weeks** after start, the remaining borders of the white vitiligo patches show darkening and the brown follicular islands within the vitiligo patches start to fuse (confluency). The unaffected skin remains darker, a few shades deeper compared with the patient's usual colour at the start of the treatment.

Stage 6 **17-26 weeks** after start, the vitiligo patches start to repigment evenly and become darker reaching a similar colour to the unaffected skin. The unaffected skin starts to lose its intense darkness and returns to baseline colour.

Stage 7 **after 26 weeks**, the process of repigmentation continues with the objective to reduce more than 50% of white vitiligo patches on the back, trunk, arms, legs and face. Unaffected and repigmented skin returns to baseline complexion.

II

Afamelanotide – melanogenesis in vitiligo



Afamelanotide-provoked melanogenesis in vitiligo

The activation of melanin-producing cells near the hair follicle in deeper layers of the skin to repigment white vitiligo patches is later than the activation of melanin-producing cells superficially in unaffected skin. The two mechanisms are occurring independently, yet at different times.

The three illustrations show two communicating barrels:

When the unaffected skin (represented as the large capacity barrel of 200%) is activated, it starts to produce melanin which is shown as first total body darkening response. Since the white vitiligo patches have lost their functional melanocytes, time is needed to activate new cells and see visible repigmentation activity. From observations it is seen that the white patches require more time to initiate follicular repigmentation than the unaffected skin. A contrast in pigmentation between unaffected and affected skin is initially shown.

However, when the unaffected skin becomes maximally dark, the affected vitiligo skin starts to “catch up” in production and intensity, and the contrast starts to diminish and fade.

When the unaffected skin starts to fade in colour, the affected vitiligo patches “catch up” in repigmentation and start to blend in with the unaffected skin returning to natural colour (pigmentation).

III

Case Reports

1. Four longer-term case reports
2. Follicular repigmentation observed in as little as 3-4 weeks
3. Drug well tolerated in all patients enrolled
4. Patients' reports excellent, NB-UVB only cohort offered afamelanotide as adjunct to NB-UVB at conclusion of initial study period
5. Physicians' reports very positive thus far

CASES 1–4 SUMMARY

Long- and short-term disease duration patients

Fitzpatrick skin types IV

7 SCENESSE® implants per patient

Up to 53 NB-UVB sessions (40 in CUV105 protocol)

Clinical Cases – CUV105

Some first observations from the four cases show:

a. follicular pigmentary response is seen within the vitiligo patches after four weeks of starting the treatment with afamelanotide.

b. the drug as adjunct to NB-UVB is well tolerated.

c. patients' reports thus far are excellent, in that all four patients have been excited about the results obtained. Those patients who initially received NB-UVB alone and continued on to receive afamelanotide as adjunct to NB-UVB are content to stay in the trial.

d. physicians are satisfied with the results seen to date.

In summary of the four cases reported:

I. variation in time from vitiligo onset (long- and short- duration)

II. all four cases are Fitzpatrick skin type IV

III. each patient received seven SCENESSE® implants

IV. patients received up to 53 NB-UVB administrations

CLINUVEL thanks the patients and treating physicians for being able to share these case reports.

III

First Clinical Observations

CASE STUDY 1

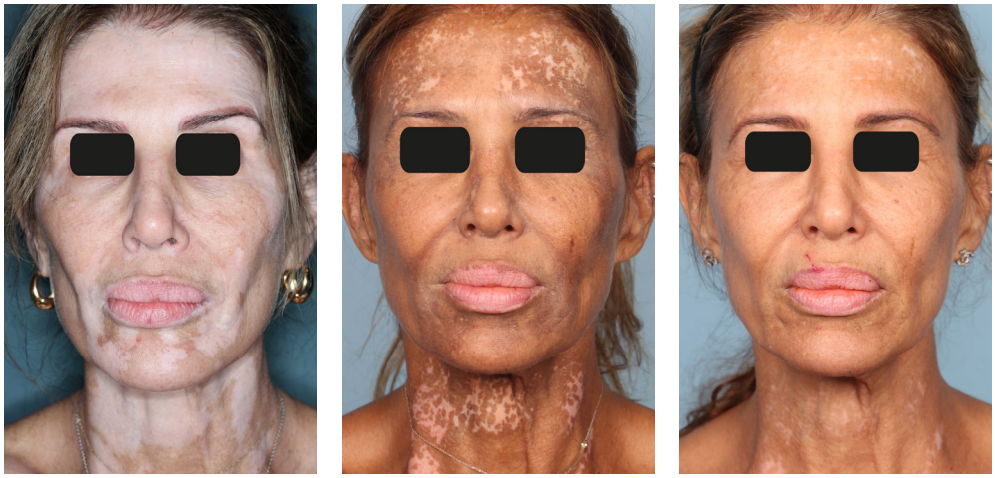
Participant A

1. Female, 55 years old, Skin Type IV
2. Diagnosed with vitiligo in 2006, slowly progressive disease activity, no previous episodes of repigmentation, and no family history of vitiligo. Unresponsive to previous vitiligo treatments.

