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Apremilast in combination to narrowband UVB in the treatment of vitiligo. A 52 weeks monocentric prospective randomized placebo-controlled study

Short title: Apremilast in combination to Nb-UVB in vitiligo

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Abstract

Background. Scientific rationale and encouraging first clinical results suggest the interest of using apremilast for treating vitiligo.

Objective. To compare the efficacy of apremilast in combination therapy with narrowband (NB)-UVB *versus* placebo and NB-UVB treatment for repigmentation in patients with non-segmental vitiligo.

Design. 52 weeks prospective randomized placebo-controlled study.

Participants. Adult patients with vitiligo

Interventions. Group A received, in addition to phototherapy, apremilast at the label dosage and group B received placebo. After 24 weeks, patients who responded (decreased VASI>30%) were re-randomized to receive apremilast or placebo, combined with twice weekly NB-UVB for 24 additional weeks.

Main outcome and measure. The primary outcome measure was the comparison between the two groups of the VASI score at 24 weeks.

Results. 80 patients were randomized (40 in each group). After 24 weeks, the mean VASI score decreased from 23.63 to 19.49 ($p=0.011$) in apremilast+UVB group and from 21.57 to 15.25 ($p<0.0001$) in the placebo+UVB group. The difference between the two groups was not statistically significant ($p=0.18$). No statistically significant differences were observed between the two groups after additional 24 weeks of treatment.

Conclusions and Relevance. Apremilast does not bring any benefit to NB-UVB for treating vitiligo.

Vitiligo is an acquired depigmentation disorder affecting 0.5 to 2% of the general population. There is strong evidence for both oxidative stress and the immune system to play a role in genetically predisposed individuals (Bellei et al., 2013, Jin et al., 2012, Passeron and Ortonne, 2012, Schallreuter et al., 2013, Spritz, 2012). The role of lymphocyte T helper (Th)1 and Th17 has been reported by several studies (Kotobuki et al., 2012, Santaguida et al., 2010, Wang et al., 2011). Recent data emphasized the key role of the interferon gamma (IFNγ) pathway in vitiligo. Under IFNγ stimulation, keratinocytes are stimulated to produce chemokines such as CXCL9 and CXCL10 which further attract and activate CD8+ T cells (Richmond *et al.*, 2016). We recently demonstrated that the innate cells play a key role in the initiation of the disease and that CXCL10 is responsible for the initial apoptosis of some melanocytes resulting in release of auto-antigens that subsequently triggers the auto-immune destruction of melanocytes by the T cells (Tulic *et al.*, 2019). These data emphasized the potential usefulness of targeting the immune system to halt vitiligo progression and to help the repigmentation when associated with ultraviolet (UV) exposure. Many treatment modalities are currently used for vitiligo, such as topical steroids, topical immunomodulators and phototherapy (Ezzedine et al., 2016, Passeron, 2017). So far, there is no treatment approved by the FDA or the EMA for repigmenting vitiligo. Narrow band UVB (NB-UVB) remains the gold standard treatment for widespread vitiligo (affecting more than 5% of the total surface body area) although providing only 30% improvement of the VASI score (validated scoring system for vitiligo (Komen *et al.*, 2015)) after 6 months of treatment. Apremilast is a phosphosdiesterase 4 (PDE4) inhibitor that showed efficacy and very good tolerance in rheumatoid arthritis and psoriasis (Papp et al., 2015, Paul et al., 2015). Apremilast induces a potent activation of the cyclic AMP (cAMP) pathway leading to anti-inflammatory effect by decreasing the Th1 and Th17 lymphocyte response. It also decreases the production of CXCL9 and CXCL10 (Schafer *et al.*, 2010) and modulates innate immunity

(Schafer *et al.*, 2014). Interestingly, the cAMP pathway is also well demonstrated to be the main pathway for promoting melanogenesis and for inducing the differentiation and the proliferation of melanocytes (Khaled *et al.*, 2010). Indeed, the cAMP pathway induces the phosphorylation of the transcription factor CREB that in return activates MITF. MITF is the key transcription factor of melanocyte which regulates their proliferation and melanogenesis by increasing the transcription of tyrosinase and DCT enzymes. Interestingly, stimulating the cAMP pathway has been proven to be effective to enhance the UVB-induced repigmentation in vitiligo patients (Lim *et al.*, 2014). Thus, by these mechanisms, we hypothesize that apremilast could potentiate the repigmentation of vitiligo lesions and at the same time, halt the disease progression thanks to its anti-inflammatory effects. A recent case report and a retrospective study further suggested that apremilast might be useful for treating vitiligo (Huff and Gottwald, 2017, Majid et al., 2019). Taking into account this strong rationale and these first encouraging cases, some dermatologists have started proposing this treatment off label as a treatment option to help their most difficult patients. The objective of the study was to compare the efficacy of apremilast at the label dosage in combination with NB-UVB *versus* placebo and NB-UVB for repigmentation in patients with non-segmental vitiligo.

Methods

We conducted a prospective randomized placebo-controlled study in the Department of Dermatology of the university hospital of Nice, France. The study was approved by the Ethics Committee (Comité de Protection des Personnes Sud-Méditerranée V – n° 16.063) and is registered on Clinicaltrial.gov (NCT03036995).

Patients above 18-years-old with vitiligo affecting at least 5% of their body surface area were included after written informed patient consent was obtained. Exclusion criteria were segmental or mixed vitiligo, pregnant or breastfeeding women, active infections, congenital or

acquired immunosuppression, personal history of malignancy, prior use of apremilast, any topical therapy within the two weeks before randomization, use of phototherapy or systemic steroids or immunosuppressive drugs within 4 weeks prior to randomization.

