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Clinical Trial

An extension of a multicenter, randomized, split-face clinical trial evaluating the efficacy and safety of chromophore gel-assisted blue light phototherapy for the treatment of acne

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Abstract

A variety of laser/light-based devices have been reported to be effective for the treatment of acne, yet no long-term data on efficacy and safety have been published. A first 12-week clinical trial ("Main trial") recently demonstrated that the KLOX BioPhotonic System, an LED blue light device using photo-converter chromophores, can significantly improve moderate and severe facial acne vulgaris with an excellent safety profile. This Extension trial followed the Main trial, using the same BioPhotonic System, with the same dose and instructions for use, on patients having already completed treatment in the Main trial. Main objectives of this open-label long-term extension 12-week study were to evaluate the efficacy of the KLOX BioPhotonic System on the untreated hemiface during the Main trial, as well as the duration of response on the hemiface treated during the first 12-week Main trial. Despite their young age (mean age: 21.6 years) and their 12-week participation in the Main trial, 49 (54.4%) of the total number of patients who participated in the Main trial enrolled in this additional 12-week Extension trial. Baseline grading of acne was performed with the Investigator's Global Assessment (IGA) scale. For each patient, the hemiface randomly selected as a control during the Main trial received 6 weeks of treatment (twice weekly) and was then followed up for an additional 6 weeks. The first hemiface treated in the Main trial was consequently observed throughout the Extension trial, allowing for a further 12-week assessment of outcomes (total 24 weeks). In light of an additional 12 weeks of treatment on the contralateral face, the patient compliance rate was excellent, with 91.9% of the total number of patients receiving at least 80% of the treatments. Patients with a baseline IGA grade of 2 (mild) on the treated hemiface demonstrated a success rate of 58.3 and 66.7% at weeks 6 and 12, respectively. At these same time points, subjects with a baseline IGA grade of 3 (moderate) demonstrated a success rate of 81.8 and 90.0%. Patients with a baseline IGA grade of 4 (severe) demonstrated a success rate of 100% at both week 6 and week 12. When evaluating the originally treated hemifaces from the Main trial, the rate of return to baseline at 24 weeks was calculated to be 15.5%. This latter outcome confirmed the long duration of effect following treatment. The patient safety profile was also excellent, with very few related adverse events. The BioPhotonic System, which is comprised of LED blue light phototherapy and photo-converter chromophores, provides long-term efficacy and safety in the treatment of acne vulgaris, with a rate of compliance above what is generally observed in a young population of patients suffering from acne vulgaris, especially in light of sequential enrollment in a study treating one hemiface.

Introduction

Acne vulgaris is a ubiquitous inflammatory skin disorder of the pilosebaceous unit.[1] Although acne is considered a multifactorial disease process, the most important pathophysiologic factors are alterations in the keratinization pattern of hair follicles and excessive androgen-mediated sebum production, with consequent follicular colonization and proliferation of *Propionibacterium acnes*, and associated inflammatory response.[2] Acne treatments include topical retinoids, topical and oral antibiotics directed against *P. acnes*, as well as oral contraceptives and isotretinoin.[3] However, the safety and efficacy profiles of all these therapies is often considered as problematic, and several studies demonstrated that these treatments are not capable of affecting all etiological factors involved in acne pathogenesis.[4,5] Therefore, there is an urgent need to further develop alternative and innovative treatments, such as light, laser, and photodynamic therapies (PDT).[6–9] Light and laser therapy for the treatment of acne vulgaris is based on the observation that *P. acnes* synthesizes chromophores such as porphyrins, more specifically, coproporphyrin.[10–12] Porphyrins enable light therapy to exert a selective cytotoxic effect on *P. acnes*. The excitation of bacterial porphyrins by light absorption induces the production of singlet oxygen and reactive radicals leading to bacterial death.[13]

Therapies commonly used include intense pulsed light (IPL), pulsed dye lasers (PDL), potassium titanyl phosphate (KTP) lasers, and broad-spectrum continuous wave visible light (blue and red).[14] Most notable among the latter is the effect of blue light on porphyrin activation.[15,16] Compared to blue light, which has limited skin penetration, red light can reach deeper sebaceous glands and may have an anti-inflammatory effect through cytokine release. However, the reduced efficacy of red light on porphyrin activation has led to investigation of combination red-blue light with or without IPL, which generated pulsed polychromatic light.[17–19] The role of IPL as acne therapy remains to be determined, given the controversial reports on its efficacy and its safety profile.[20–23]

While lasers have also been employed in acne treatment, randomized controlled trials with a reasonable number of patients are scarce, and moreover their efficacy and safety profiles are not always optimal.[24–28]