PHYSICIAN'S REPORT

80-90% repigmentation was seen after Day 140 but near total repigmentation was achieved after continued NB-UVB monotherapy.

DAY 0	DAY 134	DAY 222
Baseline	7 afamelanotide implants, 39 NB-UVB treatments	82 days after completing study 7 afamelanotide implants, 53 NB-UVB treatments



First clinical observations: Participant A

The results of the face show total repigmentation observed at day 222 (Week 32).

This patient was unresponsive to previous therapy, but saw extensive total body repigmentation. The patient was very content with the results and will be followed up to 12 months.

After completion of the study, the patient continued NB-UVB monotherapy. After three months (14 additional NB-UVB sessions), the patient saw near-total repigmentation.

III

First Clinical Observations

CASE STUDY 2

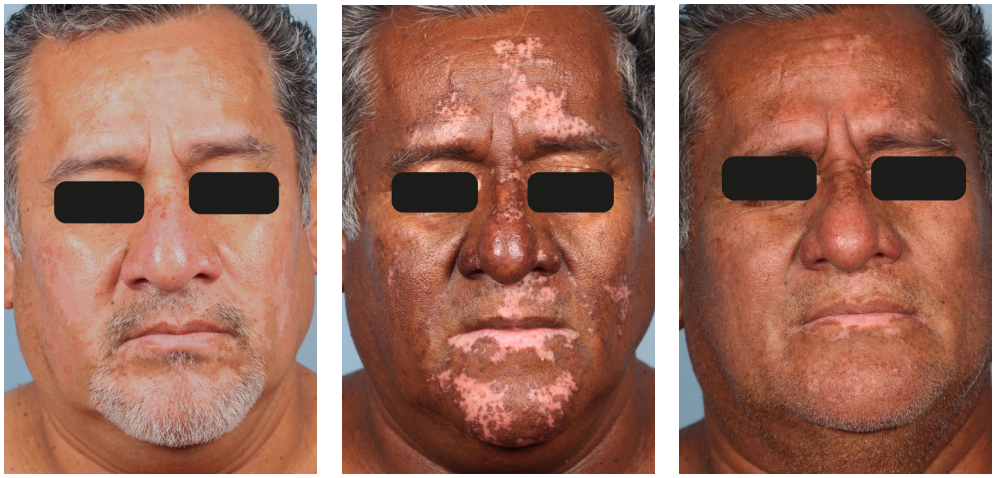
Participant B

1. Male, 52 years old, Skin Type IV
2. Diagnosed with vitiligo in 2023, progressive disease activity, no previous episodes of repigmentation, and no family history of vitiligo. No history of previous vitiligo treatments.

PHYSICIAN'S REPORT

The patient and our team are pleased with the results. Patient reports greater self esteem post-treatment.

DAY 0	DAY 140	DAY 170
Baseline	7 afamelanotide implants, 40 NB-UVB treatments	30 days after completing study, no further therapy



First clinical observations: Participant B

The results of the face show total repigmentation observed at day 170 (within six months). At day 140, the afamelanotide treatment and adjunct NB-UVB concluded.

The patient had a short disease duration at enrolment, with lesions mostly on his face, head and neck.

Treatment over the study duration saw considerable repigmentation, with darkening of unaffected skin demonstrated at day 140.

The patient continued to repigment spontaneously after completion of therapy, with vitiligo lesions on his cheeks, chin and forehead at near-complete repigmentation (see next slide). By day 170 the patient's repigmented and unaffected skin was of similar colour, while he had returned to his usual baseline colour.

A close up of the facial skin of Participant B

The images show cheeks and chin comparing start of the study to day 170 further responding up to the follow up period.