The main objective of the study was to compare, after 24 weeks of treatment, the efficacy of apremilast at the label dosage of 30mg BID with proper titration, in combination therapy with NB-UVB *versus* placebo and NB-UVB for repigmentation in patients with non-segmental vitiligo. The primary outcome measure was the VASI score (Komen *et al.*, 2015). The secondary outcomes measures were the Vitiligo Extent Score (VES) (van Geel *et al.*, 2016), the VETF (Vitiligo European Task Force) assessment (Taieb and Picardo, 2007), the DLQI score and the delay until the first signs of repigmentation.

As apremilast may also promote the proliferation of melanocytes when they have been differentiated, we wanted to assess the potential effect of apremilast in responsive patients who started to repigment after UVB treatment. Thus, all the patients who had at least 30% decrease in their VASI score at 24 weeks (W24) were re-randomized to receive either apremilast and NB-UVB or placebo and NB-UVB (part B of the study). The same criteria of evaluation were used. In addition, we compared in the two treatment arms, the rate of patients who lost their initial response, defined by a VASI score back to 10% of improvement or less at W36, W48 and W52, compared to W24.

The evaluation was performed by two physicians, blinded to the treatment received, on standardized pictures performed at W0, W12, W24, W36, W48 and W52. If the scores of the evaluators differed by more than 10% a joint assessment was done to reach an agreement.

Participants were randomly allocated to one of two treatment arms; group A received apremilast and NB-UVB phototherapy while group B received placebo and NB-UVB phototherapy. NB-UVB was performed twice a week with a starting dose of 200 mJ/cm² and an increase of 10-20% *per* week to induce an asymptomatic erythema. Placebo and apremilast

were given orally. Apremilast was given with a titration pack at the initiation of the study and afterwards at the dose of 30 mg twice a day. The scheme of the study is presented in Figure 1.

The placebo looked, tasted and smelled as the apremilast pills. The exact same number of pills were given in the arms. The labelling of the two treatments could not be differentiated from each other. Randomization was balanced (1:1) and stratified by skin phototype group (fair skin types (Fitzpatrick I, II, III) and dark skin types (Fitzpatrick IV, V, VI)). Centralized block randomization was conducted by the Department of Clinical Research and Innovation (DRCI) at Centre Hospitalier Universitaire (CHU) Nice using Nquery© Advisor v 7.0. software.

Calculation of sample size

According to the literature (Lim *et al.*, 2015), we anticipated a mean VASI score improvement in placebo + narrow UVB treatment arm at W24 of about 30%. We expected that patients in the combination group (phototherapy + apremilast) will have at least a 50% mean improvement of their VASI score. Considering a conservative standard deviation of 25 (calculated SD with data from Lim et al. is 22 (Lim *et al.*, 2015)), a power of 90%, an alpha risk of 5% and a bilateral hypothesis, a total of 34 patients were required in each group. Taking into account the potential subjects lost to follow-up within 6 months of study, a total of 80 patients (40 in each group) was chosen.

Statistical analysis

Analysis of the primary objective as well as analyses considering VETF and VES scores were performed on a modified intention-to-treat (ITTm) principle. All patients who underwent randomization and took at least one dose of medication were included in these analyses. Missing values were imputed according to the Last Observation Carried Forward (LOCF) procedure. Per-protocol analyses were also performed, considering only patients who completed the entire study (phase A or B) without violation to the protocol and with an adequate compliance.

Firstly, VASI, VETF and VES scores evolution was compared between both treatment arms using ANCOVA models adjusted on the baseline score value (W24 score value for the phase B analyses) and the phototype group. We then compared DLQI score evolution between the groups the same way. For delay until repigmentation, follow-up started on the first day of treatment, and cumulative event curves were estimated with the Kaplan-Meier method; survival curves were compared with the logrank test. In phase B, at W36, 48 and 52, loss of initial response was compared between both arms using the Fisher's exact test.

All tests were two sided. We used SAS Enterprise Guide software version 7.1(SAS institute, Inc, Cary, North Carolina, USA) for statistical analyses.

Raw anonymized data are available for research purposes upon request to fontas.e@chu-nice.fr

Results

For the first part of the study, 80 patients were randomized (40 in each group). One patient withdrew his consent in apremilast group and never started the treatment. During the 6 months treatment 2 other patients withdrew their consent (one in each group), 4 were lost to follow-up (2 in each group) and 1 patient in the apremilast group refused to continue. A total of 39 patients were included in the ITTm analysis in the placebo group and 38 in the apremilast group (Cf. Flow diagram). The description of the population is summarized in Table 1. After 24 weeks of treatment, the median (IQR, interquartile range) VASI score decreased from 12.90 (5.70 – 39.60) to 10.00 (5.50 – 24.30) (Ancova adjusted mean difference -4.12 +- 1.58; p=0.011) in apremilast + UVB group and from 13.90 (10.00 – 26.00) to 10.40 (5.10 – 20.00) (Ancova adjusted mean difference -6.81 +-1.51; p<0.0001) in the placebo + UVB group (Figure 2). The difference between the two groups was not statistically significant (p=0.18). After 24 weeks of treatment the median (IQR) VES score decreased

from 9.05 (4.60 – 36.20) to 8.00 (4.00 – 25.00) (Ancova adjusted mean difference -3.38 +- 1.43; p=0.021) in apremilast + UVB group and from 10.00 (8.00 – 24.50) to 7.70 (5.20 – 21.00) (Ancova adjusted mean difference -5.71 +-1.37; p<0.0001) in the placebo + UVB group (Suppl. Figure 1). The difference between the two groups was not statistically significant (p=0.2). No significant differences between the two groups were observed using the VETF score or when only patients with signs of activity (defined by blurry borders or confetti-like depigmentation) were analyzed. The per protocol analysis showed similar non-significant results. Both groups experienced a slight but statistically significant decrease of their DLQI scores (p=0.023 and p=0.004, for apremilast+UVB and placebo+UVB, respectively). Again, the difference between the two groups was not statistically different (p=0.656). The median timeline to observe the first sign of repigmentation was 43.5 days in the apremilast+UVB group and 65 days in the placebo+UVB group (logrank, p=0.105) (suppl. Figure 2).

