

STATISTICAL SUMMARY

RADIANCY INC.–SUMMARY OF THE *NO!NO!*
SKIN[™] ACNE CLEARANCE SYSTEM
PIVOTAL CLINICAL STUDY

V5.0

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1. INTRODUCTION

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. Some of these devices are used by the subjects in the home environment and applied according to acne evolution.

The Radiancy *no!no! skin*TM Acne Clearance System is intended for over-the-counter (OTC) treatment of mild to moderate acne. The device delivers a controlled train of pulses of broad spectrum light and heat (LHE).

The primary objective of this controlled study was to evaluate the safety and effectiveness of *no!no! skin*TM (in comparison to a placebo treatment), for the treatment of individual mild to moderate acne lesions (papules and pustules) by a blinded investigator and a blinded, independent evaluator.

The secondary objective of this study was to obtain subject's self assessment of the efficacy and safety of the *no!no! skin*TM treatment.

1.1. Summary of Study Design

The study was conducted as a two-center randomized placebo-controlled double blind study which enrolled subjects with mild to moderate acne who received no other concurrent prescription medication or any other acne treatment. Subjects must have had the presence of at least 4 inflamed lesions in the treatment area.

The principal Investigators recruited approximately 60 subjects to participate in the study. There were 2 sites, one in the USA and the second site in Israel. Only inflamed lesions of the papule and pustule types were assessed for safety and efficacy evaluation.

About 30 subjects were enrolled in the treatment group and all their designated lesions were treated with the active device and about 30 subjects were enrolled in the placebo group and all their designated lesions were treated with the placebo device.

The study personnel included the following:

Blinded Principal Investigator (PI): The PI, (dermatologist) screened and enrolled the subjects, supervised the clinical study and evaluated the clinical outcomes (blinded to the treatment/placebo arm)

Blinded Independent Evaluator (IE): The IE, evaluated the clinical outcomes (blinded to the treatment/placebo arm)

Unblinded Observer (UO): observed the clinical treatment performed by the subject and instructed the photographer to the chosen lesions for treatment. The Observer verified that the home treatment was performed and registered any adverse events that occurred during /after the clinic / home treatment (unblinded to the treatment/ placebo arm).

The investigator, initially evaluated the subject acne type and recorded it on the appropriate CRF using an acne severity Assessment which established baseline acne status. Then the patient chose at least 4 lesions ("designated lesions") on his/her face. The designated lesions were drawn on a graphic display and the lesions locations were also described literally on the CRF and in the subject dairy. Each lesion was given a number to enable specific evaluation (see CRF).The designated lesions baseline status coincided with the acne type designated for the study – papules and pustules. The treatment included 2 treatment passes on each lesion per session. The treatments were done on a twice a daily regimen with 6 – 12 hours between each treatment session (morning/afternoon), once a day at home and once at the clinic, during 4 consecutive days ("Treatment period").The treatment schedule was determined in advance by the investigator and the subject. The treatment schedule was identical for the two groups.

The subject was requested to comply with the treatment schedule and to take an active part in assessing the device usage and effect. The fifth day was for follow up. On the follow up visit photographs were taken, side effects evaluated and the subject diary and photographic assessment were performed

All enrolled subjects were photographed according to a Photography Protocol. The photos were for documentation and evaluation purposes. The photography was performed by a professional photographer. Three full face calibrated photographs (one frontal and 2 oblique) and 2 macro photos for each designated lesion were taken at each visit using a subject standard positioning system. The subject's identity was protected by painting a black bar across the subject's eyes on all photographs.

Key eligibility criteria of the study were:

- Female or male 14 years or older
- Good general health with mild to moderate clinical acne on the face.
- The subject must have the presence of at least 4 inflamed lesions in the treatment area.

1.2. Study Endpoints

Primary Efficacy:

The primary efficacy end-point assessment is time to "improvement" of acne lesions. The determination of improvement of the acne lesions was obtained from two separate evaluators, a blinded Investigator and a blinded independent evaluator. The assessment was performed off macro photographs of the lesions taken at baseline, on daily visits and on the follow-up visit. This assessment was based upon a four-point lesion improvement scale (Visual Analog Scale - VAS). The two evaluators (blinded) VAS scores were averaged per lesion (on a daily basis).

