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# Prospective Randomized Long-Term Study on the Efficacy and Safety of UV-Free Blue Light for Treating Mild Psoriasis Vulgaris

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**Key Words**
Clinical trial · Phototherapy · Psoriasis · Randomized clinical trials · Blue light · Clinical investigation · Light-emitting diode

**Abstract**
***Background:*** Blue light irradiation reduces the proliferation of keratinocytes and modulates T-cell immune response in vitro and has been shown to reduce the severity of psoriasis vulgaris (Pv) in two clinical trials. ***Objective:*** Evaluation of safety and efficacy of long-term UV-free blue light treatment at home for mild Pv. ***Methods:*** Forty-seven patients with mild Pv were randomized for receiving high-intensity blue light treatment (HI: 453 nm LED, 200 mW/cm$^2$, n = 24) and low-intensity treatment (LI: 453 nm LED, 100 mW/cm$^2$, n = 23) of one Pv plaque for 12 weeks. A contralateral control plaque remained untreated. ***Results:*** Patient compliance and satisfaction were high. The primary endpoint, change from baseline (CfB) of the Local Psoriasis Severity Index, revealed a significant improvement of the target compared to the control plaques (ΔCfB for the HI group: –0.92 ± 1.10, p = 0.0005; for the LI group: –0.74 ± 1.18, p = 0.0064). ***Conclusion:*** UV-free blue light home treatment is safe and improves Pv plaques.


## Background

Psoriasis vulgaris (Pv) is a chronic skin disease characterized by hyperproliferation and reduced differentiation capacity of skin keratinocytes accompanied by an inflammatory response. Immune cells such as T cells and dendritic cells release cytokines, which induce further keratinocyte proliferation and inflammatory infiltration [1]. This vicious circle results in a sustained inflammation of the skin, which is evident by red and often scaly plaques. Pv is a lifelong disease; success of treatments with topical creams is limited in many cases due to dissatisfaction and non-adherence. Sunlight or phototherapy using artificial light sources such as broadband or narrowband UVB improves the symptoms of psoriasis [2, 3]. However, excessive sunbaths as well as UVB alone are known to lead to premature skin aging and induce skin cancer [4]. Because of these risks phototherapy is mostly applied in hospitals and by specialized practitioners. Therefore, this form of therapy is costly and requires considerable time and effort by the patient. Recent work has shown that UV-free blue light reduces the proliferation rate of human keratinocytes by inducing differentiation; in addition, it is cytotoxic to T cells at low fluencies that are not harmful to other cells of the skin [5]. Becker et al. [6] and Fischer et



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al. [7] used blue light to improve the symptoms of eczema patients; in vitro studies by the same group of authors revealed that blue light irradiation suppresses dendritic cell activation. Therefore, UV-free blue light appears to be a promising therapeutic modality in Pv. An initial study with 40 patients performed in 2009 using UV-free blue light-emitting diodes (LEDs, 453 nm) for 4 weeks of daily treatment at home revealed a significant reduction in Pv symptoms [8]. The only reported side effect was mild hyperpigmentation in 50% of the patients, which resolved spontaneously after treatment was stopped. Kleinpenning et al. [9] investigated the effect of blue light exposure on the skin of healthy volunteers and could not detect any sign of damage or skin aging in skin biopsies taken after 5 days of irradiation. Additionally, this group conducted a clinical investigation using a 420 nm LED light source at 100 mW/cm$^2$ (120 J/cm$^2$ per treatment) 3 times weekly for 4 consecutive weeks (1,440 J/cm$^2$ in total) in patients with Pv and found no side effects associated with this treatment [10].

Blue light is also commonly used for other indications including acne [11] and newborn jaundice without significant side effects. In Crigler-Najjar disease, a rare hereditary chronic disease affecting bilirubin metabolism, even high cumulative fluencies and long-term application of blue light (400–520 nm; cumulative fluencies of more than 260,000 J/cm$^2$ in 10 years) had no adverse effects [12].

The study presented here was designed to improve treatment efficacy while reducing hyperpigmentation. We conducted a randomized, double-blinded, intraindividual, exploratory study with 47 mildly affected Pv patients who were irradiated on a randomized well-defined plaque with blue light for 12 weeks at home. Compared with previous studies, we decided to test two different peak intensities to see if we can further improve psoriasis plaques with higher peak irradiances and longer treatment periods. The main objective of this study was to prove effectiveness and to analyse the long-term safety of blue light home therapy. As a special feature, the irradiation device tested in the present study is wearable and can be used during normal daily activities.

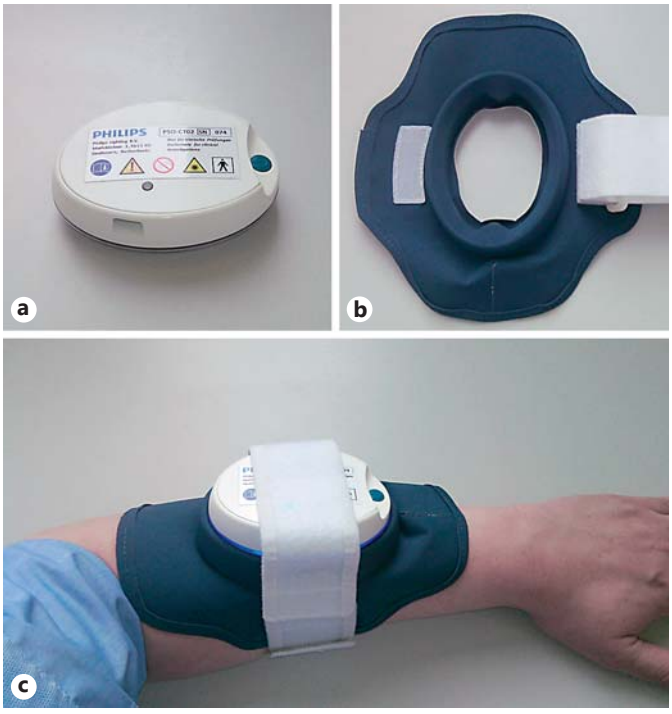


**Fig. 1.** Investigational device. Device (**a**) and textile fixation strap (**b**) for attaching the device to the extremities. The device is inserted into the oval opening. Device attached to the arm (**c**).