For the second part of the study, 39 patients were eligible and 38 underwent randomization (19 in each group). One patient never started the treatment in apremilast group. During the 6 months of treatment, 9 patients were lost to follow-up (5 in placebo and 4 in apremilast group) and 5 patients refused to continue (2 in placebo and 3 in apremilast group). A total of 19 patients were included in the ITTm analysis in placebo group and 18 in the apremilast group (Cf. Flow diagrams). After 24 additional weeks of treatment, the median (IQR) VASI score increased from 8.00 (4.70 – 28.10) to 9.00 (4.20 – 25.20) (Ancova adjusted mean difference 0.64 +- 1.15; p=0.583) in apremilast + UVB group and from 7.00 (5.10 – 14.40) to 7.50 (5.30 – 13.90) (Ancova adjusted mean difference -0.62+-1.15; p=0.594) in the placebo + UVB group (Figure 3). The difference between the two groups was not statistically significant (p=0.40). After 24 additional weeks of treatment the median (IQR) VES score increased from 6.50 (4.00 – 26.00) to 7.25 (3.80 – 25.00) (Ancova adjusted mean difference 0.08 +- 0.81;

p=0.922) in apremilast + UVB group and from 5.70 (4.60 – 18.00) to 6.50 (5.30 – 17.20) (mean difference -0.47 +-0.81; p=0.562) in the placebo + UVB group (Suppl. Figure 3). The difference between the two groups was not statistically significant (p=0.598). No significant differences between the two groups were observed using the VETF score or when only patients with signs of activity (defined by blurry borders or confetti-like depigmentation) were analyzed. Finally, when we studied the proportion of patients who lost their response during the second part of the study, in the apremilast + UVB group 3/17 (17.7%) at W36, 3/15 (20%) at W48 and 3/12 (25%) at W52 lost the response. In the placebo + UVB group, 6/19 (31.6%) at W36, 7/19 (36.8%) at W48 and 4/12 (33%) at W52 had lost their response. There was no statistical difference between the two groups at any of these time points.

Eighteen side-effects in a total of 9 patients were observed in the apremilast+UVB group. Diarrhea, abdominal pain and headache were the most frequent side-effects. There were 2 serious adverse events (one surgery for a benign tumor of the amygdales and one suicide attempt). The suicide attempt was attributed to the treatment. Nine adverse events in 9 patients were observed in the placebo+UVB group. No serious adverse events were observed in this group.

Discussion

With our improvement knowledge in the pathophysiology of vitiligo and the development of many drugs aiming to target the different biological pathways implicated in this process, physicians might be tempted to propose these approaches to help vitiligo patients who suffer from their disease. Apremilast is an orally taken drug with a good safety profile and a strong rationale for being used in vitiligo. Successful treatment with apremilast was reported in one patient with a resistant vitiligo (Huff and Gottwald, 2017) however that patient also received systemic steroids in combination with apremilast. More recently, 13 patients who failed to

respond to other approaches were treated with apremilast. None of the patients presented with progression of their disease and 8/13 (61.5%) reported repigmentation (Majid *et al.*, 2019). Our results, obtained in a prospective randomized trial of 80 patients and performed for a total of 52 weeks, show that apremilast does not bring any additional benefit to NB-UVB treatment. Not only, the apremilast combined to NB-UVB did not achieve higher repigmentation after 6 months of treatment compared to NB-UVB alone, but when given to patients who already started to respond to NB-UVB, it did not result in faster repigmentation process. Our study has shown no effect of apremilast compared to placebo patients were subdivided according to the extent or activity of their disease, however these later results must be interpreted with caution as our study was not powered for such analyses.

The main limitation of this study is the fact that apremilast was not assessed as a monotherapy. However, we designed this scheme of treatment knowing that phototherapy remains the gold standard of vitiligo treatment, and because the first data using targeted immunomodulators such as JAK inhibitors showed that optimal repigmentation required sun exposure or phototherapy (Liu *et al.*, 2017). As sun exposure of each patient cannot be controlled and is difficult to obtain during winter time, we preferred using NB-UVB. Moreover, by elevating the cAMP level, apremilast can potentially stimulate MITF and thus promote faster repigmentation following phototherapy-induced differentiation of melanocyte stem cells (Yamada *et al.*, 2013). Surprisingly, we did not observe further improvement in repigmentation in the second part of the study. We may hypothesize that the stronger efficacy of NB-UVB in the 6 first months is due to its immunosuppressive action. Interestingly, this study also confirms the efficacy of NB-UVB in halting the progression of the disease. The overall rate of repigmentation with NB-UVB during the 48 weeks of treatment was lower than expected. These relatively poor results achieved with the NB-UVB might be explained by the long disease duration of the patients included in this study (mean around 20 years), their

relatively old age and the low proportion of dark skin phototypes. These limitations should be kept in mind for further studies when evaluating the effect of drugs impacting the immune system for vitiligo treatment. Thus, patients having recently developed their lesions might be selected, at least for the proof of concept studies, to get the maximum chances of achieving repigmentation.

In conclusion, we demonstrated that apremilast does not bring any additional benefit to NB-UVB for treating vitiligo and should not be proposed as a treatment option.

