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Original Article

A randomized study comparing the efficacy and safety of blue light and topical vitamin D treatments for mild Psoriasis vulgaris

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ABSTRACT

The aim of this study is to evaluate the efficacy and safety of blue light with a high peak-intensity of 600 mW/cm² at different durations of treatment of mild Psoriasis vulgaris, compared to a topical vitamin D3-analogue (calcipotriol) treatment. In 2016 a monocentric, prospective, randomized, intra-individual study assessed the efficacy and safety of localized blue light treatment versus topical calcipotriol (Daivonex) treatment for mild Psoriasis vulgaris (Pv). 51 patients with mild Pv were randomized into two treatment groups, receiving 600 mW/cm² blue light either for 30 min (group30) or 15 min (group15) on one localised plaque, daily for 12 weeks, at home. This was compared intra-individually with a contralateral plaque treated daily with topical calcipotriol (Daivonex). Psoriasis severity was assessed by the investigator by applying the Local Psoriasis Severity Index (LPSI) and by the patient using a 100 mm visual analogue scale (VAS). Additionally, the Dermatology Life Quality Index (DLQI) was measured at different time points. The LPSI significantly decreased in both irradiated and comparator areas in group15 and in group30 patients. No difference between blue light and topical calcipotriol treatments was detected. Psoriasis severity VAS scale values assessed by the patients were significantly reduced in both groups (15 and 30 min) with a slightly, but insignificantly better outcome in group30. The DLQI was reduced by -1.76 in group15 compared to -3.39 points in group30. No adverse device effects were seen during the study other than a slight hyperpigmentation. Daily treatment for 12 weeks with blue light for 15 and 30 minutes is as efficient and safe as standard treatment for mild Psoriasis vulgaris with calcipotriol.

KEYWORDS: Psoriasis vulgaris, calcipotriol, LED, blue light.

1. INTRODUCTION

Psoriasis vulgaris (Pv) is a chronic autoimmune skin disorder clinically characterized by red and scaly plaques. Squamation is due to hyperproliferation and disturbed differentiation of keratinocytes, most likely caused by chronic inflammation. In the affected areas inflammation is mediated by immune cells including T-cells and dendritic cells. These cells release pro-inflammatory cytokines, creating a vicious cycle of keratinocyte proliferation, activation and recruitment of additional immune cells [1]. Genetic predisposition is an important factor [2]. Pv is treated in mild cases with topical formulations like moisturizers, vitamin D derivates and analogues or corticosteroids. There is often low compliance due to costs, effort and side effects. In more severe cases and as a second-line therapy, systemic agents (e.g. ciclosporin, methotrexate or acitretin) and UV phototherapy

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†This paper is dedicated to the memory of Professor Martin Leverkus (1965-2016).

with or without photosensitizing medications (e.g. psoralen) are used with good results [3, 4]. In severe Pv, systemic biologicals are applied. However, ultraviolet B (UVB) as well as psoralen and ultraviolet A (PUVA) therapy is known to cause skin aging, damage and cancer, making it unsuitable for long-term use [5]. Biologicals are very costly and antidrug antibodies may sometimes lead to resistance [6].

Experimental work has shown that UV-free blue light can reduce the proliferation capacity of primary human epidermal keratinocytes and induce the expression of differentiation markers without toxicity even at very high fluences [7]. On the other hand, it was toxic for T-cells at these fluences [7]. Additionally, blue light (BL) exposure suppressed the activation of dendritic cells and subsequent T-cell-mediated cytokine release [8]. Further experiments showed that BL between 410 and 457 nm modulates innate immune response pathways by downregulating antimicrobial peptide and pro-inflammatory cytokine expression *via* inhibition of p-NF-kB nuclear translocation in keratinocytes [9]. In this respect, a previous clinical investigation using BL for treating psoriasis gave promising results [10]. 37 patients completed that study and a statistically significant improvement of the Local Psoriasis Severity Index (LPSI) score was found after 4 weeks of treatment [10]. A second study evaluated the efficacy, safety and tolerability of two peak intensities of 453 nm BL, 200 mW/cm^2 and 100 mW/cm^2. 47 patients were randomized and treated for 12 weeks delivering 90 J/cm² daily. A significant decrease in psoriasis symptoms was found and was more pronounced with 200 mW/cm² than with 100 mW/cm² [11]. In both studies, no treatment or device-related adverse events, except for mild focal hyperpigmentation in 50% of the patients, or any serious adverse events were observed. UV-free blue light has an excellent safety profile. It has been applied for many years for a number of indications including newborn jaundice, acne [12] and Crigler-Najjar-disease [13] without significant side effects.