## Materials and Methods

*Patients*

Forty-nine male and female patients (age 18–75 years) with mild Pv [according to the Psoriasis Area Severity Index (PASI), the body surface area and the Dermatology Life Quality Index (DLQI); PASI ≤10 and body surface area ≤10 and DLQI ≤10] were enrolled in the study at the Department of Dermatology and Allergology, University Hospital, RWTH Aachen University Hospital, from October 2013 to June 2014. The patients were classified into Fitzpatrick skin types I–IV. Excluded from the study were pregnant or lactating women, patients with photodermatosis and/or photosensitivity, porphyria with erythrodermic, exfoliative or pustular psoriasis, congenital or acquired immunodeficiency, with malignoma or severe actinic damage of the skin, atypical naevi or signs of hyperpigmentation, viral lesions of the skin, fungal and bacterial skin infections, parasitic infections and atrophic skin, and genetic deficiencies associated with increased sensitivity to light or increased risk to develop dermatologic cancer (i.e. xeroderma pigmentosum). This randomized, double-blinded, intraindividual, exploratory study was approved by the medical ethics committee of the Medical Faculty of the RWTH Aachen and by the responsible competent Federal Government authority, BfArM, Germany. All patients gave informed consent before any study procedure was conducted. The study was performed according to the European and international Good Clinical Practice standard (EN-ISO 14155: 2011) and the Declaration of Helsinki. The study was registered at ClinicalTrials.gov with the identifier NCT02004847.

*Device*

The device (built by Philips Light and Health, Eindhoven, The Netherlands, fig. 1) used in this study was equipped with blue LEDs (453 ± 5 nm peak wavelength) and was powered by a rechargeable battery. The treatment area was 7 × 5 cm (oval-shaped). The aver-

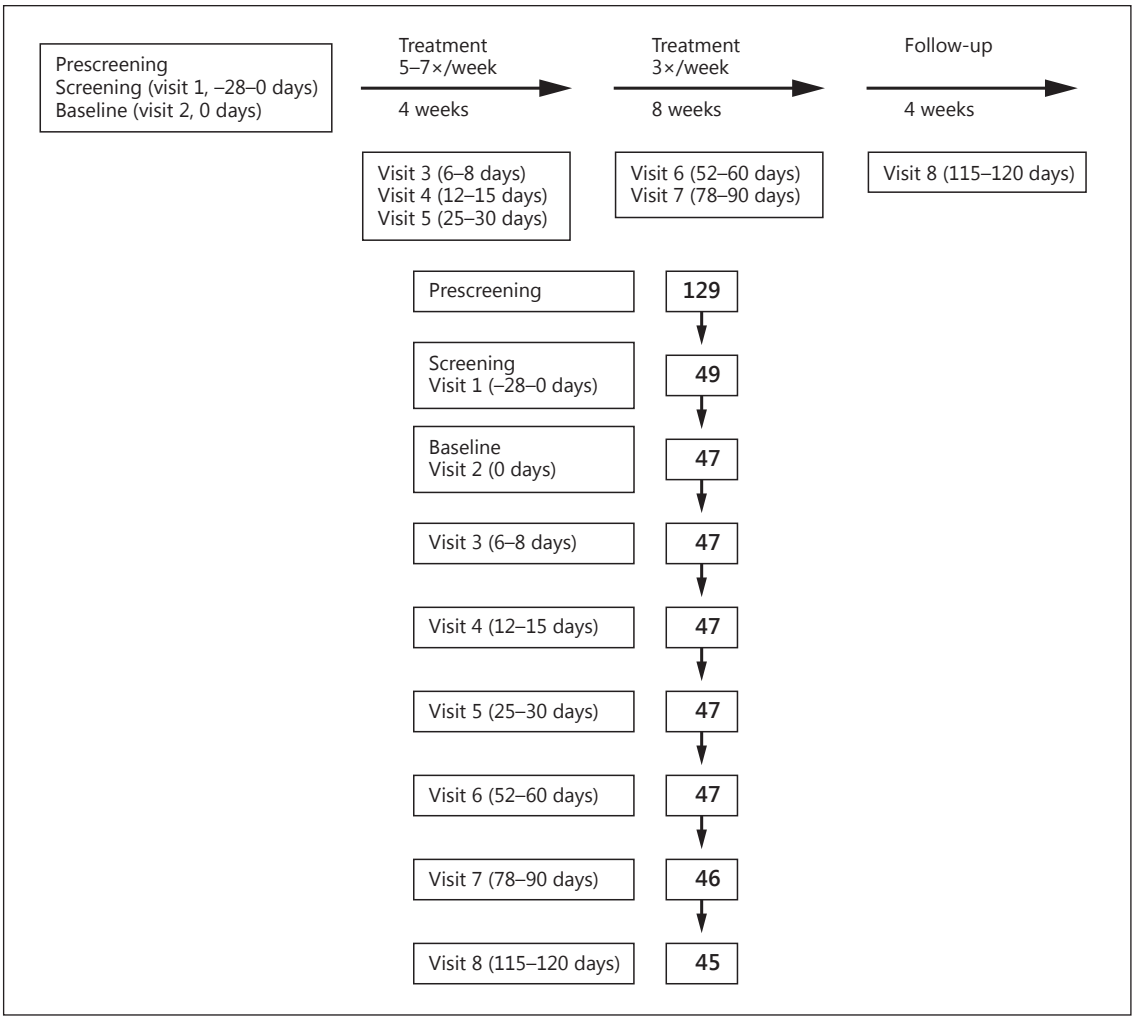


**Fig. 2.** Study design.

age irradiance of the device is 50 mW/cm$^2$, delivering a daily treatment dose of 90 J/cm$^2$ over 30 min. To reach 100 (low intensity, LI) and 200 (high intensity, HI) mW/cm$^2$ peak intensities the device is operated with two different duty cycles. The device could be fixed to the respective treatment area with a textile strap allowing the patient to move around during treatment. The device had a data logger which was read out after the end of the study to verify treatment compliance.