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Tables

Table 1. Description of the population.

	n	Arm A (n=38)	n	Arm B (n=39)
		%		%
Age (years), Mean (±SD)	40	49.5 (13.4)	39	45.4 (13.2)
Sex				
Male	14	36.8	14	35.9
Female	24	63.2	25	64.1
Height cm, Mean (±SD)	38	168.2 (10.4)	39	168.1 (7.4)
Weight Kg, Mean (±SD)	37	69.0 (13.7)	39	70.2 (14.6)
Normal clinical exam	38	100.0	39	100.0
Skin type				
I/II/III	30	79.0	29	74.4
IV/V/VI	8	21.0	10	25.6
Disease duration (years), Mean (±SD)	38	22.7 (15.0)	39	18.6 (13.8)

Table 2. Evolution of the DLQI scores

	W0 (n=38)	**W24 (n=32)**	**Diff_W0/W24 (n=32)**	**p*§**
DLQI apremilast+UVB group mean ± SD	6.89 ± 4.88	5.03 ± 4.82	-1.31 ± 3.81	0.6565
	V1 (J0) (n=39)	**V3 (S24) (n=35)**	**Diff_J0/ S24 (n=35)**	
DLQI placebo+UVB group mean ± SD	7.46 ± 6.01	5.57 ± 5.61	-2.03 ± 3.85	

Figures

Figure 1. Scheme of the study

Figure 2. Evolution of the VASI score between the two groups during the first part of the study.

The upper and lower lines of the boxes represent the 75th percentile and the 25th percentile, respectively. The line within the boxes represents the median and the dot within the boxes the mean. The upper whiskers represent the maximum observation below upper fence and the lower whiskers the minimum observation. The dots located in the upper part of the graph represent the maximum observations.

Figure 3. Evolution of the VASI score between the two groups during the second part of the study

The upper and lower lines of the boxes represent the 75th percentile and the 25th percentile, respectively. The line within the boxes represents the median and the dot within the boxes the mean. The upper whiskers represent the maximum observation below upper fence and the lower whiskers the minimum observation. The dots located in the upper part of the graph represent the maximum observations.

Supplementary files

Suppl. Figure 1. Flow diagrams of part A of the study

Suppl. Figure 2. Flow diagrams of part B of the study

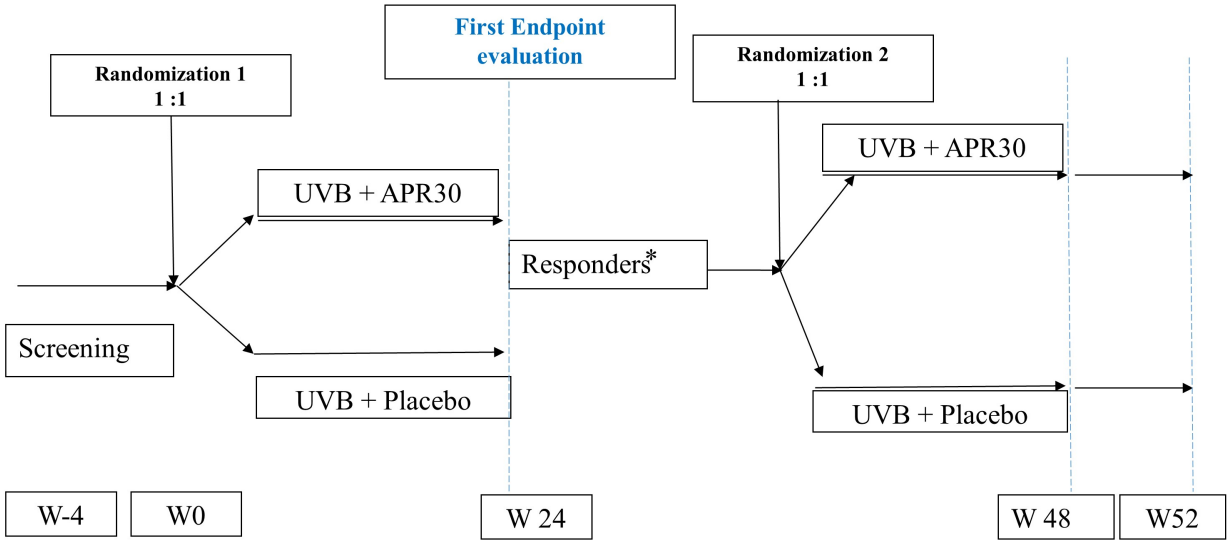
Suppl. Figure 3. Timeline to observe the first signs of repigmentation

Suppl. Figure 4. Evolution of the VES score between the two groups during the first part of the study