The present study was designed to examine the efficacy of blue light in comparison to an established standard therapy, topical calcipotriol. In addition, we tested a new light source, using irradiance levels of 600 mW/cm² comparing it with irradiance levels of 100 or 200 mW/cm² applied in previous studies [11]. Moreover, two different fluences were tested by irradiating for 15 min and 30 min delivering 38 J/cm² or 76 J/cm², respectively. In previous studies the fluence was 90 J/cm² (30 min) [11].

2. PATIENTS AND METHODS

2.1. Patients

The present monocentric, prospective, randomized, blinded, intra-individual study was conducted at the Department of Dermatology and Allergology, RWTH Aachen University Hospital, from March 2016 to August 2016. 51 patients with mild Pv (Psoriasis Area Severity Index (PASI) $\leq$ 10, Body Surface Area (BSA) $\leq$ 10 and Dermatology Life Quality Index (DLQI) $\leq$ 10) were enrolled. Pregnant or lactating women, patients with photodermatosis, photosensitivity, porphyria, erythrodermic, exfoliative or pustular psoriasis, congenital or acquired immunodeficiency, cancer, severe actinic skin damage, atypical naevi, hyperpigmentation or skin atrophy, viral, fungal, bacterial or parasitic skin infections, and genetic deficiencies associated with increased sensitivity to light or increased skin cancer risk (i.e. Xeroderma pigmentosum) were excluded. All patients gave informed consent before any study procedure was conducted. This clinical investigation was approved by the Ethical Committee, Medical Faculty, RWTH Aachen and by the competent German Federal Government authority, BfArM. The study was performed according to the European and International Good Clinical Practice standards (EN-ISO 14155:2011) and the Declaration of Helsinki. The study was registered at ClinicalTrials.gov with the identifier NCT02735187.

2.2. Device

The investigational medical device (Philips Light & Health, Eindhoven, The Netherlands, Fig. 1A) was equipped with blue light-emitting diodes (LEDs) with a peak wavelength of 453 ± 5 nm and was powered by a rechargeable battery. The treatment area was 38 cm² (oval shaped). The average irradiance was 40 mW/cm² with an adjusted duty cycle to deliver 600 mW/cm² peak irradiance. Two versions of the device were used with different software settings delivering a daily treatment dose of 38 J/cm² (15 min) or 76 J/cm² (30 min) after which the device switched off automatically. This wearable

Fig. 1. Investigational medical device and study design. **A.** The IMD was equipped with blue light-emitting diodes (LEDs) powered by a rechargeable battery. **B.** Number of participants (n) performing the visits.

device could be applied to the treatment area on the patient's extremities by means of a textile strap and worn during minor activities at home.

2.3. Study design

140 patients were pre-screened. 51 were enrolled during the screening visit (visit 1, week 0) and randomized into two groups with 15 min (group15) or 30 min (group30) BL treatment. The investigator pre-selected two study areas which were marked as 1 and 2. The plaques were randomized to treatment with 453 nm BL (target) or treatment with calcipotriol (active comparator, Daivonex, medical approval 1-2x/d, Leo Pharma GmbH, Neu-Isenburg, Germany). The investigator was blinded regarding the BL treatment time. However, he/she could not be blinded regarding which area was treated with BL vs. comparator. Target and comparator plaques were photo-documented at every visit. After randomization, patients were instructed how to use the device (demonstrator device to ensure blinding of the investigator) and how to apply the comparator ointment. Additionally, all patients were supplied with a moisturizing lotion (Excipical U10 Lipolotio, Galderma Laboratorium GmbH, Düsseldorf, Germany) for use on both the treated and the comparator plaque to provide basic care. Patients applied light-treatment as well as comparator

once daily (5-7 times/ week) throughout the 12-week treatment period. Patients returned to the clinic for safety and efficacy assessments at week 2 (visit 4), week 4 (visit 5), week 8 (visit 6) and week 12 (visit 7; end of treatment). At week 1 (visit 3), a phone call was conducted to check for problems or adverse events. The patients were followed-up for another 4 weeks without treatment; the final visit was at week 16 (visit 8, end of study) (Fig. 1B). Each patient kept a diary to document treatments and adverse events. Additionally, at the end of treatment (week 12, visit 7) the patients were asked to fill out a questionnaire to assess their satisfaction with the device, including thermal comfort. The questionnaire was evaluated using the System Usability Scale (SUS) which gives a range of possible values from 0 (negative or worst imaginable) to 100 (positive or best imaginable) [14].