*Study Design*

All patient visits were conducted at the Department of Dermatology and Allergology, RWTH Aachen University Hospital. One hundred and twenty-nine patients were prescreened and 49 patients were enrolled in the study at the time of screening (visit 1, –28–0 days, fig. 2). At the baseline visit (visit 2, 0 days), 47 eligible patients were randomized into two groups of a confidential block size (HI group: 24 patients, LI group: 23 patients). The investigator selected two comparable study areas which were numbered 1 and 2 and then opened a randomization envelope containing information which plaque to treat with 453-nm light (target) and which plaque served as a control (no treatment). Randomization envelopes were prepared by the CRO, Cromsource GmbH in preparation of the study. Randomization was performed double-blinded. However, which area was treated and which served as a control could not be blinded. After randomization, patients received their first treatment at the investigational site and were instructed in the self-usage of the device. All patients received a moisturizing lotion (Excipial U10 Lipolotio, Spirig Pharma GmbH, Augsburg, Germany) for use on both the treated and the control plaque. Non-study areas could be treated with calcipotriol, but also with WHO group I–II corticosteroids or mometasone. The patients were asked to apply the light treatment to the target area once daily, 5–7 times per week at home for an initiation treatment period of 4 weeks (fig. 2). To evaluate compliance, patients were asked to keep a diary where they marked each treatment and adverse events. Additionally, the device contained a logger which facilitated comparison with the diary.

During these 4 weeks, the patients returned to the investigational site for assessments of safety and effectiveness at visit 4 (12–15 days) and visit 5 (25–30 days). A phone call visit (visit 3, 6–8 days) was performed after 1 week of treatment to check for any adverse events or problems in handling the device. This was followed by a period of 8 weeks with at least 3 applications per week (maintenance treatment). Patients visited the investigational sites every 4 weeks (visit 6, 52–60 days; visit 7, 78–90 days). The visit at week 12 served as the end of treatment visit (visit 7, 78–90 days). The patients were followed up for another 4 weeks (visit 8, 115–120 days) without treatment. Treated and control plaques were photodocumented at the investigational site. At or after visit 5 (after 4 weeks of treatment) and based on the discretion of the investigator, temporal topical rescue treatment of the target and control areas could be performed using the vitamin D analogue calcipotriol (Daivonex, Leo Pharma GmbH, Neu-Isenburg, Germany) to be applied after treatment with blue light to both study areas. To evaluate the acceptance of the device by the users and to assess patient satisfaction, patients were asked to fill in a standardized usability and comfort questionnaire [13]. The questionnaire was evaluated using the System Usability Scale (SUS) [14], which gives a range of possible values from 0 (negative or worst imaginable) to 100 (positive or best imaginable).

*Clinical Assessment*

To evaluate the effect of blue light treatment on individual localized plaques in analogy to the PASI [15], a Local Psoriasis Severity Index (LPSI) was used by the investigator, grading the severity of erythema, induration, and scaliness on the study areas. The LPSI is the sum score of these symptoms on a scale of 0–4 (0 = no sign to 4 = very marked) giving a total severity score of 0–12. Pigmentation and erythema of the plaque and its surrounding area were analysed with a Mexameter® (Courage + Khazaka electronic GmbH, Cologne, Germany) at each visit as a safety measure. Additionally, at visit 8 patients were asked if hyperpigmentation of the treated area occurred as this was the only known side effect of blue light treatment so far. At screening (visit 1) and visit 7, the patients were asked to fill in the DLQI questionnaire. At visit 7, they were also asked to fill in a questionnaire on system usability and thermal comfort. The treated and control plaques were photodocumented at every visit.

*Statistical Analysis*

The investigational data were collected, processed, validated and analysed according to the intention-to-treat principle by the Clinical Data Management and Statistics Department of Cromsource GmbH, Aachen, Germany. The SAS system was used for generating listings as well as tables comprising descriptive and analytical statistics of the collected data. The primary endpoint was the analysis of the change from baseline (CfB) of the LPSI of the target area (HI group) as compared to the control area (HI) at the end of treatment (visit 7).

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 was performed. Figures were generated with Excel using the SAS output tables.

**Table 1.** Demographics

| Intensity group | Available, n | Missing, n | Min–max | Median | Mean | SD |
|---|---|---|---|---|---|---|
| Age, years | | | | | | |
| HI | 24 | 0 | 24.00–66.00 | 48.50 | 46.54 | 13.80 |
| LI | 23 | 0 | 28.00–67.00 | 51.00 | 49.09 | 10.68 |
| Total | 47 | 0 | 24.00–67.00 | 49.00 | 47.79 | 12.30 |
| PASI score | | | | | | |
| HI | 24 | 0 | 2.00–9.60 | 3.90 | 4.38 | 2.14 |
| LI | 22 | 1 | 1.20–7.80 | 4.25 | 4.20 | 1.75 |
| Total | 46 | 1 | 1.20–9.60 | 4.00 | 4.30 | 1.94 |
| BSA score | | | | | | |
| HI | 24 | 0 | 1.00–8.00 | 3.00 | 3.79 | 2.13 |
| LI | 22 | 1 | 1.00–6.00 | 3.00 | 3.55 | 1.47 |
| Total | 46 | 1 | 1.00–8.00 | 3.00 | 3.67 | 1.83 |
| DLQI (baseline) | | | | | | |
| HI | 24 | 0 | 1.00–10.00 | 4.00 | 4.33 | 2.73 |
| LI | 23 | 0 | 1.00–9.00 | 4.00 | 3.78 | 2.63 |
| Total | 47 | 0 | 1.00–10.00 | 4.00 | 4.06 | 2.67 |

n = Number of subjects. BSA = Body surface area.