Photodynamic therapy (PDT), which uses a light-activated cream absorbed into the pilosebaceous gland and amplifies the effect of the light, has also been tested.[29,30] However, this technique is not well tolerated, is not approved for the treatment of acne, and concerns have been raised about its long-term safety.[14] As with lasers, most studies published are not convincing in terms of safety, efficacy, and number of patients treated.[16,31–34]

Over the last decade, light-emitting diode (LED) therapy has shown promising results in a variety of conditions, including acne.[35,36] There has been an increasing amount of biomedical research to substantiate physiological responses to visible light. The first consideration involves the assumption that for low power visible light to affect a living biological system such as the skin, the photons must be absorbed by electronic absorption bands belonging to some molecular chromophore or photoacceptor.[14] The second important consideration involves the use of the definition of photobiomodulation (PBM) as the most suitable term to describe the molecular process and resulting beneficial photobiological responses involved in the treatments of nonthermal low-dose light therapies.[15]

The studied BioPhotonic System consists of two medical devices: the Photo Converter Gel (primary device) and the Multi-LED lamp (secondary device). The topical gel contains specific chromophores, which are not absorbed by the skin but, when excited with the LED lamp, release photons that comprise wavelengths in the spectra of visible light, ranging from 500 to 610 nm. The completed Main trial was performed with the same BioPhotonic System (class IIa medical device) delivering noncoherent blue light and resulted in highly significant improvement of the clinical signs of acne on the treated hemiface, providing a novel approach for safe and effective treatment of acne vulgaris.[38] Since it is crucial to develop therapies with prolonged efficacy, this study was designed to assess the duration of response on the randomly selected hemiface previously treated with the Biophotonic System for 6 weeks, during the Main trial.[38] A secondary aim of this prospective, multicenter, open-label, long-term extension study was to treat the previous control (Untreated) side of their face, in order to confirm clinical improvement between baseline and week 6, as well as between baseline and week 12.

Materials and methods

Different clinical studies have been conducted to investigate low energy light treatments in the cure of several skin conditions, including rejuvenation of photoaged skin, acne, skin inflammation, and wound healing.[21,39–41] After application in a 2-mm homogenous layer, the photo converter gel was then illuminated with the Multi-LED light for 5 minutes at a distance of 5 cm from the light source. Once treatment was completed, the gel was removed. The design of this study was closely related to the Main trial, and the treatment procedures were identical.[38] Briefly, the first hemiface treated in the Main trial was observed for an additional 12 weeks in order to evaluate duration of response. Thus, patients in the extension study were observed for 24 weeks. The second hemiface, untreated in the Main study, received 6 weeks of treatment (twice weekly) and was also followed up for a 6-week follow-up period. The study took place from March 2012 to December 2012 and patients, as for the previous Main study, were enrolled in the same five Dermatology University Departments based in Athens and Thessaloniki, Greece. The study was performed in accordance with the Declaration of Helsinki and the International Conference of

Table 1 Treatments administered during the first study and the extension study

	CL-K1005-P001 (Main)		CL-K1005-P003 (Extension)	
Groups	**Weeks 1–6**	**Weeks 7–12**	**Weeks 1–6**	**Weeks 7–12**
Randomized to LEFT hemiface				
Left side	KLOX BPS twice a week	No treatment	No treatment	No treatment
Right side	No treatment	No treatment	KLOX BPS twice a week	No treatment
Randomized to RIGHT hemiface				
Left side	No treatment	No treatment	KLOX BPS twice a week	No treatment
Right side	KLOX BPS twice a week	No treatment	No treatment	No treatment

BPS, BioPhotonic System.

Harmonization (ICH) Guidelines for Clinical Practice. Study approval was given by the Greek Competent Authority and the National Ethics Board (Clinicaltrials.gov registration number: NCT01584674). All participants gave their written informed consent prior to any study procedures. Inclusion criteria included patients who completed the first study. According to the Investigator's Global Acne (IGA) scale,[42] only patients with an IGA of 1 or greater on their untreated hemiface were treated, most of them (57.1%) being IGA 3 and 4. A clinical examination was planned prior to the first treatment, and patients had to accept to return for follow-up visits after the end of the 6-week treatment period. Enrolled female subjects had a negative pregnancy test, and participants were willing to practice birth control during their participation into study. Patients meeting any of the exclusion criteria outlined in the first study protocol were excluded.[37] There was an average of 39.3 days between the last visit of the first study and the screening visit of this extension study. No minimum period was required between the two studies. Table 1 presents the treatments administered during the first study and this extension study. Patients were treated on the second hemiface, which had not been treated in the main study. The second hemiface was treated with a 2 mm thick layer of the photoconverter gel and illuminated with the KLOX-Multi-LED light source at a 5 cm distance from the light