2.4. Clinical efficacy

To assess the efficacy of target and comparator the investigator determined the LPSI in analogy to the PASI of both plaques determining the extent of erythema, induration and scaliness on a scale of 0-4 (0 (no sign) to 4 (very marked)) [15]. The resulting LPSI was the sum score of these three symptoms giving a severity score of 0 to 12. Additionally, the patients were asked to assess the severity of both plaques themselves using a 100 mm VAS scale ranging from 0 (no symptoms) to 100 (worst symptoms imaginable). At visit 1 (week 0) and visit 7 (week 12) patients completed a DLQI questionnaire. Pigmentation and erythema of the study plaques were measured using the Mexameter® (Courage + Khazaka electronic GmbH, Köln) device at each visit, as a safety measure. Patients needed to bring their diary to every study visit to monitor adverse events.

2.5. Statistical analysis

The investigational data were collected, processed, validated and analysed according to the intention to treat (ITT) principle on the Full Analysis Set (FAS) by X-act Cologne Clinical Research GmbH, Hansaring 97, 50670 Cologne, Germany using the SAS software (SAS® STATISTICAL ANALYSIS SYSTEM, Version 9.3 or higher, SAS Institute, Cary, NC, USA). Results of the descriptive analysis of continuous data are reported by means of mean and standard deviation, median, minimum, and maximum, and number of observed and missing values. For categorical data, absolute and relative frequencies (percentages) are reported. A paired t-test was applied to test the primary hypothesis. In case the requirements for normality were not met, a non-parametric analysis (Wilcoxon signed rank test) was performed. Figures were generated with the use of Excel using the SAS output tables.

3. RESULTS

3.1. Demographics and baseline characteristics

All 51 patients (group15, n = 26 or group30, n = 25) enrolled in this study received at least one treatment with the investigational medical device (IMD) and the active comparator, respectively. 1 patient (3.8%) in group15 and 4 patients (16.0%) in group30 discontinued the study prematurely either because they were lost to follow up or due to the investigator's decision. The remaining 46 patients performed follow-up visit 8, i.e., they completed the study regularly. The demographic data and baseline characteristics are described in Table 1a. The age distribution was comparable between the groups. Overall, slightly more female patients participated in this study (56.9% female vs 43.1% male) and there was a similar distribution of genders in both groups. Most participants had skin type II or III with high to moderate susceptibility to sun burns (Table 1a). Disease severity parameters showed comparable baseline characteristics (PASI, BSA and DLQI, Table 1b) in both groups. The local PSI of the selected study plaques was comparable at baseline (Table 1c).

3.2. Study results

3.2.1. Investigator assessment of severity

Psoriasis severity assessed by LPSI in group15 showed a significant reduction at all study visits (week 4-16) post baseline, and this is expressed as change from baseline (CfB) in Fig. 2A. The highest CfB was evident at visit 7 (week 12) which marked the end of treatment with -2.4 ± 1.65 in the target area and -2.5 ± 1.56 in the comparator-treated area (Fig. 2A). No significant difference between target and comparator plaques was seen ($p = 0.678$). When treatment was stopped at visit 7, no further improvement at visit 8 (week 16, follow up visit) for target (-2.5 ± 1.85) or comparator areas (-2.15 ± 1.84) could be seen.

Table 1. Demographics and baseline characteristics.

(a)

Parameter		Statistics	Group15 (N = 26)	Group30 (N = 25)	Overall (N = 51)
Age (years)		Mean	47.9	42.4	45.2
		SD	13.7	13.4	13.7
		Median	49.5	43.0	47.0
		Range	18 – 75	19 – 73	18 – 75
Gender	Female	n (%)	10 (38.5)	12 (48.0)	22 (43.1)
	Male	n (%)	16 (61.5)	13 (52.0)	29 (56.9)
Race	Caucasian	n (%)	26 (100.0)	25 (100.0)	51 (100.0)
Skin Type	Type I	n (%)	0 (0.0)	1 (4.0)	1 (2.0)
	Type II	n (%)	17 (65.4)	12 (48.0)	29 (56.9)
	Type III	n (%)	9 (34.6)	12 (48.0)	21 (41.2)

n = number of patients; (%) = percentage of patients among total (N).

