

# Treatment of Mild to Moderate Acne Vulgaris Using a Combined Light and Heat Energy Device: Home-Use Clinical Study

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*Introduction:* Light and heat devices have become widely used for the treatment of mild to moderate inflammatory acne as an alternative to retinoids and antibiotics. The purpose of this study was to examine whether a handheld device which emits both light and heat energy can safely and effectively be applied at home to shorten time to improvement and time to resolution of acne papules and pustules.

*Materials and Methods:* A two-center, randomized, placebo-controlled double blind study was conducted on sixty three (63) subjects with at least four inflamed, facial, acne lesions. Treatments were self administered twice a day for four days. All lesions were photographed on a daily basis. Treatment results were assessed by two blinded evaluators, based on the macro photographs, using a 4-point VAS scale and a lesion reference scale (PLRS), as well as by the subjects. Safety was assessed based on evaluators and subjects' reported side effects and adverse events.

*Results:* Twenty nine (29) subjects in the treatment arm and thirty two (32) subjects in the placebo arm, with skin types II-VI, successfully completed the study. Based on blinded VAS scores, 92.24% of the lesions treated with an active device improved within a median time of 1 day vs. 75.78% and a median time of 2 days for the placebo arm. At 24 hours the improvement rate was 76.72% for the active arm vs. 15.63% for the placebo arm. Based on blinded PLRS scores, 87.07% of the lesions treated with an active device improved within a median time of 2 days vs. 64.8% and 3 days for the placebo. 51.7% of the active arm lesions resolved within a median time of 4 days vs. 36% (no median) for the placebo arm lesions. No device related adverse events occurred throughout the study .

*Conclusion:* This study clearly demonstrates the safety and effectiveness of the handheld, combined light and heat energy device for at home treatment of individual mild to moderate inflammatory acne lesions. A statistically significant shorter lesion improvement and lesion resolution rates were found.

## Introduction

Acne vulgaris is a common, multifactorial disorder of the sebaceous glands, with propionibacterium acne (*P. acne*) involvement, which usually begins during adolescence. Although typically a self-limited disease, acne may persist into adulthood or develop during the post adolescent period.

In spite of various oral and topical therapies available for the treatment of acne, many subjects fail to respond adequately .It has also been recently clear that antibiotics prescription medication, apart from the drawbacks of long term usage and possible side effects, has limited efficacy and in some cases is no better than OTC benzyl peroxide. Physicians emphasize that the goal of acne treatment is prevention of new lesions and scars. Current lesions are expected to heal independently while the subject awaits visible improvement from medication or OTC preparations. Improvement often occurs between 8-12 weeks of treatment

initiation. This situation has yielded a variety of device solutions that enhance treatment and shorten the lesion resolution process<sup>1,2</sup>. While most of these devices are applied by physicians in a clinic environment, some of these devices are used by the subjects in their home environment and applied according to acne involvement.

ClearTouch™ light and heat energy (LHE™) device (Radiancy Inc.) has been demonstrated to treat acne by using a broad spectrum light combined with a direct heat process. Broad spectrum light is directed at the infected area to activate a photochemical reaction in the P. Acne bacteria, causing the release of singlet oxygen which then destroys the bacteria. Simultaneously, heat is delivered to the skin to accelerate the photochemical reaction and to thermally alter sebaceous glands at the site where acne lesions occur. LHE based systems have been cleared by the FDA for prescription use. These are designed to treat large acne affected skin areas in a standard treatment protocol of 8 treatments applied twice a week for 4 weeks. A controlled, multicenter clinical study of the ClearTouch™ in the treatment of inflammatory acne demonstrated mean reduction of 60.2% in lesion count at the 12 week follow-up period<sup>3</sup>.

Currently, only two home based acne devices are cleared by the FDA. Zeno™ (Tyrell Inc) and ThermaClear™ (DermaCare Inc). These electronic over the counter (OTC) medical devices transfer heat to an individual acne lesion at a pre-set temperature range known to generate a 'heat shock response'. 'Heat shock response' is the reaction of bacteria to heat whereby they transcribe a number of genes and activate heat-shock proteins. The heat-shock proteins participate in the bacteria's death by causing the bacteria to self-destruct. Heat is conducted to the lesion from a small treatment tip placed in direct contact with the lesion. These devices claim to deliver a safe and painless dose of heat that is able to reduce the P. acne colony counts within a forming acne lesion, thus promoting quicker resolution of the lesion. The Zeno<sup>4</sup> device was evaluated by a placebo controlled clinical trial on 51 subjects with mild to moderate acne. Subjects received three treatments in the clinic on similar individual lesions chosen by the clinical staff, with both active and placebo devices and were followed up for 5 days. The results demonstrated that 55% of the lesions treated with the active device showed resolution by day 5 with a mean time to resolution of 4 days. No adverse events were reported.