Table 2 IGA grades by hemiface at baseline

	Hemiface treatment sequence (Main/Extension)[a]	
	Left Treated/Untreated	**Right Treated/Untreated**
Main Study Baseline (MV1) IGA score: First hemiface[a]		
n	22	27
3 (Moderate)	13 (59.1%)	14 (51.9%)
4 (Severe)	9 (40.9%)	13 (48.1%)
Main Study Baseline (MV1) IGA score: Second hemiface[a]		
n	22	27
3 (Moderate)	13 (59.1%)	14 (51.9%)
4 (Severe)	9 (40.9%)	13 (48.1%)
Extension Study Baseline (EV1) IGA score: First hemiface		
n	22	27
0 (Clear)	1 (4.5%)	0
1 (Almost clear)	8 (36.4%)	7 (25.9%)
2 (Mild)	10 (45.5%)	15 (55.6%)
3 (Moderate)	3 (13.6%)	5 (18.5%)
4 (Severe)	0	0
Extension Study Baseline (EV1) IGA score: Second hemiface		
n	22	27
0 (Clear)	0	0
1 (Almost clear)	4 (18.2%)	4 (14.8%)
2 (Mild)	5 (22.7%)	8 (29.6%)
3 (Moderate)	10 (45.5%)	14 (51.9%)
4 (Severe)	3 (13.6%)	1 (3.7%)

IGA, Investigator's Global Assessment.
n represents the number of subjects contributing to summary statistics. Percentages are based on *n* for each characteristic.
[a]As randomly assigned in the main study.

Table 3 Duration of best response[a] using Kaplan–Meier estimate by hemiface

	Hemiface treatment sequence (Main/Extension)	
	Treated/Untreated	**Untreated/Treated**
Total number of events (*n*)	49	49
Kaplan–Meier estimate (%)		
Rate of return to Baseline (95% CI) at		
2 weeks (14 d)	6.3 (2.1, 18.3)	20.4 (11.5, 34.6)
4 weeks (28 d)	10.6 (4.5, 23.5)	22.6 (13.2, 37.0)
6 weeks (42 d)	10.6 (4.5, 23.5)	24.7 (14.8, 39.4)
12 weeks (84 d)	10.6 (4.5, 23.5)	27.0 (16.6, 42.0)
18 weeks (126 d)	15.5 (6.7, 33.5)	27.0 (16.6, 42.0)
24 weeks (168 d)	15.5 (6.7, 33.5)	27.0 (16.6, 42.0)

IGA, Investigator's Global Assessment; CI, Confidence interval.
Percentages are based on *n*. Treated/Untreated denotes hemiface that was treated in the main study (CL-K1005-P001) and untreated in the extension study (CL-K1005-P003). Untreated/Treated denotes hemiface that was untreated in the main study and treated in the extension study.
[a]Best response is defined as the lowest IGA grade achieved after the first treatment during the main study.

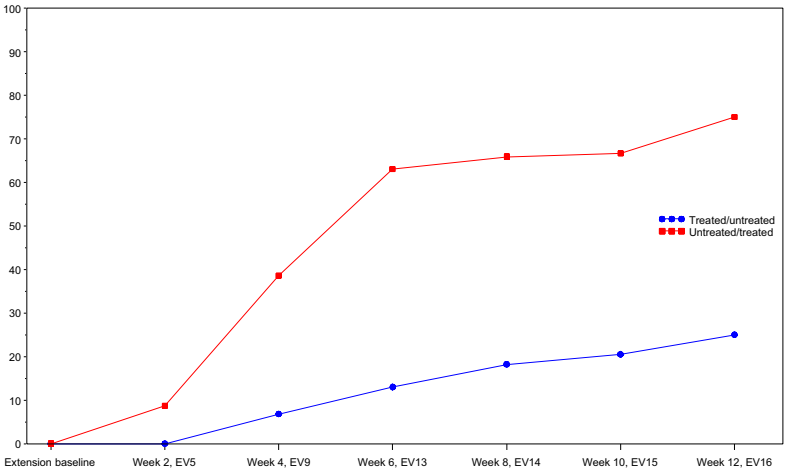

Figure 1 Proportion of patients with a reduction of at least 1 IGA grade over time (Analysis set: ITT)