## Results

*Demographics and Baseline Characteristics*

Initially, 49 patients were enrolled for this study. Two patients were screening failures and 47 were randomized. From these 47, two dropped out prior to study finalization due to the initiation of immunosuppression (1 patient: tinnitus treated with systemic corticosteroids; second patient: allergic rhinitis and asthma treated with systemic corticosteroids). The full patient characteristics are summarized in tables 1 and 2.

*Study Results*

To measure the efficacy of blue light therapy on localized plaques, an LPSI score grading the severity of erythema, induration, and scaliness on the local study areas was applied. The LPSI is the sum score of these symptoms each on a scale of 0–4 (0 = no sign, to 4 = very marked) giving a total severity score of 0–12 (based on the PASI of Fredriksson and Pettersson [15], see also Clinical Assessment in Materials and Methods). The analysis of the CfB at visit 7 (78–90 days, end of treatment) in the HI group as primary endpoint revealed a significant improvement of the target plaque as compared to the control plaque with a difference in CfB of –0.92 ± 1.10 (p = 0.0005, t test; p = 0.0006, Wilcoxon signed-rank test; mean 95% CI –1.38, –0.45; fig. 3c). Additionally, the LI group showed a

**Table 2.** Demographics

| | Intensity group | | |
|---|---|---|---|
| | HI | LI | total |
| Gender | | | |
| Female | 9 (37.50) | 8 (34.78) | 17 (36.17) |
| Male | 15 (62.50) | 15 (65.22) | 30 (63.83) |
| Missing | 0 (0.00) | 0 (0.00) | 0 (0.00) |
| Total | 24 (100.00) | 23 (100.00) | 47 (100.00) |
| Type of skin | | | |
| Type I: light, white; very fair | 1 (4.17) | 1 (4.35) | 2 (4.26) |
| Type II: white; fair | 14 (58.33) | 10 (43.48) | 24 (51.06) |
| Type III: cream white; fair | 7 (29.17) | 11 (47.83) | 18 (38.30) |
| Type IV: brown; typical Mediterranean Caucasian skin | 2 (8.33) | 1 (4.35) | 3 (6.38) |
| Type V: dark brown | 0 (0.00) | 0 (0.00) | 0 (0.00) |
| Type VI: black | 0 (0.00) | 0 (0.00) | 0 (0.00) |
| Missing | 0 (0.00) | 0 (0.00) | 0 (0.00) |
| Total | 24 (100.00) | 23 (100.00) | 47 (100.00) |

Number of subjects; figures in parentheses are percentages.

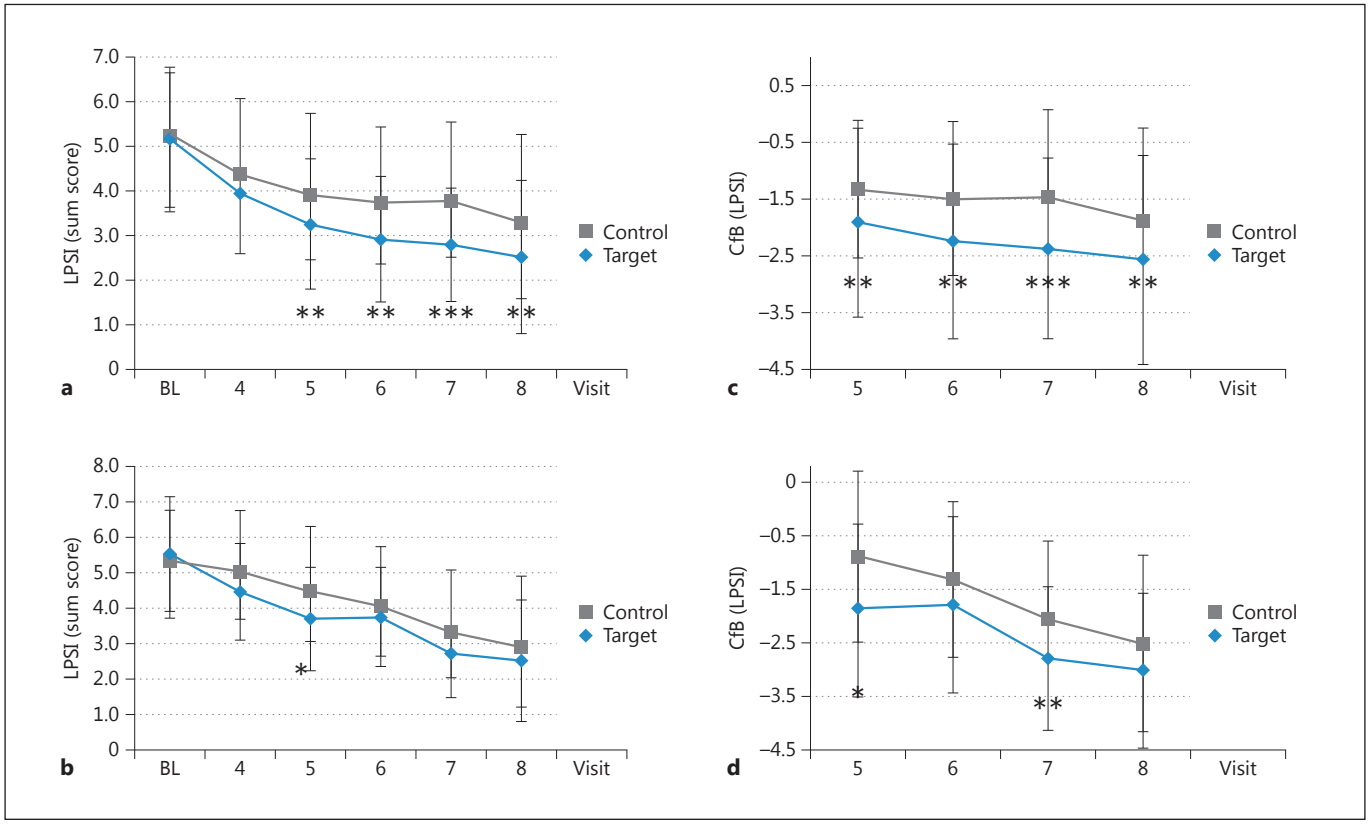


**Fig. 3.** LPSI score and CfB over time. **a**, **b** LPSI score at baseline (BL) and over the course of the clinical investigation for the HI group (**a**) and the LI group (**b**). **c**, **d** CfB in LPSI score over the study visits for the HI group (**c**, n = 24) and the LI group (**d**, n = 23). Visit 7 of the HI group (**c**) was defined as the primary endpoint of the study. * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$. Error bar: SD.