III

First Clinical Observations

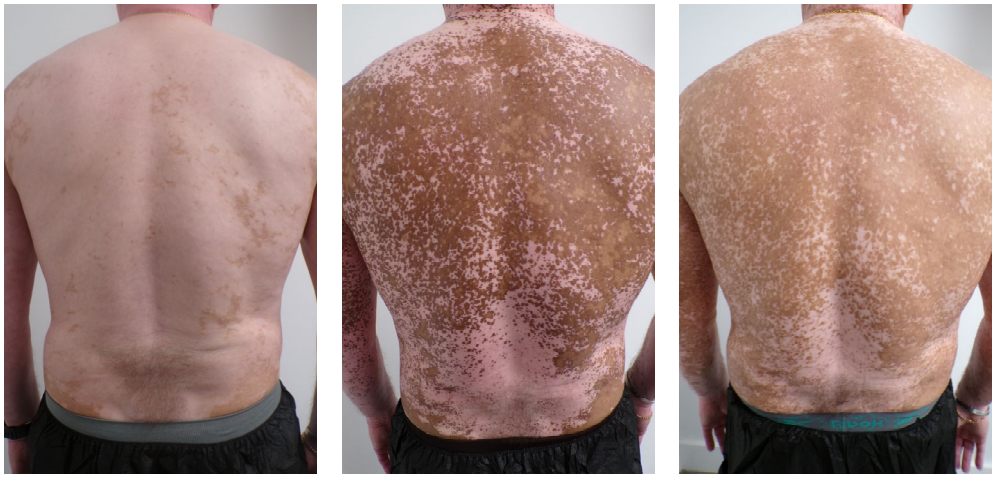
CASE STUDY 3

Participant C

1. Male, 56 years old, Skin Type IV
2. Diagnosed with vitiligo in 1999

PHYSICIAN'S REPORT

First repigmentation seen around day 42, considerable repigmentation seen by day 106. Patient continued to repigment after conclusion of treatment protocol with no further therapy.



The skin surface of the back of Participant C

The patient had long-standing disease and extensive depigmentation across his whole body.

Repigmentation was seen on the body and face over the course of the study (140-day treatment period).

Spontaneous repigmentation was seen after completion of treatment, while unaffected skin returned to baseline colour.

No relapse of disease is seen five months after completion of treatment.

III

First Clinical Observations

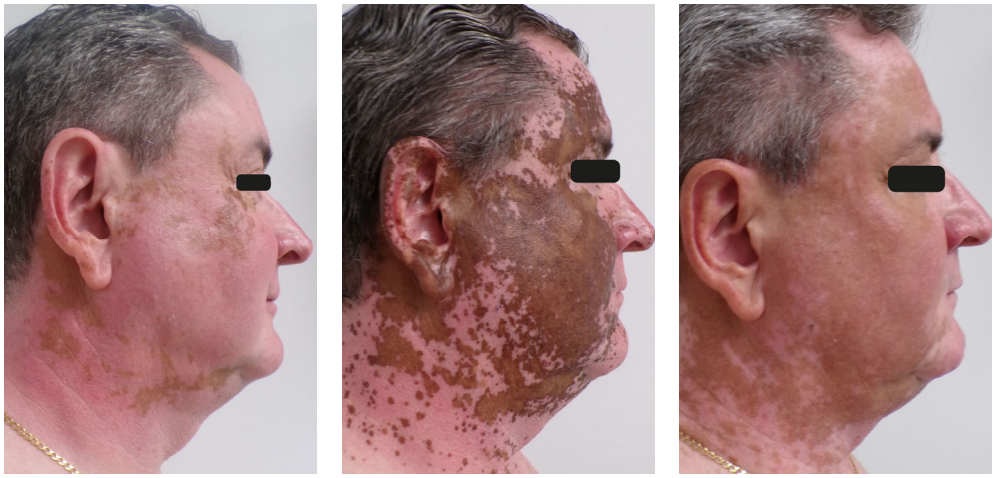
CASE STUDY 3

Participant C

1. Male, 56 years old, Skin Type IV
2. Diagnosed with vitiligo in 1999

PHYSICIAN'S REPORT

First repigmentation seen around day 42, considerable repigmentation seen by day 106. Patient continued to repigment after conclusion of treatment protocol with no further therapy.



The facial skin of Participant C

The face of the participant shows a similar pattern of repigmentation.

By day 140 the patient had seen considerable repigmentation, contrasted by melanogenesis of unaffected skin activated by afamelanotide.

By day 308, the unaffected skin returned to shades close to baseline, while vitiligo patches show repigmentation.

The patient was very content with the results achieved.

III

First Clinical Observations

CASE STUDY 4

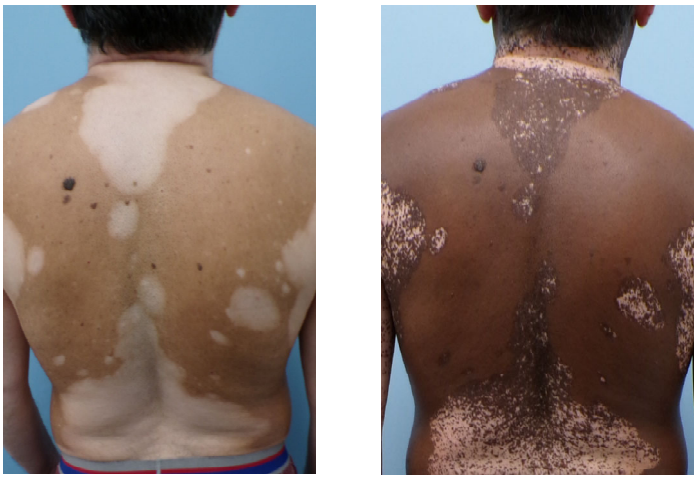
Participant D

1. Male, 56 years old, Skin Type IV
2. Diagnosed with vitiligo in 1986

PHYSICIAN'S REPORT

Due to extensive depigmentation, patient is yet to fully repigment. Patient continued to receive NB-UVB treatment following the study and continued to repigment (not shown).