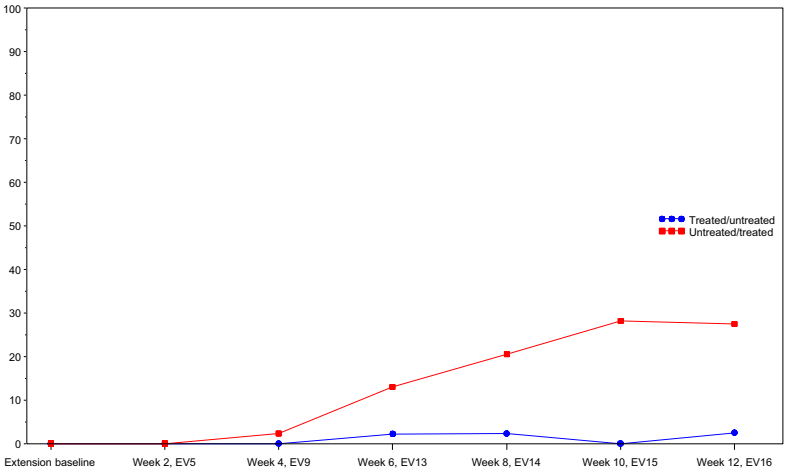

Figure 2 Proportion of patients with a reduction of at least 2 IGA grades over time (Analysis set: ITT)

source for 5 minutes, twice a week, for 6 weeks. The first hemiface, treated in the first study, was not treated for the whole trial duration but was still assessed with the IGA scale. The hemiface to be treated was divided into three areas (forehead, cheek including half of the nose, and chin), while the other areas and the untreated hemiface were covered with a disposable cloth during the whole procedure. All patients were provided with the Cetaphil™ facial cleanser and a Cetaphil™ moisturizing lotion with sun protection. These products were used twice daily to clean and hydrate the hemifaces during the whole study.

Efficacy assessments

Investigator's Global Assessment (IGA) grading was the key assessment for the efficacy demonstration in this study. The primary endpoint was the duration of response on the hemiface treated during the first study, which was defined as the time from best response during the main study to return to baseline (IGA 3 or 4). A secondary endpoint was the proportion of patients having a decrease in at least 1 IGA grade on the hemiface treated during this extension study. The percentage of patients with a decrease to grade 0 or 1 on the IGA scale was calculated at weeks 6 and 12 and compared to baseline. Standardized photographs of the face

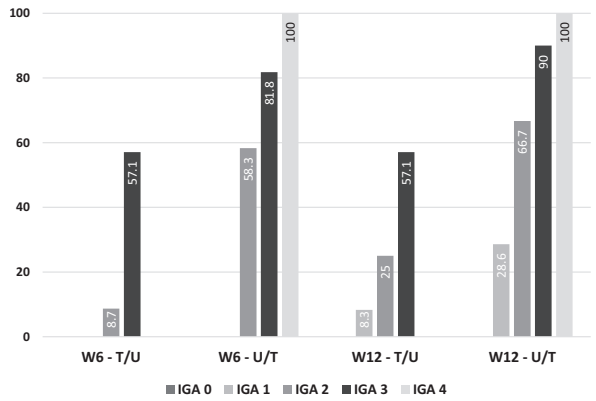

Figure 3 Proportion of patients achieving success (decrease in at least 1 IGA grade) by hemiface and baseline IGA grade (Analysis set: ITT)

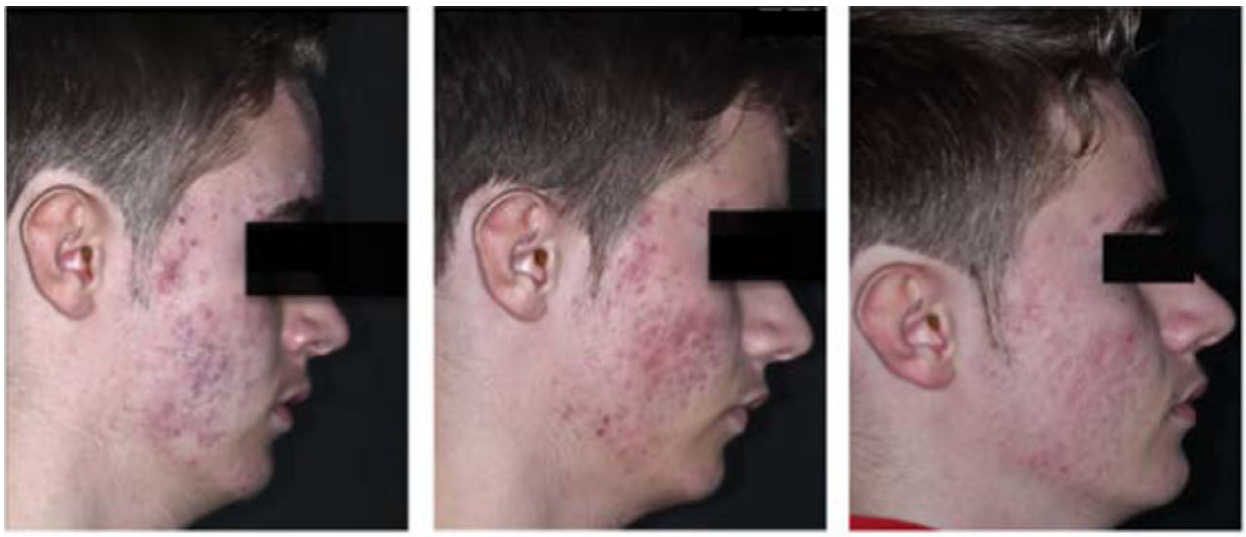

Figure 4 Clinical response in the hemifaces treated during the Main and the Extension trials: at baseline (main trial) (a), week 12 (end of main trial) (b), and week 24 (end of extension trial) (c)

were taken by a professional photographer at baseline, week 6, and week 12.