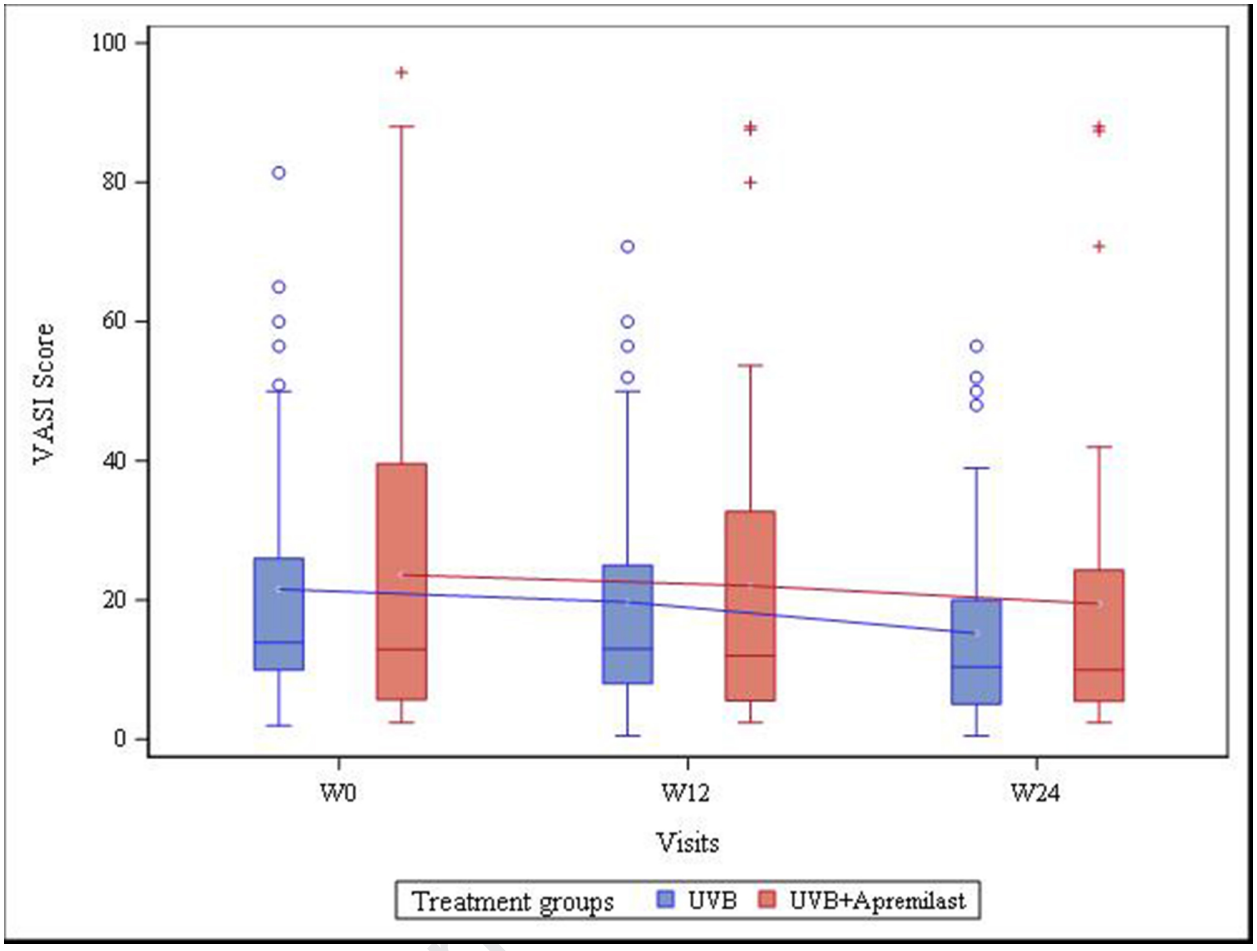
The upper and lower lines of the boxes represent the 75th percentile and the 25th percentile, respectively. The line within the boxes represents the median and the dot within the boxes the mean. The upper whiskers represent the maximum observation below upper fence and the lower whiskers the minimum observation. The dots located in the upper part of the graph represent the maximum observations.

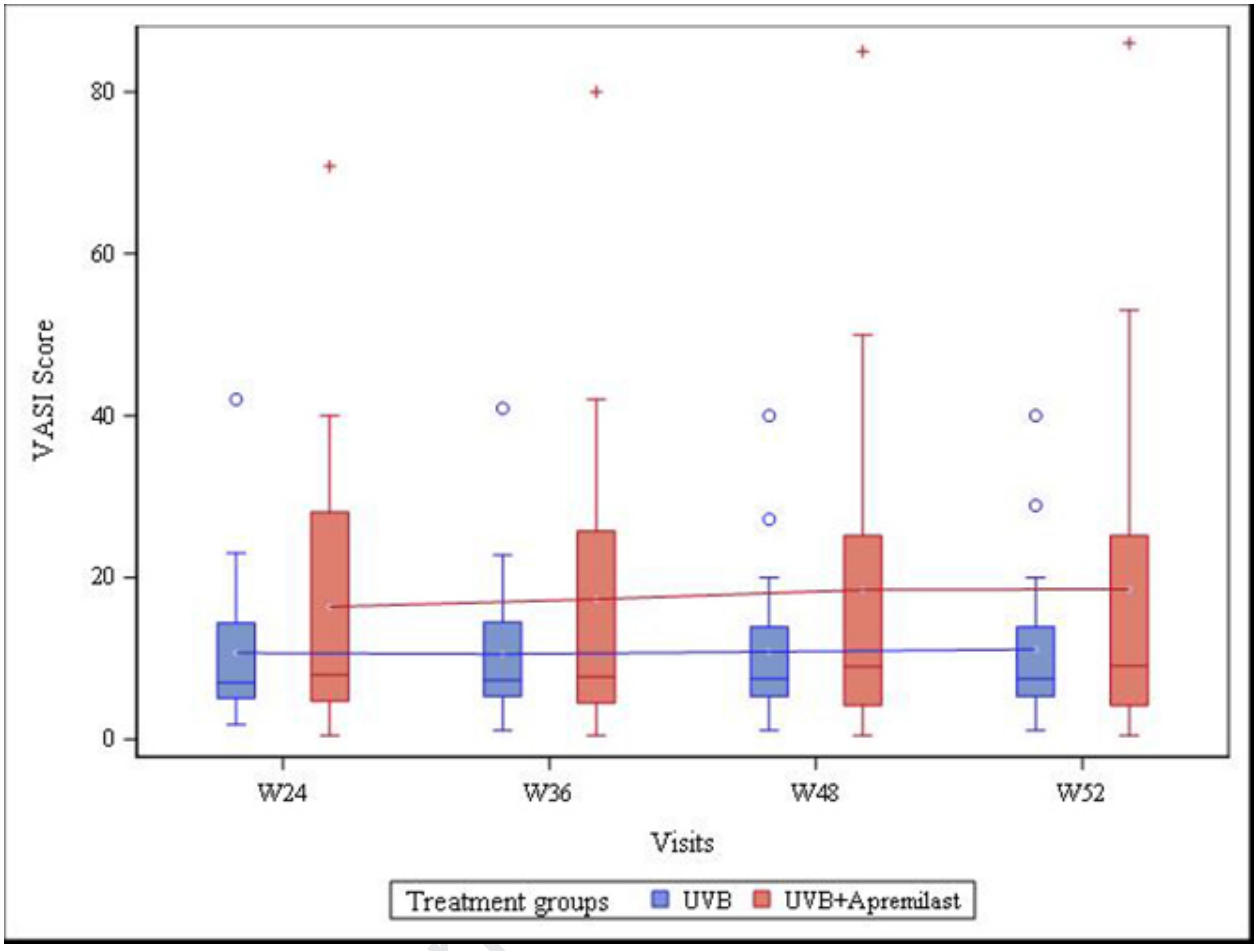
Suppl. Figure 5. Evolution of the VES score between the two groups during the second part of the study

The upper and lower lines of the boxes represent the 75th percentile and the 25th percentile, respectively. The line within the boxes represents the median and the dot within the boxes the mean. The upper whiskers represent the maximum observation below upper fence and the lower whiskers the minimum observation. The dots located in the upper part of the graph represent the maximum observations.