(b)

	Group15					Group30					Overall				
	n	Mean	SD	Min	Max	n	Mean	SD	Min	Max	n	Mean	SD	Min	Max
Total PASI score	26	3.02	0.787	1.0	4.6	25	2.81	1.012	1.1	5	51	2.92	0.901	1	5
BSA	26	2.38	0.637	1.0	4.0	25	2.32	0.476	2.0	3.0	51	2.35	0.559	1.0	4.0
DLQI	26	5.62	3.213	1.0	9.0	25	5.20	2.986	0.0	9.0	51	5.41	3.08	0.0	9.0

(c)

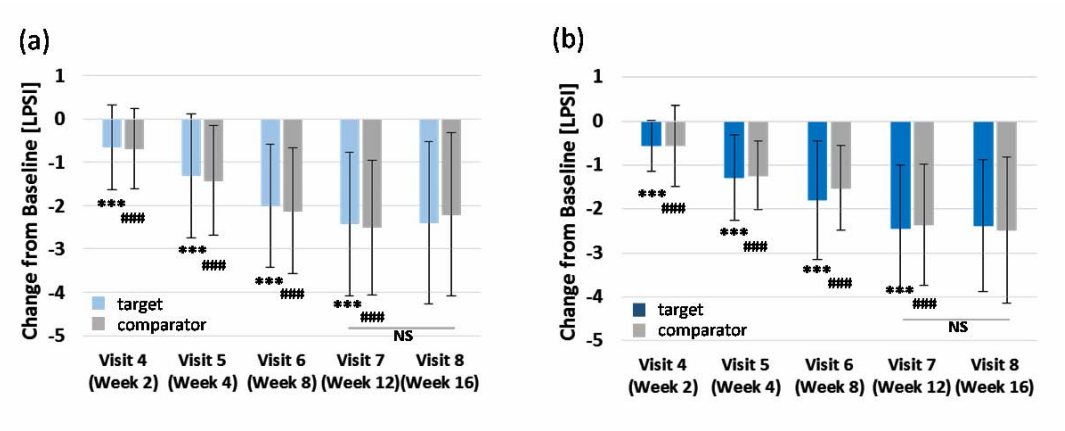
	Target (Blue light)					Comparator (Daivonex)					Difference				
LPSI	n	Mean	SD	Min	Max	n	Mean	SD	Min	Max	n	Mean	SD	Min	Max
Group15	26	5.31	1.49	3.0	9.0	26	5.31	1.49	3.0	9.0	26	0.0	0.000	0.0	0.0
Group30	25	4.80	1.258	2.0	7.0	25	4.84	1.405	2.0	8.0	25	-0.04	0.351	-1.0	1.0

In group30, there was a statistically significant CfB at all study visits post baseline for both target and comparator-treated plaques. The CfB of the local PSI at the end of treatment (week 12) for patients in group30 was defined as primary endpoint. The CfB was -2.4 ± 1.45 in the target area and -2.4 ± 1.38 in the comparator area with statistical significance compared to baseline in both ($p < 0.0001$ each). Comparing the CfB between target area and comparator area at week 12, we observed that there was no significant difference ($p = 0.6469$) (Fig. 2B). Again, in group30 the improvement persisted to visit 7 (end of treatment). No worsening was seen during the follow up period of 4 weeks for the target (-2.4 ± 1.50) or comparator (-2.5 ± 1.66) plaques.

There was no difference between the 15 min vs. 30 min treatments (Fig. 2B) in the target group. The treatments were observed to have similar efficacy at all visits. This is also valid when looking at the comparator plaques of both groups, which showed a comparable reduction in LPSI severity (Fig. 2B).

Both target groups had an average reduction in severity of about 50% at the end of treatment visit.