Safety assessments

Safety was assessed through physical examination, laboratory evaluations, and physician or patients' reporting of adverse events. Three different categories were used to describe the severity of adverse events: mild (awareness of symptoms but easily tolerated), moderate (enough discomfort to interfere with usual activities), or severe (incapacitating, with inability to perform usual activities). Adverse events, device incidents, and device deficiencies were recorded at each visit.

Statistical analysis

The population for this extension trial had a total of 49 patients who had completed the Main trial[38] and who benefitted from the treatment of their second hemiface. Therefore, there was no formal statistic sample size calculation for this study. Descriptive summaries of the data collected from the Intent To Treat (ITT) population were produced. ITT population was defined as all

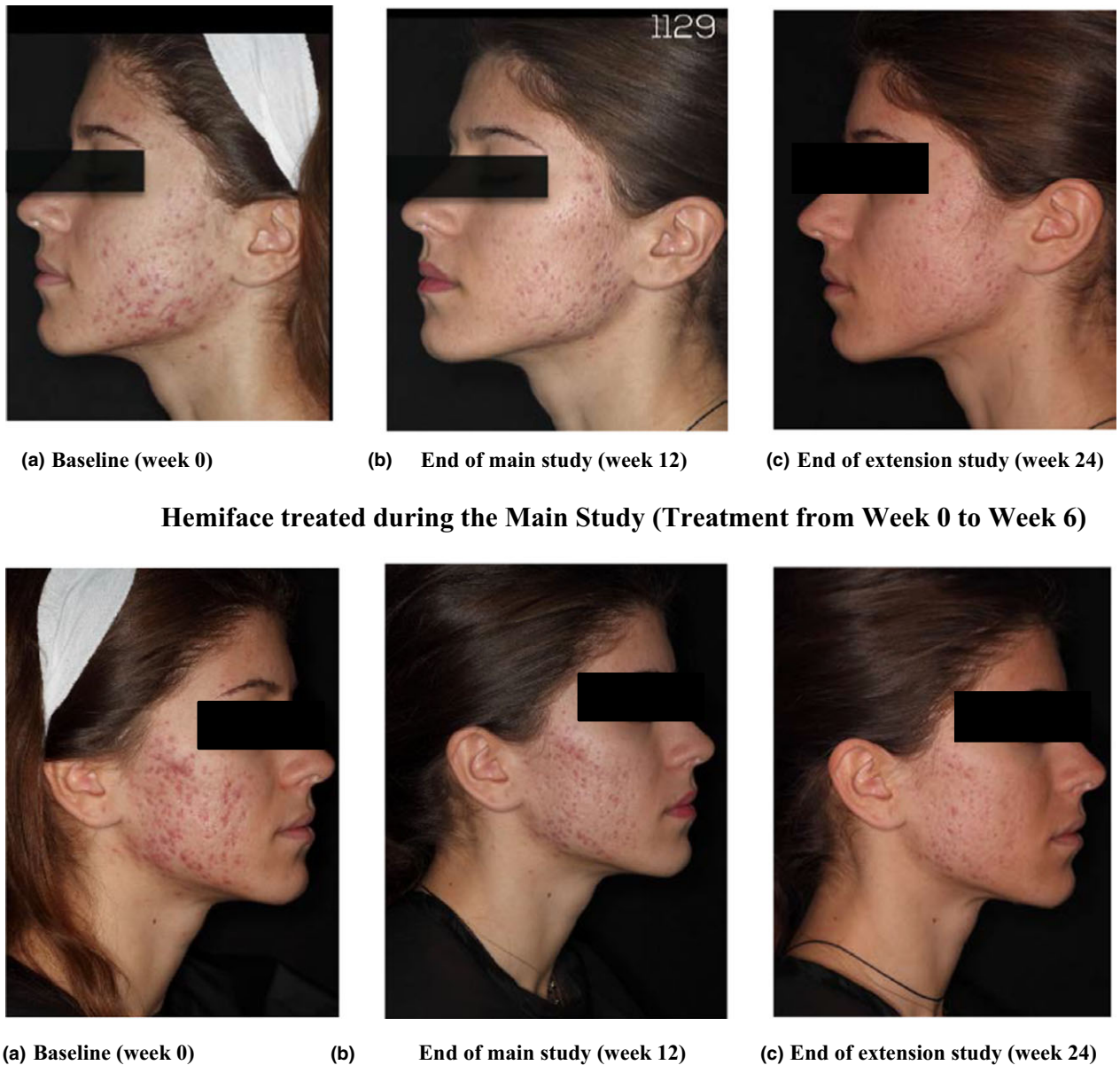

Figure 5 Clinical response in the hemifaces treated during the Main and the Extension trials: at baseline (main trial) (a), week 12 (end of main trial) (b), and week 24 (end of extension trial) (c)

patients having received at least one treatment with the KLOX BioPhotonic System during the study. All data collected on Clinical Report Forms (CRFs) were provided in listings. Kaplan–Meier analysis was used to analyze the rate of return to IGA baseline.