ThermaClear<sup>5</sup> was evaluated by a blind clinical trial on 46 subjects with mild to moderate acne. For each participant, 2 acne lesions were chosen by the clinical staff. One lesion (on one side of the face) was treated by the clinical staff with the ThermaClear™ device once daily for 5 days, while the other lesion (on the other side of the face) was left untreated as control. ThermaClear™ treated lesions showed a 44% rate resolution by day 5. No adverse events were reported.

The *no!no! skin™* (Radiancy Inc.) is a handheld acne clearance system intended for at home treatment of individual mild to moderate acne lesions. Unlike the Zeno™ and ThermaClear™ devices which only use heat, this device delivers broad spectrum light and heat (LHE™)

similar to the ClearTouch™ device. To assure safety for home use, energy from the *no!no! skin™* device is delivered in a controlled train of pulses instead of the single, short pulse as in the ClearTouch™ device.

This clinical study was undertaken to evaluate the safety and effectiveness of the *no!no! skin™* device for the treatment of individual mild to moderate acne lesions at home. A separate user comprehension study was performed to evaluate the compatibility of the device with the requirements of an over-the-counter (OTC) device.

## Materials and Methods

The *no!no! skin™*, shown in Figure 1, is a small handheld device intended for the treatment of individual mild to moderate inflammatory acne lesions (papules and pustules). It delivers a flash of broad spectrum light of 450-2000 nm with a fluence level of 6J/cm<sup>2</sup> per treatment cycle. The energy delivered to the lesion is a combination of focused light emitted from the device together with heat accumulated in the chamber placed over the acne lesion.



Figure 1: *no! no! skin™* device

Treatment is applied by placing the device's treatment chamber over the lesion and pressing the operating button to activate one treatment cycle. Audio signals indicate the beginning and the end of the treatment cycle. Treatment is repeated 6-12 hours later until complete resolution of the lesion occurs.

A two-center, randomized, placebo-controlled double blind study was undertaken to evaluate the safety and effectiveness of the *no!no! skin™* device for at home treatment of individual mild to moderate inflammatory acne lesions. Following IRB approval, sixty three (63) subjects with a least four inflamed lesions (papules or pustules) on the face were enrolled for the study. Only subjects who were at least 14 years old, who met all inclusion and exclusion criteria, were not on any other acne treatment regimen and who signed the informed consent

form were enrolled. Thirty one (31) subjects were randomly assigned to the treatment group where all lesions were treated with active devices, while thirty two (32) subjects were randomly assigned to the control group where all lesions were treated with placebo devices. Lesions assigned for treatment, in both groups, were designated by the subjects themselves. Treatments were self administered twice a day for 4 days, once a day at home and once a day at the clinic in front of an unblinded observer. Each treatment included two passes of the device on each lesion. Subjects returned to the clinic on day 5 for final follow-up. All lesions were photographed at baseline and at each of the daily clinic visits. Subjects maintained a diary in which treatments and outcomes were recorded on a daily basis. The unblinded observer also maintained a daily log to record treatments and any adverse events.

Treatment results were assessed and recorded daily by the subjects using a 4-point VAS scale (1-worsening, 2-no improvement, 3-improvement, 4-resolution). At the end of the study the blinded investigator and a blinded independent evaluator each assessed the effect of treatment on each treated lesion based on the macro photographs of the lesions. Their assessment was recorded based on a similar 4-point VAS scale as well as on a 5-grade photographic lesion reference scale (PLRS), showing inflamed lesions at different stages from fully resolved (1) to a nodule (5). The two blinded VAS scores were averaged per lesion, daily, as were the PLRS scores to obtain earliest time to improvement and earliest time to resolution.

Safety was assessed based upon daily evaluation by the subjects and the unblinded observer of any possible side effects, such as erythema, edema, crusting, blistering or pigmentary changes. Subjects were also asked to report any subjective side effects such as pain, heat sensation, itching, skin dryness or tightness.