A



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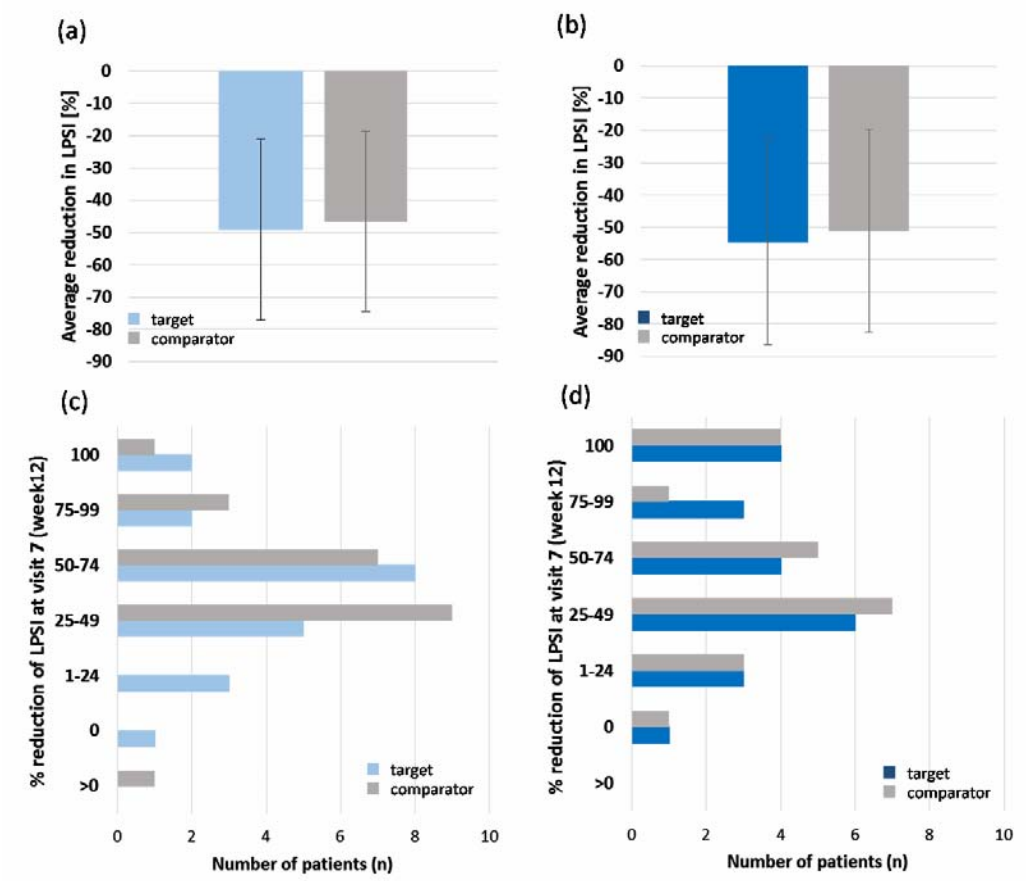

Fig. 2. Assessment of local psoriasis severity index (LPSI) by investigators. **A.** Assessment of LPSI over the complete study period for (a) group15 and (b) group30 including the change from baseline (CfB; ***$p \leq 0.0001$ (target); $^{###}p \leq 0.0001$ (comparator), Error bar: SD). **B.** Average percent reduction of LPSI at visit 7 (week 12) of (a) target - blue light-treated- and the (b) comparator plaque – calcipotriol-treated, (c) group15 (n = 21) and (d) group30 (n = 21).

In group15 one patient had a slight worsening of symptoms of the comparator plaque while no patient experienced a worsening in the target area. One patient did not respond to target therapy. One patient experienced cleared comparator and target plaques. A second patient was cleared of the target plaque while showing 80% reduction of the comparator plaque (Fig. 2B).

In group30 no patient experienced a worsening of the comparator or target plaque. One patient did not show any response of the comparator plaque while one showed no response of the target plaque (0% reduction). Three patients had cleared comparator and target plaques while one patient had a cleared comparator plaque and 75% clearance of the target plaque. Another patient had a cleared target plaque while showing 80% reduction of the comparator-treated plaque (Fig. 2B).

3.2.2. Patient self-assessment

Patients were asked to rate disease severity using a 100 mm VAS, where 0 denotes no symptoms and 100 the worst symptoms imaginable. Fig. 3 displays the results in cm obtained for both groups expressed as change from baseline (CfB). In group15 the baseline VAS showed comparable mean values of 4.44 ± 2.37 for target and 4.50 ± 2.392 for comparator and slightly higher, but still comparable values in group30 for target (5.06 ± 2.44) and comparator (5.06 ± 2.44). In group15 the CfB decreased continuously for all study visits with -2.86 ± 2.64 for the target area and -2.24 ± 3.04 for the comparator area at visit 7 (week 12). This resembles the VAS reduction of 63.5% and 52.2% for the target and comparator plaques, respectively, at visit 7 in group15 (Fig. 3c).