Results

Forty-nine patients (14 men and 35 women) were enrolled in this Extension study. Despite the young age of the study population with a mean age of 21.6 years (SD $\pm$ 4.29), and given that these patients already participated in the 12-week Main trial, where only half their face was treated, the compliance rate was excellent. A 100% compliance rate was observed in 59.2% of patients, and 91.9% of the total number of patients received at least 80% of the treatments. All patients who entered the Main trial initially had an IGA score of 3 or 4 on both hemifaces. Following completion of the Main trial, more than 50% of subjects had a decrease in at least 2 IGA grades on their treated hemiface. Alternatively, a decrease in at least 2 IGA grades on the

Table 4 Treatment emergent related adverse events (TEAEs) in treated patients

System organ class/Preferred term	All patients (*N* = 49)
Total patients with at least one AE	3 (6.1%)
Total number of events	3
Skin hyperpigmentation	3 (6.1%)

For each preferred term, multiple occurrences of the same event for a patient are counted once. For each system organ class, multiple occurrences of different preferred terms for a patient are counted once. Percentages are based on *N*. Related adverse events are those possibly or likely causally related to treatment.

Table 5 IGA Success rates by Hemiface (Analysis Sets: Extension ITT and PP)

Analysis time point	Total reduction from Baseline in IGA	Hemiface treatment sequence (Main/Extension)	
		Treated/Untreated	Untreated/Treated
Extension ITT			
Extension Week 6	*n*	46	46
	≥1 grade (Success)	6 (13.0%)	29 (63.0%)
	<1 grade (No success)	40 (87.0%)	17 (37.0%)
Extension Week 12	*n*	40	40
	≥1 grade (Success)	10 (25.0%)	30 (75.0%)
	<1 grade (No success)	30 (75.0%)	10 (25.0%)
Extension PP			
Extension Week 6	*n*	14	14
	≥1 grade (Success)	2 (14.3%)	10 (71.4%)
	<1 grade (No success)	12 (85.7%)	4 (28.6%)
Extension Week 12	*n*	13	13
	≥1 grade (Success)	4 (30.8%)	12 (92.3%)
	<1 grade (No success)	9 (69.2%)	1 (7.7%)

IGA, Investigator's Global Assessment; ITT, Intent-to-Treat; PP, Per-Protocol. Baseline is the baseline for Extension study at Visit 2. Treated/Untreated denotes hemiface that was treated in the Main study and untreated in the Extension study. Untreated/Treated denotes hemiface that was untreated in the Main study and treated in the Extension study. Percentages are based on *n*.

untreated hemifaces was reported in 18% of the subjects. Table 2 shows the distribution of IGA grades in all patients enrolled in this extension study. The primary endpoint was the duration of response on the hemiface treated during the Main trial and untreated during this extension study (first hemiface). As shown in Table 3, for hemifaces treated in the main study, the rate of return to baseline at 24 weeks was 15.5% (Kaplan–Meier estimates), demonstrating a long-lasting effect of the treatment with a persistence of efficacy for at least 6 months. For the hemifaces untreated in the main study but treated in the extension study, this rate of return to baseline was 27.0% (Kaplan–Meier estimates). Figures 1 and 2 show the proportions of patients with a decrease in at least 1 or 2 IGA during the extension study on both hemifaces, that is, the hemiface treated during the main study (treated/untreated) as well as the hemiface treated during the extension study (untreated/treated). For the reduction of at least 1 IGA grade, similar to the results observed in the main study, the treatment effect starts to be perceivable at week 4 and continues to increase even after treatment completion (Fig. 1). Although less pronounced, a similar curve was obtained analyzing the reduction of at least 2 IGA grades over time (Fig. 2). Patients with a baseline IGA grade of 2 on the treated hemiface showed a success rate of 58.3 and 66.7% at weeks 6 and 12, whereas patients with a baseline IGA grade of 3 showed a success rate of 81.8 and 90.0% at these same time points. For patients with a baseline IGA grade of 4, 100% of these subjects showed a success rate of 100% at both week 6 and week 12 (Fig. 3). In the *per protocol* population, at week 12, a decrease in at least one IGA grade was observed in 92.3% of hemifaces treated during the Extension study. Clinical response is demonstrated with photography (Figs. 4 and 5) of the treated hemiface compared to the untreated/control hemiface at baseline, week 12, and week 24.