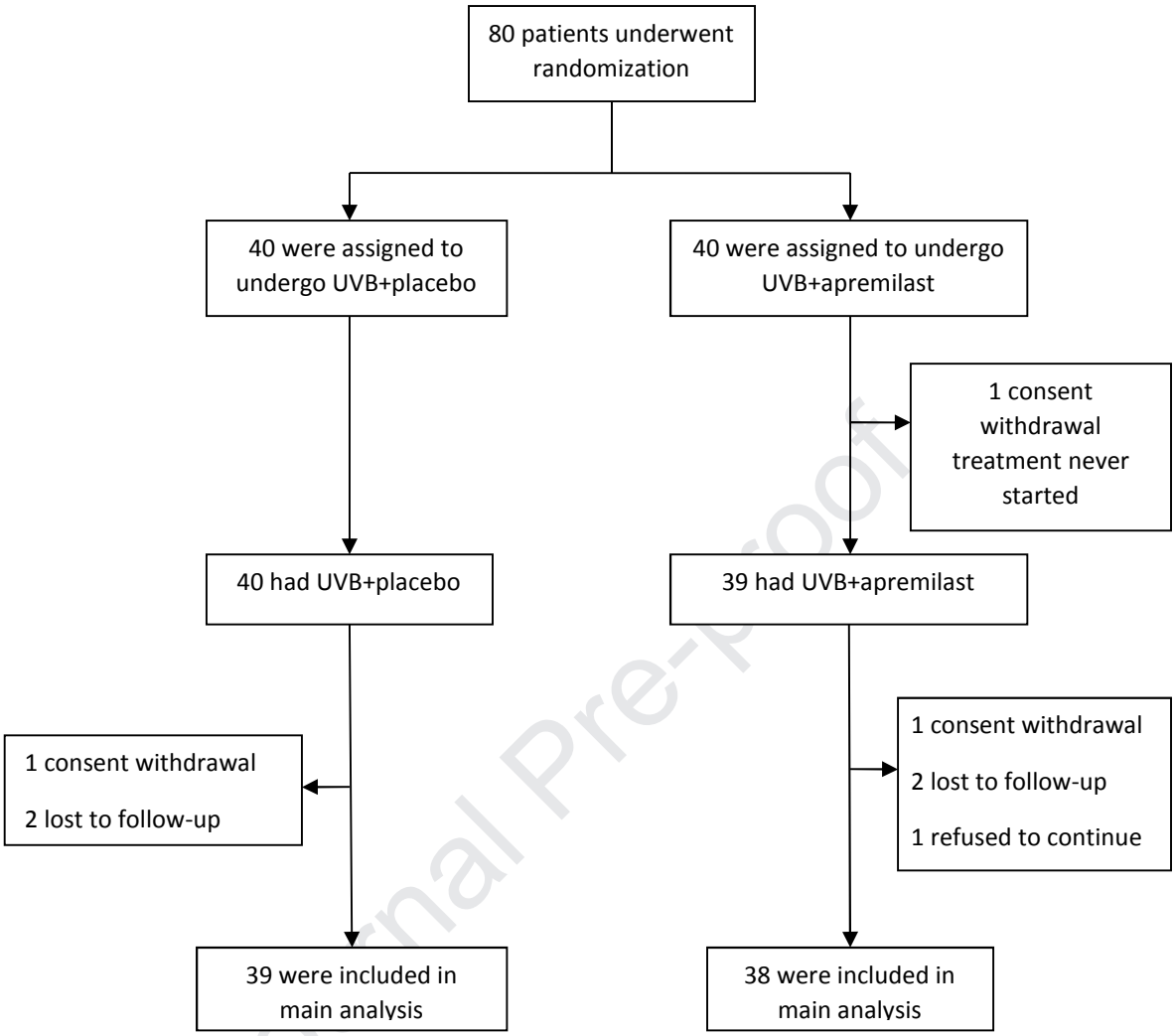


Response is defined as a decrease of at least 30 % in the VASI score at W24

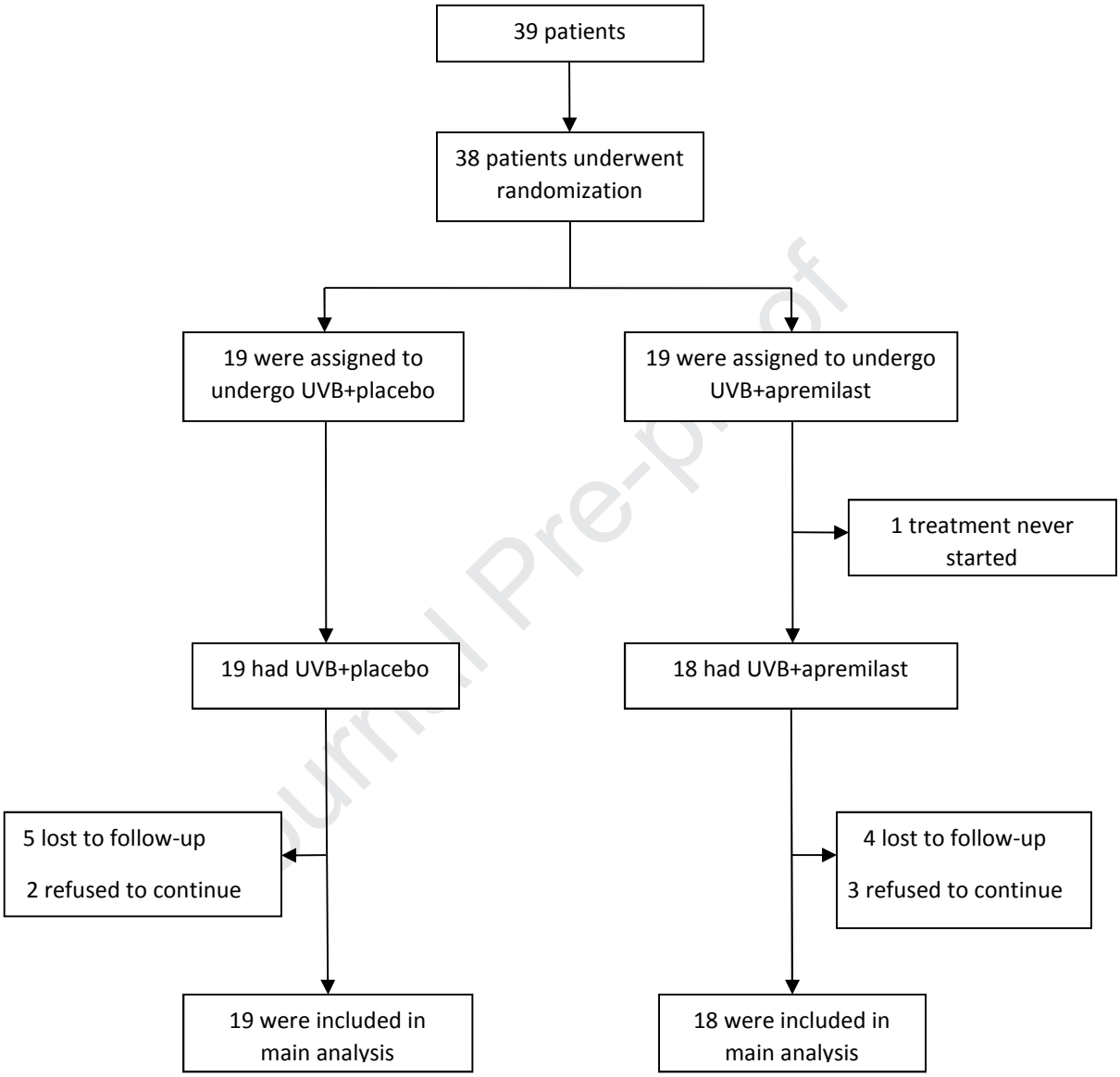

100
80
60
40
20
0
VASI Score
W0
W12
W24
Visits
Treatment groups