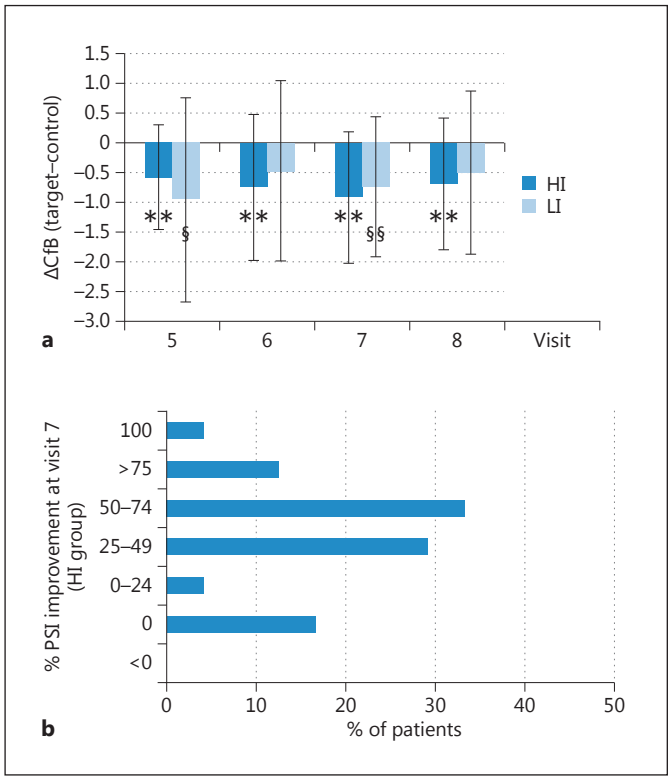


**Fig. 4.** ΔCfB and percent of LPSI score reduction. **a** Difference of target and control (ΔCfB) over the study visits for HI and LI groups. § $p \leq 0.05$; **,§§ $p \leq 0.01$. **b** Percentage of LPSI reduction from baseline visit at visit 7 (end of treatment) for the HI group. Error bar: SD.

significant improvement of the LPSI of the treated plaque compared to the control plaque at visit 7 (end of treatment) with a difference in the CfB of –0.74 ± 1.18 ($p = 0.0064$, t test; $p = 0.0083$, Wilcoxon signed-rank test; mean 95% CI –1.25, –0.23; fig. 3d). The LPSI scores at baseline were comparable for both, target and control plaques, with a mean value of 5.17 ± 1.37 and 5.25 ± 1.22 in the HI group (fig. 3a) and 5.52 ± 1.62 or 5.35 ± 1.40 in the LI group (fig. 3b), respectively. The analysis of the single treatment visits over time as shown in figure 3 demonstrated a significant improvement of the LPSI sum score (fig. 3a) at visits 5, 6, 7 and 8 for the HI group. This was confirmed in the CfB of the LPSI score compared to the control at all visits for the HI group (fig. 3c). For the LI group, only visit 5 revealed a significant difference in the LPSI sum score (fig. 3b) and a significant difference in CfB at visit 5 and 7, which marks the end of treatment (fig. 3d). This difference in efficacy of HI versus LI is also illustrated in figure 4a, when comparing the ΔCfB [= CfB (target) – CfB (control)]. Except for visit 5 the HI group always showed a higher degree of reduction in ΔCfB compared to the LI group.

Additionally, the percentage of LPSI reduction at visit 7 (end of treatment) from the baseline visit for the HI group (n = 24) was calculated to alternatively evaluate the benefit for the patients (fig. 4b). Clearly, some patients did not benefit from blue light treatment, with 16.7% showing no measurable response (0% LPSI reduction). However, regarding treated plaques, none of the patients showed a deterioration, 4.2% had an LPSI reduction between >0 and <25%, 29.2% between ≥25 and <50%, 33.3% between ≥50 and <75%, and 16.7% of more than 75%. One patient of the HI group showed a complete clearance of the lesion at visit 6 and another 1 at visit 7 (end of treatment, 4.2%). The control plaques were not cleared. Figure 5 provides an example comparing target and control areas of one of the patients at different time points.

The use of topical vitamin D analogues was examined in both groups (HI and LI); there was no relevant difference in the number of patients for whom calcipotriol was initiated (HI = 17; LI = 16) nor was there a relevant difference in the mean initial day of use, which was 46.35 ± 17.68 for the HI group and 48.25 ± 26.36 for the LI group (table 3). When analysing all patients together irrespective of their treatment group, no significant difference between those receiving and those not receiving calcipotriol treatment at any time point during the study (fig. 6a) was observed.

User acceptance of the device and patient satisfaction were assessed by the patients through a standardized usability and comfort questionnaire [13] as described in Materials and Methods. Twenty patients considered the usability between 90 and 100 (best imaginable), 13 between 80 and 89 (excellent), 5 between 70 and 79 (good) and 2 between 60 and 69 (marginal). The average SUS score was 88.4 ± 10.46 (excellent). No patient considered the usability as unacceptable (fig. 6b).