The safety profile observed during this extension study was remarkable, and there were no serious adverse events throughout the study. Of the 49 patients who underwent treatment, a total of three subjects (6.1%) reported a treatment emergent related adverse event (TEAEs). These three adverse events were different cases of mild or moderate hyperpigmentation (Table 4). The decrease in the number of TEAEs in this trial compared to the number observed during the Main trial (17.8% of the total number of patients included in the Main trial) is interesting to note as the same investigators participated in both studies. It might be explained by a learning curve from investigators in the use of the BioPhotonic System.

Discussion

Acne vulgaris is a common and chronic skin disease,[43] but current therapeutic approaches are frequently insufficient to affect all etiological factors and improve acne severity. Moreover, although the pathogenesis of acne vulgaris remains to be fully elucidated, the association with significant morbidity is unquestionable, with disease burden ranging from facial scarring to severe emotional and psychological stress.[44] In this context, the disorders that may be treated with visible light phototherapy cover a broad range of conditions, including the treatment of different skin disorders such as acne vulgaris.[45] Light-based therapies can improve acne severity, and LED phototherapy has gained considerable interest as a new light source for the treatment of acne. In particular, several studies have demonstrated the efficacy of blue light in treating acne with minimal side effects. The mechanism of blue light inactivation of *P. acnes* occurs through photoexcitation of intracellular porphyrins and subsequent production of cytotoxic reactive oxygen species.[46]