DAY 0	DAY 140
Baseline	7 afamelanotide implants, 40 NB-UVB treatments



The skin surface of the back Participant D

The image shows the extent of repigmentation on lower and upper back.

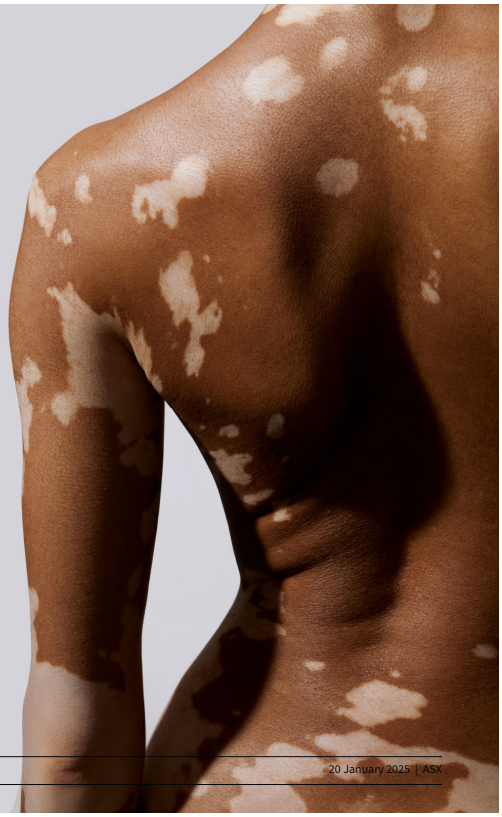
By day 140 considerable repigmentation had been seen, while the unaffected skin showed darkening following treatment.

The patient elected to continue NB-UVB therapy at the conclusion of the study period, with further repigmentation (not shown) believed by the physician to have been “jump started” by afamelanotide.

IV

Summary

1. Total body darkening of unaffected skin demonstrates systemic effect, followed by visible repigmentation of vitiligo lesions
2. Patients counselled to anticipate total body darkening, broadly accepted in skin type III-VI
3. In two cases, spontaneous repigmentation months after treatment – previously unreported
4. Positive feedback from patients and physicians on clinical benefit
5. NB-UVB treatment-only-patients are completing protocol, receiving afamelanotide adjunct to NB-UVB



Summary of four cases evaluated

1. in all four patients there is total darkening observed of unaffected skin
2. in all four patients white vitiligo patches repigmented
3. all patients are counselled before the start of the treatment preparing them for temporary darkening of their unaffected skin
4. in two cases repigmentation of white vitiligo patches occurred after completion of treatment
5. two patients previously unresponsive to NB-UVB responded to the afamelanotide and NB-UVB treatment
6. physicians and patients are enthused by the clinical benefit provided thus far
7. patients who had received NB-UVB only agreed to stay in trial, in a second phase of the trial they will receive afamelanotide and NB-UVB treatment
8. the treatment regimen is well tolerated

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Thank you for your interest

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About CLINUVEL PHARMACEUTICALS LIMITED

CLINUVEL (ASX: CUV; ADR LEVEL 1: CLVLY; Börse Frankfurt: UR9) is a global specialty pharmaceutical group focused on developing and commercialising treatments for patients with genetic, metabolic, systemic, and life-threatening, acute disorders, as well as healthcare solutions for specialised populations. As pioneers in photomedicine and the family of melanocortin peptides, CLINUVEL's research and development has led to innovative treatments for patient populations with a clinical need for systemic photoprotection, assisted DNA repair, repigmentation and acute or life-threatening conditions who lack alternatives.

CLINUVEL's lead therapy, SCENESSE® (afamelanotide 16mg), is approved for commercial distribution in Europe, the USA, Israel, and Australia as the world's first systemic photoprotective drug for the prevention of phototoxicity (anaphylactoid reactions and burns) in adult patients with erythropoietic protoporphyria (EPP). Headquartered in Melbourne, Australia, CLINUVEL has operations in Europe, Singapore, and the USA. For more information, please go to https://www.clinuvel.com.

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