*Safety Analysis*

Safety variables analysed were (serious) adverse events, (serious) adverse device events, device deficiencies, hyperpigmentation of normal skin areas exposed to blue light including the recovery at the end of the study, and thermal comfort. There were no serious adverse events nor were any device- or treatment-related adverse events reported during the whole study period of 16 weeks. The number of adverse events reported was similar in the HI and LI groups (HI 16, 45.83%; LI 12, 34.78%). Only 2 device deficiencies occurred, 1 in the HI and 1 in the LI group (table 4). The adverse events with no causal rela-

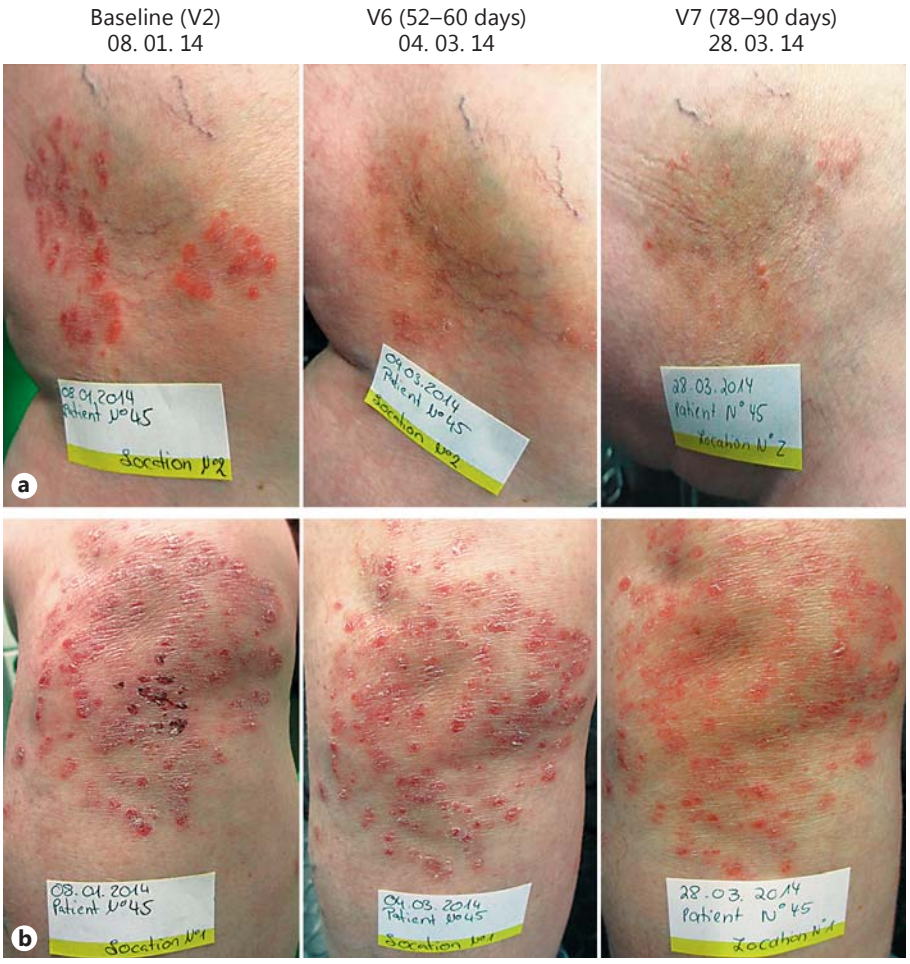


**Fig. 5.** Clinical course of target and control plaques of a representative patient. **a** UV-free blue light-treated plaque. **b** Control plaque.

tionship to blue light treatment were tinnitus (n = 1), gastro-oesophageal reflux disease (n = 1), influenza-like illness (n = 1), drug hypersensitivity (n = 1), seasonal allergy (n = 1), cystitis (n = 1), gastroenteritis (n = 3), herpes virus infection (n = 1), herpes zoster (n = 1), nasopharyngitis (n = 3), sinobronchitis (n = 1), sinusitis (n = 1), tonsillitis (n = 1), musculoskeletal stiffness (n = 1), sacroiliitis (n = 1), drug eruption (n = 1), psoriasis (new plaques on other locations: n = 5), knee operation (n = 1), tooth extraction (n = 1) and hypertension (n = 1).

Even though patients reported a slight hyperpigmentation of the area surrounding the target plaque in half of the cases, the objective measurements by Mexameter® did not show any significant increase in melanin levels for the HI and LI groups. Interestingly, the measurements of the area surrounding the control plaques revealed a slight decrease in pigmentation compared to the treated area in both groups (fig. 7).

**Table 3.** Vitamin D analogue use

| Intensity group | Calcipotriol use, n | No use, n | Min–max | Median | Mean | SD |
|---|---|---|---|---|---|---|
| First use, days | | | | | | |
| HI | 17 | 7 | 25.00–88.00 | 54.00 | 46.35 | 17.68 |
| LI | 16 | 7 | 25.00–117.00 | 39.50 | 48.25 | 26.36 |
| Total | 33 | 16 | 25.00–117.00 | 52.00 | 47.27 | 21.97 |
| Total duration, days | | | | | | |
| HI | 17 | 0 | 6.00–93.00 | 62.00 | 62.65 | 23.82 |
| LI | 16 | 0 | 1.00–93.00 | 61.50 | 53.44 | 33.66 |
| Total | 33 | 0 | 1.00–93.00 | 62.00 | 58.18 | 28.92 |

n = Number of subjects.

**Table 4.** Adverse events

| | Intensity group | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | HI | | | LI | | | total | | |
| | E | n | % | E | n | % | E | n | % |
| Type of event | | | | | | | | | |
| AEs | 16 | 11 | 45.83 | 12 | 8 | 34.78 | 28 | 19 | 40.43 |
| TEAEs | 16 | 11 | 45.83 | 12 | 8 | 34.78 | 28 | 19 | 40.43 |
| IMD-related TEAEs | 0 | 0 | 0.00 | 0 | 0 | 0.00 | 0 | 0 | 0.00 |
| SAEs | 0 | 0 | 0.00 | 0 | 0 | 0.00 | 0 | 0 | 0.00 |
| Treatment-emergent SAEs | 0 | 0 | 0.00 | 0 | 0 | 0.00 | 0 | 0 | 0.00 |
| IMD-related treatment-emergent SAEs | 0 | 0 | 0.00 | 0 | 0 | 0.00 | 0 | 0 | 0.00 |
| Deaths | 0 | 0 | 0.00 | 0 | 0 | 0.00 | 0 | 0 | 0.00 |
| Device deficiencies | 1 | 1 | 4.17 | 1 | 1 | 4.35 | 2 | 2 | 4.26 |

E = Number of events; n = number of subjects with an event; % = of subjects relative to all subjects in the respective treatment group; AEs = adverse events; TEAEs = treatment-emergent adverse events; SAEs = serious adverse events; IMD = investigational medical device.