The same trend is seen for group30 with a CfB in VAS of -3.82 ± 2.70 and -3.56 ± 2.73 for the comparator plaques (Fig. 3b) at visit 7. Here, the average reduction in VAS is 84.05% for target and 78.01% for comparator-treated plaques (Fig. 3b). No significant differences between target and comparator values in either groups were observed, again showing similar efficacy of target and comparator treatment.

The change in DLQI from baseline to visit 7 was analysed descriptively. The results are displayed in Fig. 3e. Here, comparable to the VAS results, patients showed a stronger improvement of DLQI values in group30 with a change from baseline of -3.39 ± 2.92 points, or 70% reduction, than group15 with -1.76 ± 4.88 points or 32% reduction.

Patient diaries were analysed to check for compliance to treatment procedures and revealed a high compliance rate of 98.6 in both groups (Table 2). Analogously, the system usability scale (SUS, Table 2) values reflecting the information provided by the patients on the usability of the devices were high in both groups (89.0 ± 8.71 in group15 and 88.6 ± 7.92 in group30).

3.3. Safety analysis

Because UV-free blue light can induce hyperpigmentation, Mexameter measurements were performed during the entire study period. Fig. 4 shows the results of these measurements for group15 and group30. A slight increase in average pigmentation was found in group15 (Fig. 4a) and in group30 patients (Fig. 4b). A slight tendency towards increased pigmentation could also be measured in group15 comparator-treated plaques between visits 6 and 8.

Adverse events were classified as any untoward medical occurrence collected throughout the study from screening to follow-up visit and were classified as treatment emergent (TEAE) when occurring between first treatment and visit 7 (week 12), end of treatment whether related to the device or medical procedure or not. A comprehensive overview of the Adverse event categories is given in Table 2b. No TEAE related to the investigational medical device was registered during the study. One TEAE related to the medical procedure occurred (allergic reaction to the moisturizing crème supplied to the patient for basic care). Overall, three serious TEAEs were registered, none related to the device or medical procedure, and they were intervertebral disc protrusion, malignant melanoma *in situ* (not on study site) and mental disorder.

4. DISCUSSION

This prospective, monocentric, randomized, blinded, intra-individual clinical trial investigated the use of high peak irradiances (600 mW/cm²) of BL at 453 nm for treating localized Pv plaques in comparison with the standard therapy calcipotriol over a period of 12 weeks. Two different fluences were compared delivering either 38 J/cm² in 15 min or 76 J/cm² in 30 min.