A determination of the event "improvement" was made if the mean VAS score was greater than 2.5. The earliest time at which this event occurs is considered as the time of improvement.

Secondary Efficacy:

1. The secondary efficacy end-point assessment is time to “resolution” of acne lesions. Resolution is determined in a similar manner as improvement, as detailed above, with the exception that the mean VAS score should be 3.5.
2. Subjects assessed and registered treatment efficacy, twice a day, in a subject diary. The assessment is based upon a four-point reference scale – VAS. In this case time to improvement score equals 3 and time to resolution score equals 4 were based upon the determination of the status from a single VAS score.
3. Change from baseline in the 5 – point photographic lesion reference scale averaged over the scores as given by the two blinded evaluators.

Safety:

Investigator assessed any device related side effects such as erythema, edema, or other adverse events that arose during the study period and recorded them in the Case Report Form (CRF). In addition the Subject was to report any side effects in the subject diary.

1.3. Statistical Considerations

1.3.1 Study Hypotheses

Null Hypothesis: The time to improvement on the designated lesions in the no!no! skinTM treatment arm is equal to the time to improvement in the placebo arm.

Alternative Hypothesis: The time to improvement on the designated lesions in the no!no! skinTM treatment arm is not equal to the time to improvement in the placebo arm.

1.3.2 Sample size Estimation

Main Assumptions:

- Length of follow-up: 4 days

- It is estimated that the Median time to improvement of a mild acne lesion in the placebo arm will be 3 days.
- Sample size calculated under the assumption of proportional hazards
- Sample size equation from: Survival Analysis - Mahesh K.B. Parmar & David Machin, Wiley, pp193-207
- The level of significance is 5% (two-sided) and power required is 80%

From the literature, under the above assumptions, i.e. that $S(t) = e^{-\lambda t}$ we calculate that $Sp(4days)=39.7\%$ in the placebo arm (i.e. improvement free probability). The minimally important effect of treatment with the no!no! skin™ is a reduction of 40% in the time to improvement, the minimally important hazard ratio is thus 1.67. These assumptions provide the estimate of $St(4days)=21.43\%$ in the treatment arm. Substituting these numbers into the sample size equation, results in a required number of at least 182 lesions (91 lesions per study arm).

1.3.3 General analysis considerations:

The primary analysis will be performed on an intent-to-treat basis. Per-protocol analysis also will be performed as secondary analysis. The required significance level of findings will be equal to or lower than 5%. All statistical tests will be two-sided. Where confidence limits are appropriate, the confidence level will be 95%. All statistical analyses are performed using SAS v9.1 (SAS[®], SAS Institute Cary, NC USA) software.

For comparison of time to event data, the log rank test will be used. For comparison of means (continuous variables), the two-sample t-test or the Wilcoxon rank sum test will be used as appropriate. For comparison of proportions (categorical variables), the Chi-square test or Fisher's exact test will be used as appropriate.

A stratified log-rank test or Cox regression models will be used to adjust for baseline covariates if necessary.

1.3.4 Study Populations

The **intent-to-treat (ITT)** population will include all subjects enrolled in the study as randomized. This population will include all subjects who receive at least one treatment and have at least one post-baseline assessment. According to the ITT principle all subjects will be analyzed in the treatment group as assigned by randomization.

All subjects who complete the entire 4 day treatment protocol and arrive at the 5 day follow-up visit without major protocol violations will be included in the **per-protocol (PP)** subset.

1.3.5. Efficacy analysis

Baseline demographics and lesion characteristics will be compared between the study groups. The statistical evaluation of baseline characteristics will include all available data from the ITT population.

Baseline demographic parameters and lesion characteristics include:

- Age
- Gender
- Fitzpatrick Skin Type
- *no!no! skin*TM Treatment Area
- Placebo treatment area
- Baseline Investigator evaluation

Baseline characteristics (age and gender) of the study population will be compared between the centers with the T-test or the Chi-squared test depending on the type of data. These comparisons will provide support combining the results of the study centers.

The primary and secondary efficacy end-point evaluations will be performed based on both the ITT and the per-protocol populations.