UVB
UVB+Apremilast


VASI Score
80
60
40
20
0
W24
W36
W48
W52
Visits
Treatment groups
UVB
UVB+Apremilast

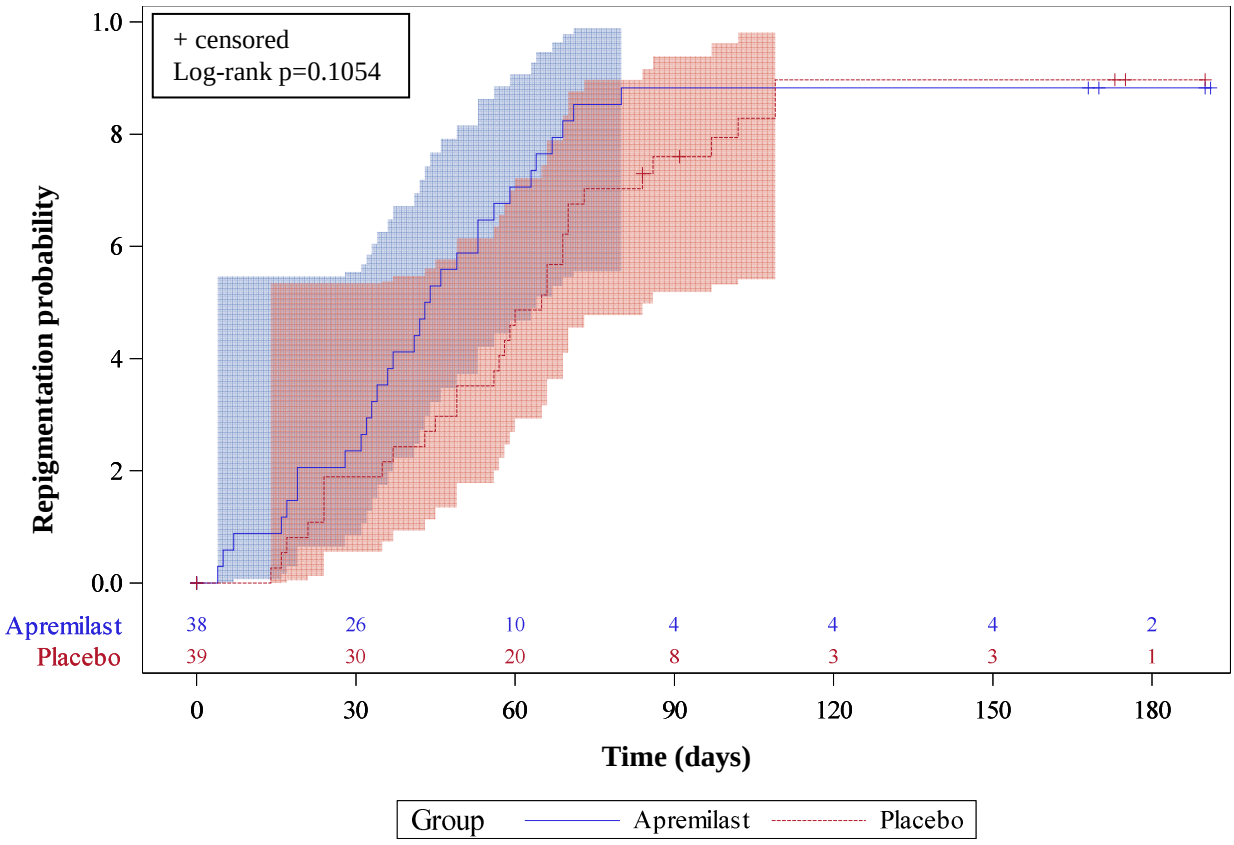
Supplementary figure 1. Flow diagram of the Part A of the study