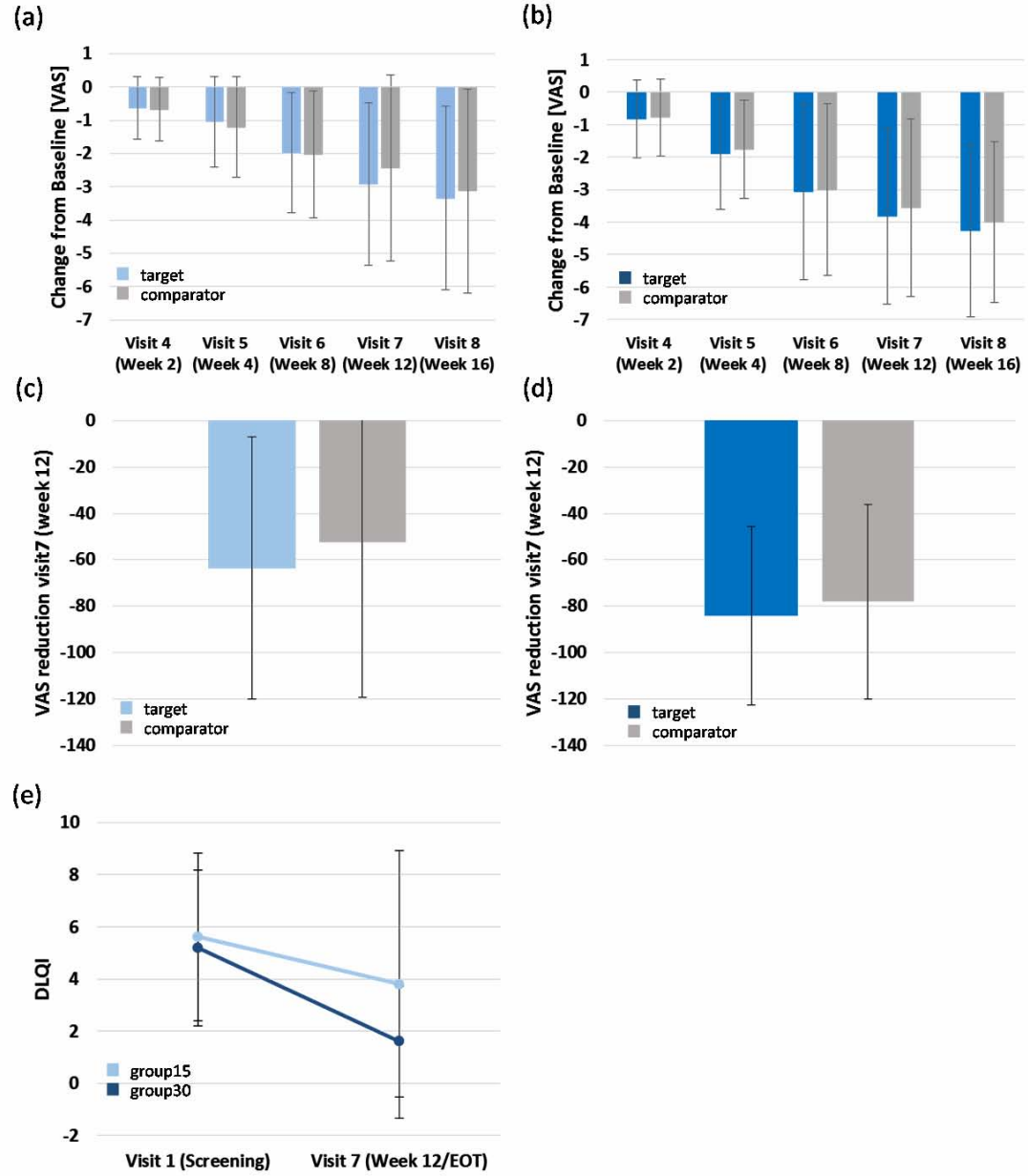

Fig. 3. Assessment of plaque severity by patients. Plaque severity assessed by visual analogue scale (VAS) for **(a)** group15 and **(b)** group30 shown as change from baseline. Average percent reduction of VAS at visit 7 (week 12) of group15 (**c**) and group30 **(d)**. **(e)** Development of the DLQI score throughout the study at screening and end of treatment (Error bar: SD).

We found that BL was as effective as calcipotriol applied daily over 12 weeks as assessed by the investigator using the LPSI. Additionally, both fluences used have a similar outcome regarding LPSI severity reduction of about 50%. Therefore, longer treatment times with higher fluences do not appear to be beneficial *per se*. In a previous study using 200 mW/cm² for 30 min the higher peak irradiance did not increase the efficacy either, which was around 50% in both that study and the current one [11]. However, it was not tested if a 15-min treatment with the lower peak irradiance (e.g. 200 mW/cm²) is as effective as the higher one used in the present study. Increasing peak

Table 2. Compliance, system usability score (SUS) and adverse events (AE). **(a)** SD = standard deviation, n = number of patients, (%) = percentage of patients among total (N). **(b)** Adverse events that occurred during the study period.

(a)

Parameter	Statistics	Group15 (N = 26)	Group30 (N = 25)	
Compliance (%)	n	26	25	
	Mean	98.6	98.6	
	SD	4.53	5.69	
Parameter	**Statistics**	**Group15 (N = 26)**	**Group30 (N = 25)**	**Overall (N = 51)**
SUS	n	20	21	41
	Mean	89.0	88.6	88.8
	SD	8.71	7.92	8.21

(b)

Adverse event category	Group15 (N = 26)		Group30 (N = 25)		Overall (N = 51)	
	n (%)	[AE]	n (%)	[AE]	n (%)	[AE]
AEs (including AEs events prior to treatment)	10 (38.5)	[13]	4 (16.0)	[4]	14 (27.5)	[17]
TEAEs	10 (38.5)	[13]	4 (16.0)	[4]	14 (27.5)	[17]
TEAEs related to IMD	0 (0)	[0]	0 (0)	[0]	0 (0)	[0]
TEAEs related to medical procedure	0 (0)	[0]	1 (4.0)	[1]	1 (2.0)	[1]
TEAEs leading to discontinuation	1 (3.8)	[1]	1 (4.0)	[1]	2 (3.9)	[2]
Serious TEAEs	3 (11.5)	[3]	0 (0)	[0]	3 (5.9)	[3]
Serious TEAEs related to treatment	0 (0)	[0]	0 (0)	[0]	0 (0)	[0]

n = number of patients reporting at least 1 adverse event with the specification. (%) = percentage of patients among total (N); [AE] = number of individual adverse events which occurred among the n patients.

irradiance could have the benefit of the same efficacy in a shorter treatment time, reducing the burden for the patient.