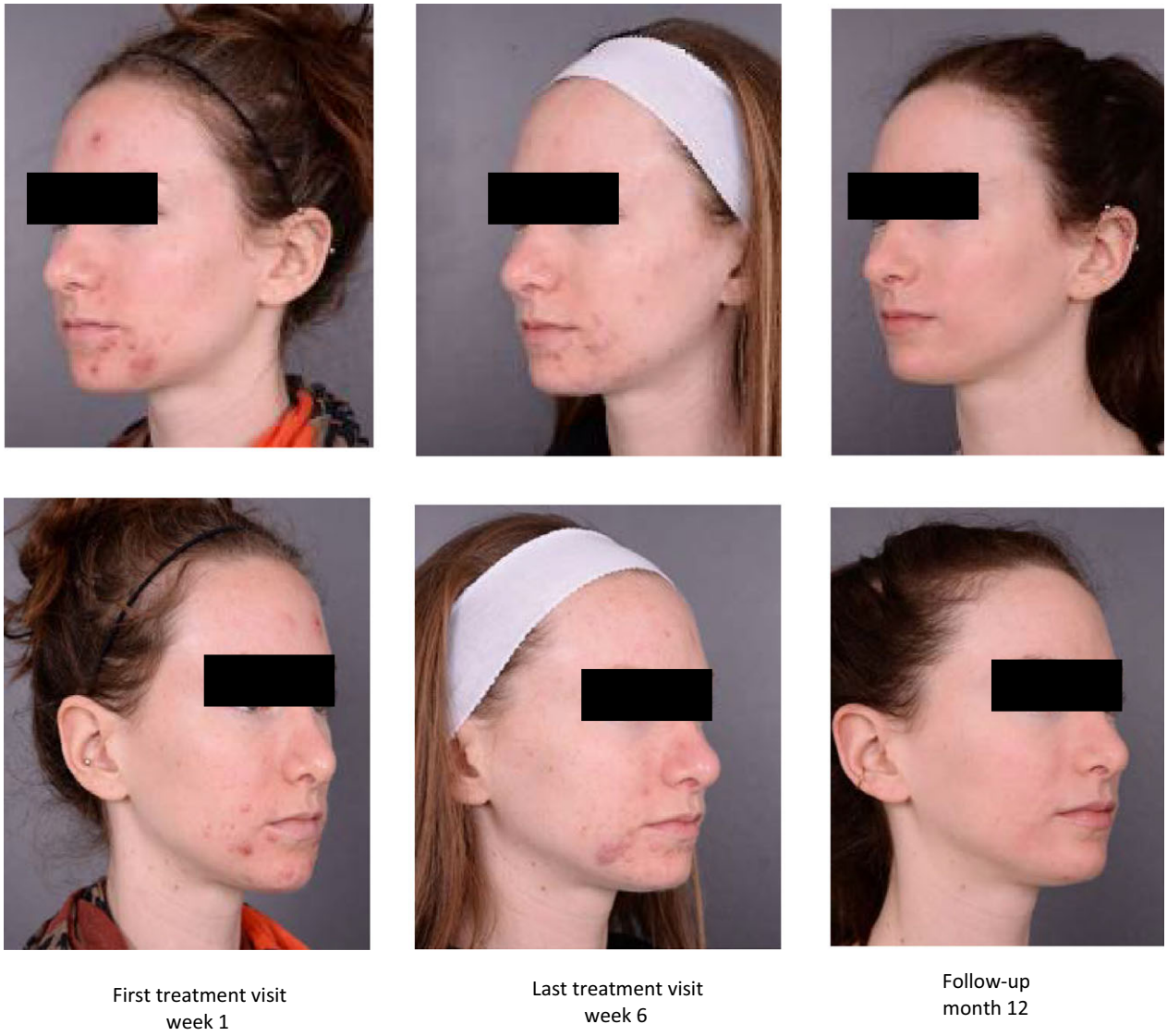

Figure 6 Clinical response at 6 weeks and 12 months in patient treated on both hemifaces after the study completion with same treatment regimen as in the study. First treatment visit, last treatment visit 6 weeks later, and follow-up 12 months later

Although the molecular mechanisms that might determine the clinical efficacy of blue light have not been fully explored, it has been suggested that blue light phototherapy can positively alleviate inflammatory but also noninflammatory acne lesions at the level of gene transcription by suppressing nuclear factor-κB (NF-κB) and inflammatory cytokines.[47] There are insufficient randomized controlled studies on blue light therapy for acne. However, phototherapy using blue light has been shown to significantly reduce inflamed acne lesions when irradiated for over eight treatment sessions in 30 subjects with mild to moderate facial acne.[48] Recently, a randomized controlled study by Ash *et al.*[49] reported that blue light therapy at 414 nm significantly reduces inflammatory acne lesions by 50.02% at the 12-week assessment. In our previous multicenter, randomized, split-face study, we demonstrated that the use of chromophore-assisted blue light phototherapy twice weekly for 6 weeks was efficacious, resulting in a reduction of at least 2 grades in the IGA scale in a statistically significant number of treated hemifaces of patients at 12 weeks (51.7% compared to 18.0% of the untreated hemifaces).[37] To build on these results, long-term studies should also be carried out to demonstrate maintenance of efficacy and to assess safety parameters of blue light phototherapy in the treatment of acne. Therefore, the aim of this multicenter, open-label long-term extension study was to evaluate the duration of response on the hemiface treated during the main study, defined as time from best response during this first study to a return to baseline (IGA grade 3 or 4). Kaplan–Meier analysis was used to analyze the rate of return to IGA baseline,

and it was calculated to be 15.5% after 24 weeks (Table 3). It is noteworthy that subjects with a baseline IGA grade of 3 showed a success rate of 90% at week 12, while patients with a baseline IGA grade of 4 responded with a success rate of 100% at the 12 week time point (Fig. 3). These results are similar to those already reported in the Main trial for baseline IGA grades 3 and 4 and confirm the efficacy profile of the BioPhotonic System observed in this Main trial. Moreover, and in addition to the efficacy results already observed during the Main trial, we observed a decrease in at least one IGA grade at week 12 on 75% of hemifaces treated during the Extension trial compared to their baseline level at the beginning of this Extension trial (Table 5). The timing of the onset of efficacy started to be perceivable at week 4, and it was similar to what had been observed into the Main trial. Furthermore, delayed evaluation of patients with the same treatment regimen in an *a posteriori* analysis has demonstrated the same efficacy profile after a 1-year follow-up period (See Fig. 6, clinical response after 1 year of a patient followed with the same treatment regimen – Data on file).

Compliance was excellent despite the young age of the patients and the long study period (at least 24 weeks considering the total duration of the Main and the Extension trials). Serious adverse events after treatment were not observed and as previously reported the BioPhotonic System was safe and well tolerated.[37,50] One limitation of this trial might be that most the patients included were female (71%). This is however observed in the majority of clinical trials on acne, and the percentage of men (29%) may be considered as reasonable. Despite a variety of therapies, many of the acne treatments are coupled with poor safety profile and serious side effects. LED phototherapy with chromophores offers a safe, noninvasive, and innovative way to treat acne in a reasonable short period of time. With this extension trial, the use of the BioPhotonic System demonstrated a persistence of efficacy of 6 months' duration on the hemiface treated during the Main trial. The 6-week treatment period on the treated hemiface during the Extension trial may have indirectly and partially helped maintain the efficacy level obtained on the hemiface treated during the Main trial, as this persistence of efficacy is of significant interest and warrants further investigation. Most of the patients who responded to treatment in the first Main trial kept their improvement in IGA scores following their long-term assessment. The Biophotonic System using photo-converter chromophores provides an effective option to treat patients with moderate and severe facial acne, and can be considered as a first line treatment of moderate to severe acne vulgaris based on the safety and efficacy data presented.

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