#### Data analysis

The required significance level of findings was equal to or lower than 5%. All statistical tests were two-sided. All statistical analyses were performed using SAS v9.1 (SAS®, SAS Institute Cary, NC USA) software. For comparison of time to event data, the log rank test was used. For comparison of means (continuous variables), the two-sample t-test or the Wilcoxon rank sum test was used as appropriate. For comparison of proportions (categorical variables), the Chi-square test or Fisher's exact test was used as appropriate. A stratified log-rank test or Cox regression models were used to adjust for baseline covariates when necessary.

## Results

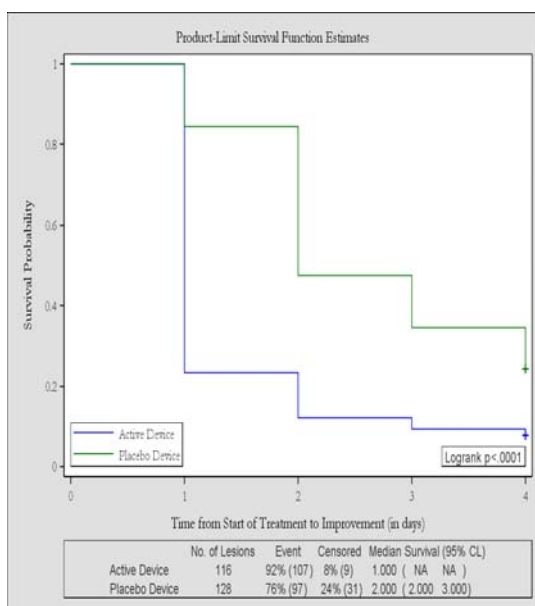
The study was conducted in Israel from April to May 2008 and in the U.S. from May to June 2008. Of the 63 subjects enrolled in the study two withdrew early, one due to non compliance with the treatment regimen and the other due to consent withdrawal. Both early withdrawals were from the randomly assigned active device group so in total 61 subjects successfully completed the study, 29 in the treatment arm and 32 in the placebo arm.

Study patients were both females and males aged 14-47 (mean 23.6), of different ethnic origins which included Caucasian, African, Asian and Hispanic and of Skin types II-VI.

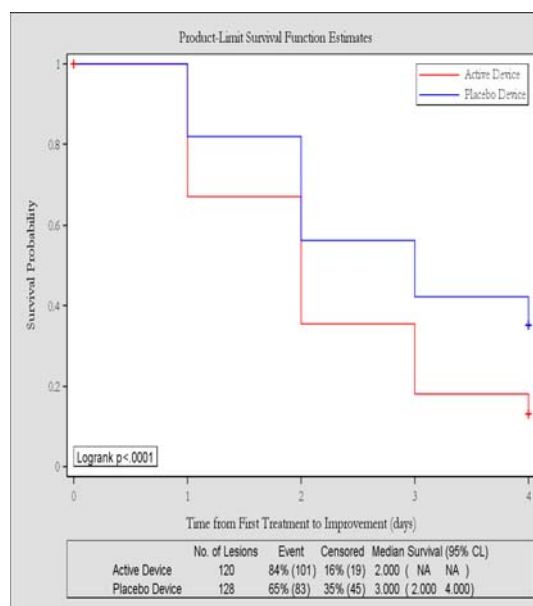
No statistically significant differences were found between the arms with regard to gender, age, race or skin type. No statistically significant difference was found between the arms with regard to the number of lesions, anatomical site and global acne assessment; however a difference was found in the type of lesion. The active arm had a higher percentage of pustules (45% vs. 26%) and lower percentage of papules (55% vs. 74%) compared to the placebo arm (p=0.0012).

A total of 120 lesions were treated by the active device and a total of 128 lesions were treated by the placebo device. Time to improvement based on blinded VAS scores is shown for the two lesion groups in figure 2 which presents the Kaplan-Meier (KM) survival analysis results for the study patients. From the KM curves it can be seen that improvement is more frequent and occurs sooner in the course of treatment in the actively treated lesions than in placebo treated lesions (p<0.0001). The KM estimated improvement rate in the actively treated lesions was 92.24 % (s.e. =2.48%) versus 75.78% (s.e.=3.79%) for the placebo arm. Median time to improvement of lesions in the active arm was found to be 1 day while median time to improvement of lesions in the placebo arm was found to be 2 days. A particularly important difference between the 2 study arms was seen at 24 hours. The 24h improvement rate is 76.72% (s.e.=3.02%) for the active arm and 15.63% (s.e.=3.21%) in the placebo arm according to the blinded VAS scores.