**Table 5.** Compliance and SUS

**a** Compliance

| Treatment period | Intensity group | | |
|---|---|---|---|
| | HI | LI | total |
| Daily treatment period | 24 (100.00) | 23 (100.00) | 47 (100.00) |
| Maintenance period | 24 (100.00) | 22 (95.65) | 46 (97.87) |
| Overall | 24 (100.00) | 22 (95.65) | 46 (97.87) |

**b** SUS

| Intensity group | Available, n | Missing, n | Score | | | |
|---|---|---|---|---|---|---|
| | | | min–max | median | mean | SD |
| HI | 23 | 1 | 60.00–100.00 | 92.50 | 88.37 | 11.62 |
| LI | 17 | 5 | 75.00–100.00 | 87.50 | 88.53 | 9.02 |
| Total | 40 | 6 | 60.00–100.00 | 90.00 | 88.44 | 10.46 |

n = Number of subjects. Figures in parentheses are percentages.

*Treatment Compliance*

The treatment compliance was very high in both groups and also in both study phases (daily treatment and maintenance period). The data recorded by the data logger of the device were identical to the data recorded by the patients. In the daily treatment period both groups showed 100% compliance with the treatment protocol. During the maintenance period the HI group showed 100%, and the LI group showed 95.65% compliance (table 5). Two patients discontinued the study early due to the intake of systemic corticosteroids (1 patient developed tinnitus with systemic corticosteroid therapy and the other patient allergic rhinitis and asthma with systemic corticosteroid therapy).

## Discussion

In 2011, a first clinical trial using UV-free blue LED light to treat the symptoms of Pv was conducted [8] at the Department of Dermatology and Allergology, RWTH Aachen University Hospital, Germany. We found that 4

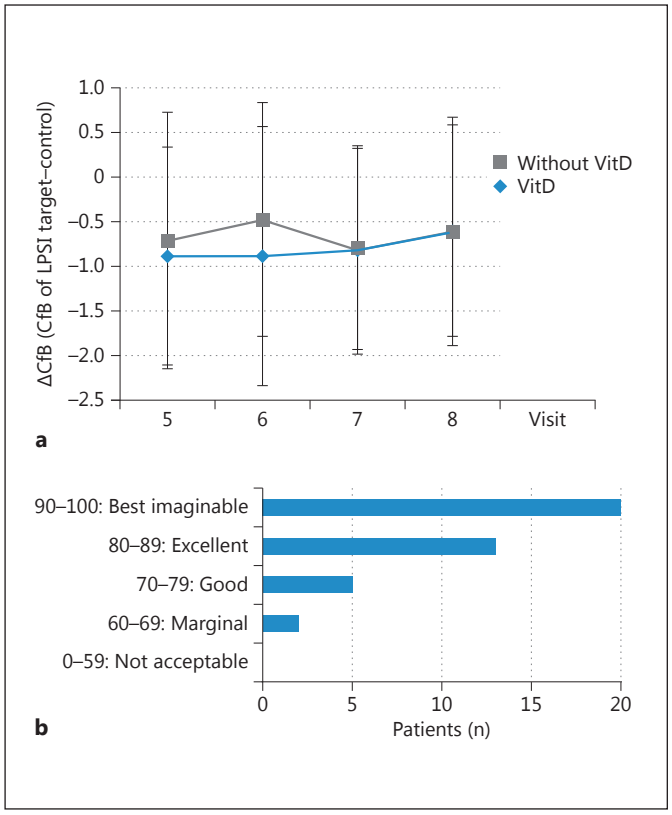


**Fig. 6.** ΔCfB of patients using vitamin D and evaluation of the SUS score. **a** Comparison of CfB of all patients (HI and LI) using vitamin D (n = 30) and patients not using vitamin D (n = 17) during the maintenance phase. **b** Evaluation of usability by SUS from 'not acceptable' (0–59) to 'best imaginable' (90–100).

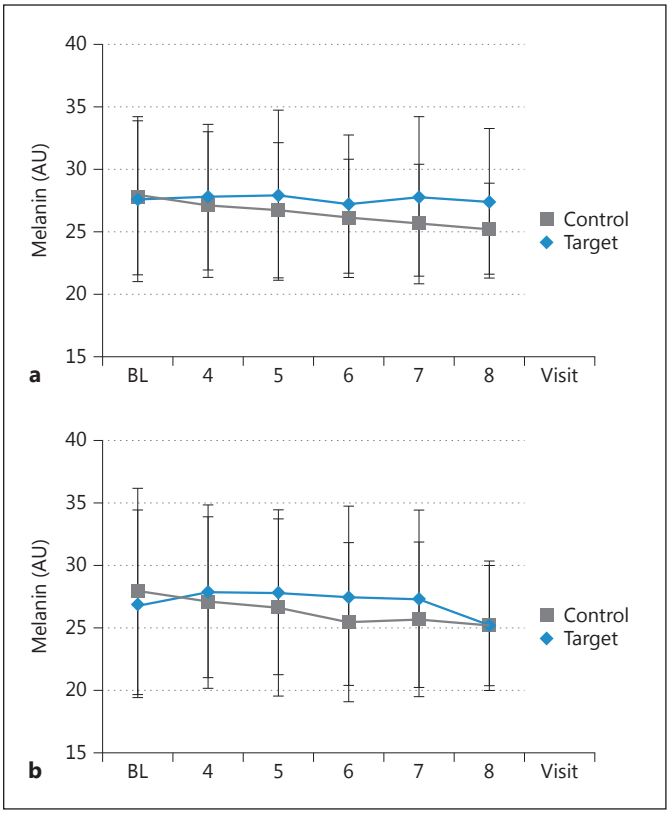


**Fig. 7.** Melanin content measured by Mexameter®. Assessment of skin pigmentation by measuring melanin content of the areas surrounding the target plaque and the control plaques in the HI group (**a**) and in the LI group (**b**).