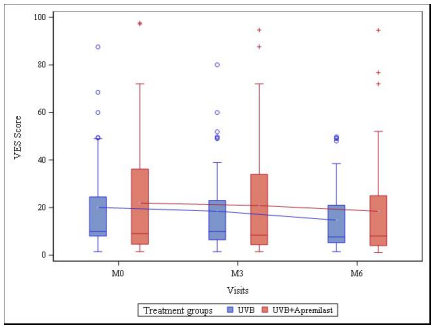


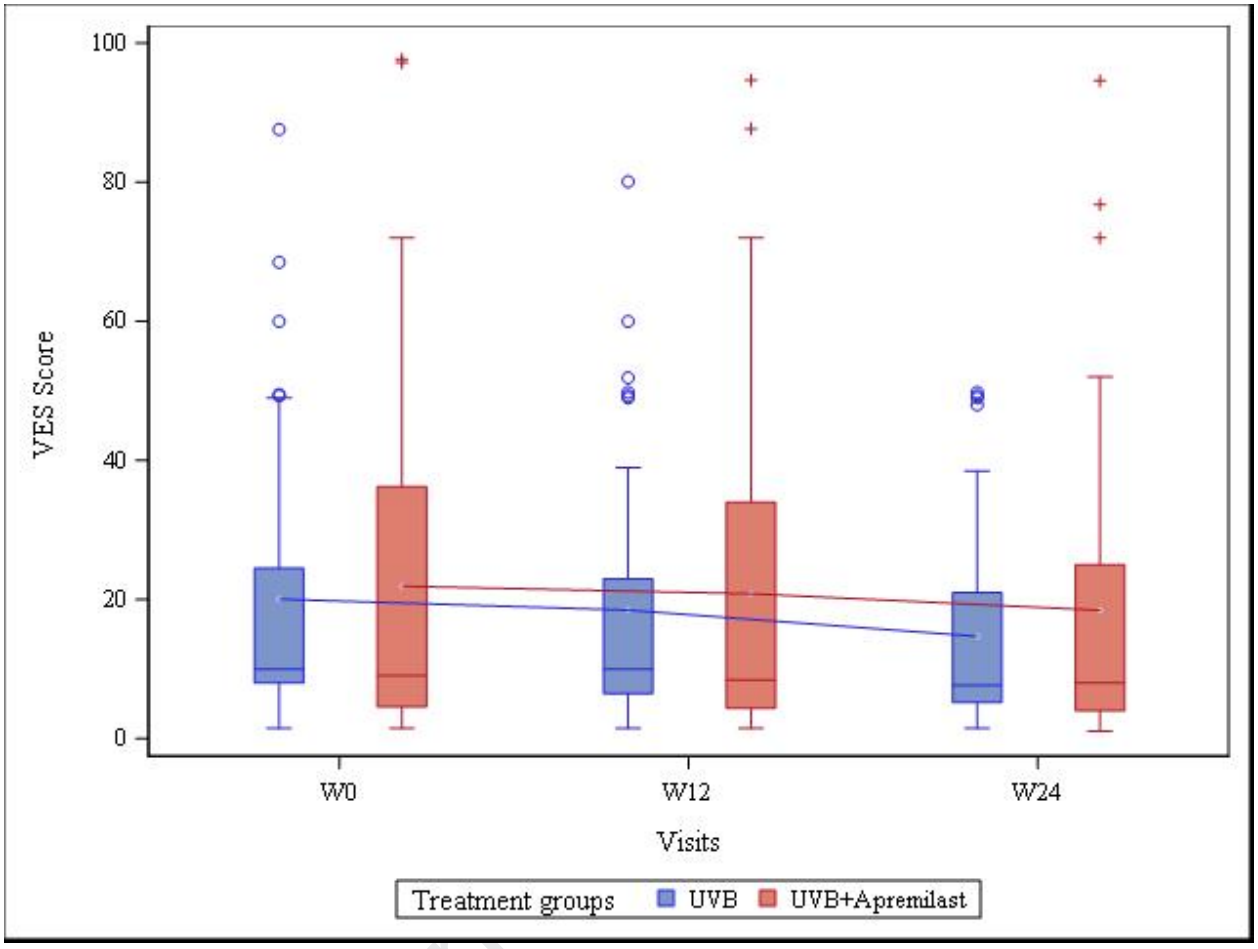
Supplementary figure 2. Flow diagram of the part B of the study



Suppl. Figure 3. Timeline to observe the first signs of repigmentation






100
80
60
40
20
0
VES Score
W0
W12
W24
Visits
Treatment groups
UVB
UVB+Apremilast

Supplementary files

Suppl. Figure 1. Flow diagrams of part A of the study

Suppl. Figure 2. Flow diagrams of part B of the study

Suppl. Figure 3. Timeline to observe the first signs of repigmentation

Suppl. Figure 4. Evolution of the VES score between the two groups during the first part of the study

The upper and lower lines of the boxes represent the 75th percentile and the 25th percentile, respectively. The line within the boxes represents the median and the dot within the boxes the mean. The upper whiskers represent the maximum observation below upper fence and the lower whiskers the minimum observation. The dots located in the upper part of the graph represent the maximum observations.

Suppl. Figure 5. Evolution of the VES score between the two groups during the second part of the study

The upper and lower lines of the boxes represent the 75th percentile and the 25th percentile, respectively. The line within the boxes represents the median and the dot within the boxes the mean. The upper whiskers represent the maximum observation below upper fence and the lower whiskers the minimum observation. The dots located in the upper part of the graph represent the maximum observations.