**Figure 2: Time to Improvement (VAS score)– ITT/PP**



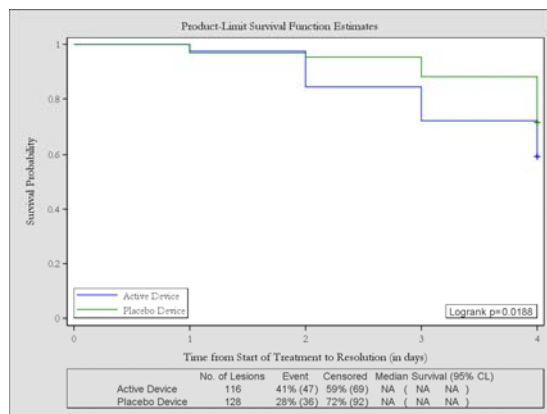
**Figure 3: KM analysis of time to Improvement based on the Photographic Reference Scale:**



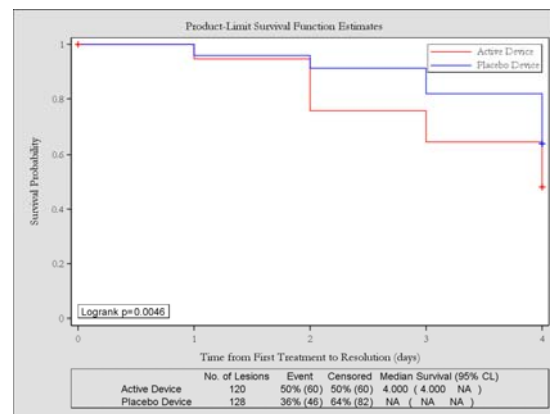
Improvement when based on the blinded PLRS scores (fig.3) is more frequent and occurs significantly sooner in the course of treatment in the actively treated lesions versus placebo ( $p<0.0001$ ). The improvement rate at the end of the follow-up is 87.07% (se=3.12%) in the active arm versus 64.8% (se=4.22%) in the placebo arm. The median time to improvement is 2 days in the active treatment arm versus 3 days in the placebo arm.

Time to resolution based on the blinded VAS is shown for the two lesion groups in Fig. 4 and for the PLRS in Figure 5. Time to resolution is significantly shorter for the actively treated lesions based on both scales ( $p=0.0188$  (VAS) and  $p=0.0046$  (PLRS)). The KM estimate of the resolution rate, at the end of the follow-up, is 51.72% (se=4.64%) in the active treated lesions whereas in the placebo treated lesions the rate is 36.00% (se=4.24%) according to the PLRS (fig.5) and 40.52% (active) versus 28.13% (placebo) according to the VAS score (fig.4).

**Figure 4. Time to Resolution (VAS) – ITT/PP**

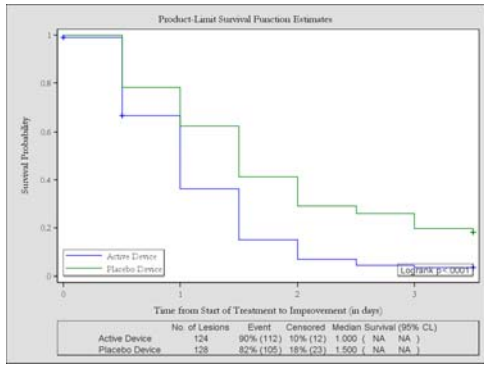


**Figure 5: KM analysis of time to Full Resolution based on Photographic Reference Scale:**



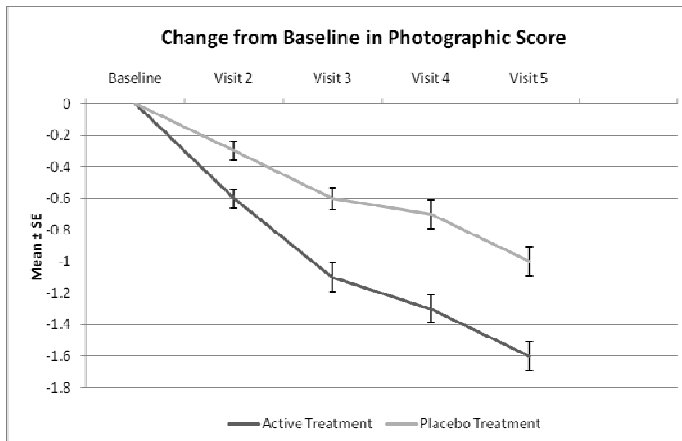
Subjects reported a VAS score twice a day. Fig. 6 presents the 'time to improvement' survival analysis results based on patients' VAS scores using the Kaplan-Meier (KM) method. It can be seen that improvement is more frequent and occurs sooner in the actively treated lesions versus placebo treated lesions ( $p<0.0001$ ). Median time to improvement of lesions in the active arm is 1 day while mean time to improvement in the placebo arm is 1.5 days.