Interestingly, the investigator assessment differs substantially from the patients´ self-assessment using the VAS. In group15, patients rated higher symptom reduction due to BL treatment, with 63.5% improvement against 52.2% for the comparator calcipotriol. This is even more evident in group30 with 84.05% improvement for target and 78.01% improvement for comparator treatment. Thus, outcome after irradiation was evaluated more positively by the patients than by the investigator. In general, it seems that satisfaction with the UV-free blue light treatment was high (high compliance rate, high SUS, see Table 2). Additionally, the DLQI values improved in group30 with 70% reduction and in group15 with 32% reduction. Therefore, the patients´ knowledge of, which plaque was treated with light and which with calcipotriol could have led to a biased preference to the innovative therapy option. In this context, a longer treatment time could have been viewed as beneficial by the patient. Another explanation may be the previously reported experience of the patients with topical ointments which are often considered to be inconvenient and are hampered by low compliance in the long run. However, this does not explain the differences in both groups regarding the comparator treatment which showed a higher level of improvement in group30 than in group15.

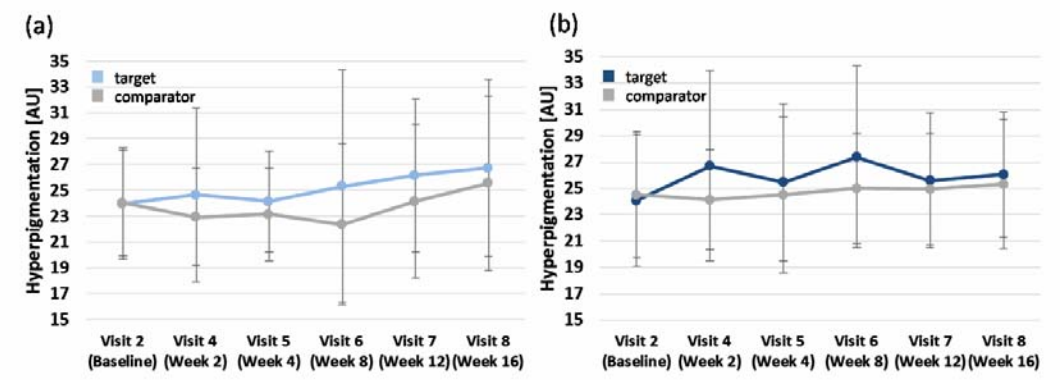

Fig. 4. Assessment of pigmentation. Mexameter measurement in arbitrary units [AU] in (**a**) group15 and (**b**) group30 (Error bar: SD; EOT: End of treatment; FU: Follow-up).

In previous studies, BL irradiation led to slight hyperpigmentation [11, 10]. In the present trial, Mexameter measurements revealed low-level hyperpigmentation in both BL-treated and calcipotriol-treated areas. This might be due to post-inflammatory hyperpigmentation. Moreover, BL treatment *per se* might increase melanin levels. Mexameter measurements showed that low-level hyperpigmentation was maintained at about the same level in both BL and Daivonex-treated areas during the 4-week follow-up, even though no case of hyperpigmentation was reported as a finding of the dermatological examination at the end of the follow-up phase.

5. CONCLUSION

In summary, the present study confirms and extends our previous results, demonstrating the efficacy of blue light in the treatment of mild Pv [11, 13]. As additional new findings, we present evidence that 600 mW/cm² blue light is as effective as calcipotriol, and that extending the treatment duration (15 vs. 30 min per day) does not lead to a significantly better outcome. Close monitoring of the pigmentation using Mexameter confirmed the low-level hyperpigmentation caused by UV-free blue light application, which was, however, not perceived as a substantial negative side effect by the patients. Otherwise, the UV-free blue light at the doses applied, was without adverse effects and yielded a high degree of patient satisfaction.

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CONFLICT OF INTEREST STATEMENT

M. Born and J. Liebmann are paid employees of Philips GmbH, Innovative Technologies. L. Krings received a grant (6 monthly salaries) from Philips. V. von Felbert has received several research grants from Philips GmbH for *in vitro* studies and clinical trials (including salary for 2.5 months) in the past.

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