weeks of treatment with 453 nm light significantly improved the LPSI. The decrease in symptoms after 4 weeks showed no signs of saturation; thus, we concluded that it would make sense to increase peak intensities and to extend the treatment period to reach further improvement. We now investigated the effects of 12 weeks of irradiation with blue light of localized plaques of mildly affected Pv patients using two different intensity settings (HI = 200 mW/cm$^2$; LI = 100 mW/cm$^2$). The treatment phase consisted of 4 weeks of almost daily irradiation (5–7 days/week) and 8 weeks of at least three irradiations per week. The main result of the present study was that the LPSI after the end of the treatment period (visit 7) showed a significant improvement of symptoms compared with the control in both groups. For the HI group, significant improvement of LPSI symptoms compared with the control group was obtained at each interval. Improvement continued in both groups throughout the whole study period and no saturation level was observed. In some patients, complete clearance of Pv plaques in the blue light treatment groups was achieved. In contrast, in the previous clinical trial we could not accomplish complete clearance of Pv lesions in any of the patients treated. Thus, compared to the 2011 study, long-term blue light treatment can further improve the clinical outcome of mild Pv. The patient satisfaction was comparable in both intensity groups. Even though the HI group showed a trend to better improvement when taking the control plaque into account the overall difference in efficacy between HI and LI groups was rather small. This is probably due to the fact that the daily treatment dose in both groups was 90 J/cm$^2$ and the different peak intensities have only a minor effect on efficacy.

The study presented here also demonstrated a clear improvement in the control area. This could be due to the required use of moisturizing creams (Excipial U10

Lipolotio), which has been implemented due to the long study period of 4 months. However, a placebo effect of this order is not unusual; previous clinical investigations testing biologicals [16] or topicals such as vitamin D analogues or corticosteroids for Pv treatment also demonstrated a clear improvement in the control group similar to the one found in the present study [17]. The LI group showed a better improvement in the control plaque than the HI group. This could be due to the limited number of patients; such differences in control values would most likely level out if the number of patients were increased.

Increased proliferation and reduced differentiation capacity of keratinocytes accompanied by infiltration of immune cells (e.g. T cells) are the hallmarks of psoriasis. Therefore, the effects of blue light observed here could be explained by effects observed in vitro, like inhibition of keratinocyte proliferation, increased keratinocyte differentiation and/or increased apoptosis of T cells [5]. Additionally, blue light has been shown to inhibit cytokine production by dendritic cells [18], which could also play a role for reducing Pv symptoms. The results of the present clinical study are also in line with a previous trial comparing blue and red light to treat Pv. In this study [10] on 20 patients, an improvement in psoriasis plaques was found after irradiation with both blue and red light.

In contrast, an earlier study on blue light by Maari et al. [19] did not demonstrate significant improvement in psoriasis. One reason for this discrepancy might be the use of different light sources in these trials. Maari et al. [19] used fluorescent tubes whereas in our study LED-based devices with narrow bandwidth were used. Additionally, Maari et al. [19] applied 10 J/cm$^2$; in the present study, 90 J/cm$^2$ was applied by using pulsed intensities. Finally, we chose a treatment protocol lasting 12 weeks compared to just 4 weeks in the study by Maari et al. [19].

In our study, blue light at 453 nm had no detectable side effects. All reported adverse events were not related to the investigational medical device or to the treatment procedure. The only known side effect of blue light exposure so far is a mild hyperpigmentation which spontaneously vanishes after the cessation of treatment [8, 9]. An increase in melan-A-positive cells has been described [9]. Weinstabl et al. [8] reported after blue light irradiation (LED 420 nm and LED 453 nm for 15 min with 100 mW/cm$^2$, 90 J/cm$^2$) a temporary hyperpigmentation in the treated area in both groups for 50% of the patients. In the present study, almost 50% of the patients reported a slight hyperpigmentation, but objective measurements of skin pigmentation using a Mexameter® did not reveal any significant increase in pigmentation compared to the baseline value (fig. 7). This discrepancy can be explained by taking into account that the study was started in late autumn and was mainly conducted during wintertime when the skin gets paler anyway. This is reflected by the fact that the skin surrounding the control plaque showed reduced melanin levels towards the end of the investigation. In contrast, the skin surrounding the treated plaque keeps the initial level of pigmentation probably due to the exposure to blue light. This is likely perceived by the patient as hyperpigmentation even though this is actually not the case. In comparison with the hyperpigmentation observed by Weinstabl et al. [8], pulsed LED light used in this study induced less intensive pigmentary changes even when light intensity was increase to 200 mW/cm$^2$.

Because of the innovative nature of this treatment, long-term safety data for blue light exposure of patients' skin are scarce. There are several studies assessing the risk of developing moles in children 8–9 years after receiving neonatal blue light phototherapy for jaundice treatment [20–22]. Some of these studies find an association of naevus count with phototherapy, some do not. Additionally, direct evidence that the increase in the incidence of naevi is also associated with an increased risk of melanoma later in life is lacking in all studies.

Crigler-Najjar disease is a rare hereditary disorder which affects bilirubin metabolism, causing non-haemolytic jaundice. It is treated with blue light at wavelengths between 400 and 520 nm as standard therapy. Patients with severe forms are often required to receive phototherapy for the entire night (2 mW/cm$^2$, continuous mode) reaching cumulative fluencies of more than 260,000 J/cm$^2$ in 10 years. No adverse events have been observed so far [12].

In summary, UV-free blue LED home treatment has been shown to be an effective and safe therapy with a high level of patient satisfaction and compliance. Treatment led to a significant reduction in the CfB of the LPSI of the target plaques compared with the control plaques (HI: $-0.92 \pm 1.10$, $p = 0.0005$, t test; LI: $-0.74 \pm 1.18$, $p = 0.0064$, t test).


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