**Figure 6. Time to Improvement (patient VAS) – ITT**



Time to resolution based on patients' assessment is more frequent and occurs sooner in the course of treatment in the actively treated lesions versus placebo treated lesions, however in this case the difference observed was not statistically significant.

**Figure 7. Mean Change from baseline Photographic scale**



Finally the change from baseline in the average PLRS score for the two study arms is shown in fig 7. The rate of change in the scores was found to be significantly different between the active and placebo treatment groups ( $F(1,910)=6.25, p=0.0126$ ). Mean overall reduction in the scores of the active treated lesions was 1.30 points ( $se=0.1184$ ) while in the placebo treated lesions it was 0.89 ( $se=0.1138$ ).

No device related adverse events that necessitate treatment modification or discontinuation were detected during the trial. Treatments are painless and safe even on skin types VI with no risk of any dyspigmentation effects.

## Discussion

The mainstays of current acne treatments are retinoids and antibiotics however these carry a poor side-effect profile, display teratogenicity and potentially develop bacterial resistance. Acne phototherapy avoids these limitations and has therefore become widely used as an alternative treatment modality for mild to moderate inflammatory acne. Professional phototherapy systems can simultaneously irradiate large tissue areas typically resulting in lesion count reduction of 60-65% following 8-10 treatments sessions spaced over a period of 4-5 weeks. The need for multiple sessions combined with the simplicity and extremely high

safety profile of this treatment modality has led to the introduction of various heat devices designed to be self-administered by the patients at home. These home devices may be applied on entire acne infected skin areas using protocols similar to those of the professional devices<sup>6</sup>, or may be applied to individual lesions as they appear using shorter treatment intervals and only until the lesion resolves<sup>7</sup>. The *no!no! skin*<sup>TM</sup> device was designed and is intended for such individual lesion treatment, specifically for papules and pustules which are typical to mild to moderate inflammatory acne.

This study clearly demonstrates the safety and effectiveness of the *no!no! skin*<sup>TM</sup> device for at home treatment of individual mild to moderate inflammatory acne lesions. A statistically significant shortening in time to improvement and resolution of acne lesions was found in all study parameters.

Based on blinded VAS scores the improvement rate of a lesion treated with an active device was found to be 92% of all active lesions within a median time of 1 day versus 75% with a median time of 2 days for the placebo treated lesions. A particularly important difference between the 2 study arms was seen at 24 hours. The 24h improvement rate was 76.72% for the active arm and only 15.63% in the placebo arm.

Based on blinded PLRS scores, the improvement rate of a lesion treated with an active device was found to be 87% of all active lesions (median time 2 days) versus 65% (median time 3 days) for the placebo treated lesions.

Patients' self assessment reports indicated a shortening in improvement rate with an active device as well.

Based on the PLRS scores 51.7% of the actively treated lesions resolved (median time 4 days), versus 36% (no median) for the placebo treated lesions.

The differences observed between the active and placebo groups in time to improvement, time to resolution, improvement rate and resolution rate were all highly significant. Additionally when compared to previously reported at-home acne treatment devices this difference may be enhanced by the fact that *no!no! skin*<sup>TM</sup> treatment in this study was self-performed by the subjects at home and included more severely inflamed lesions in the active arm as compared to the placebo arm.

The *no!no! skin*<sup>TM</sup> appears to be particularly efficacious in the initial acne inflammatory phase, when *p. acne* bacteria are most active, and during the first day of treatment .

Finally, as will be reported separately, the usability study conducted on the *no!no! skin*<sup>TM</sup> device showed that users can comprehend the product instructions and operate the device successfully as designed and intended by the manufacturer, assuring compatibility with OTC device requirements.

## **Conclusion**

Based on this study the *no!no! Skin™* light and heat energy device appears to be safe and effective for at-home treatment of individual mild to moderate acne lesions on all skin types.

Statistically significant shorter lesion improvement and lesion resolution rates were found.

A particularly important difference between the 2 study arms was seen at 24 hours. The 24h improvement rate, based on blinded VAS scores, was 76.72% for the active arm and only 15.63% in the placebo arm.

The results suggest that for treatment to be most effective application of the device should commence early at the onset of a developing acne lesion. The compactness and portability of this device enables such early treatment as soon as a new lesion is detected.

## References

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