Kaplan-Meier curves of “improvement” free survival will be constructed for each study arm. Subjects who do not achieve the success criteria will be right censored at the time of their last follow-up or the end of study, whichever comes first.

The null hypothesis will be tested using the Log-rank Test.

The first two secondary end-points will be assessed in a similar manner.

The change from baseline in the 5 – point photographic lesion reference scale will be compared between the study groups using a repeated measures analysis of variance model (PROC MIXED in SAS). The change from baseline will modeled as a function of group, time and the time*group interaction with baseline measurement entered as a covariate in the model.

Additional evaluations will be made for the main efficacy parameter adjusting for significant baseline covariates such as baseline lesion characteristics with Cox regression models.

When necessary, adjustment for multiple testing will be conducted using Hochberg's step-up Bonferroni method.

1.3.6. Pooling

Subgroup analysis of the primary efficacy endpoint by center will be used to evaluate the ability to combine results. The significance of center-to-center variability in treatment effect will be evaluated by including an interaction term of treatment by center in a Cox regression model. In the case that ability to combine results is called into question, the reasons for differential treatment effect, such as subject and lesion characteristics, will be investigated and reported.

1.3.7 Handling of missing data

For the primary efficacy endpoint, missing data is accounted for in the statistical model with survival analysis.

1.3.8 Safety Analysis

The analysis of all adverse events will include incidence tables and will include incidence tables by severity, relationship to treatment and baseline parameters when relevant.

Adverse event rates will be compared between the study groups with the Mantel-Haenszel test.

2. RESULTS

A total number of 63 subjects were enrolled in the study. Eligible and consenting patients were randomized to either the active treatment group or the Placebo group. 31 subjects were randomized to receive active treatment and 32 to receive placebo treatment.

2.1. Study Efficacy Results

2.1.1. Data Sets Analyzed

Table 2 displays the patient accountability.

Table 1 Patient Accountability

	Number of Patients Enrolled
Number of patients screened	85
Number of patients enrolled	63
Reasons for non-enrollment	Inclusion/exclusion criteria

Table 2 displays the participating clinical centers, the principal investigator at each center, and the number of patients enrolled at each center.

Table 2 Clinical Centers

Clinical Site	Principal Investigator	Number of Patients Enrolled
USA	Dr. Neil Sadick	33
Israel	Dr.Zehava Laver	30

Two data analysis sets are defined the Intend-to-treat (ITT) analysis set and the Per-protocol (PP) analysis set. The Intend-to-treat (ITT) population includes 63 randomized patients. The per-protocol (PP) analysis set includes 61 subjects who completed the 5 days of the study without any major protocol violation. The number of patients and reasons for their early withdrawal are shown in **Table 5**. One subject was non compliant with the treatment regimen, and another withdrew consent, there were no other major protocol violations. One other subject was enrolled despite the fact that he was two weeks from his 14th birthday.

Table 3 Patient Analysis Sets

Analysis Population	Study Arm		Total
	Placebo	Active Device	
ITT	32	31	63
Patient consent withdrawn	0	1	1
Patient Non-Compliance	0	1	1
Per-Protocol	32	29	61

Table 4 Major Protocol Violation

Protocol Violation	Study Arm		Total
	Placebo Device	Active Device	
Non Compliance	0	1	1
Withdrew Consent	0	1	1

Table 5 Patients Who Withdrew Before End of Study

Patient ID	Reason	Treatment Assigned	Treatment Received	No. of Treatments Received	Last Follow-up Visit
IL-004	Consent withdrawn	Active	Active	1	Day 1
US-029	Non-Compliance	Active	Active	1	Day 1

The above two subjects that withdrew from the study have no available data regarding efficacy i.e. VAS scores, therefore there will be no difference between the ITT and PP analyses for the efficacy data.

Table 66 presents the patient accountability table by visit according to the ITT population. As shown, very few patients were lost to follow-up during the course of the study.

Table 6 Patient Accountability by Visit

Visit	BL	Day 2	Day 3	Day 4	Day 5
Active Device					
Expected	31	29	29	29	29
Withdrawal (cumulative)	2	0	0	0	0
Placebo Device					
Expected	32	32	32	32	32
Withdrawal (cumulative)	0	0	0	0	0

2.1.2. Patient Demographics

Table 7 presents patients' gender and age (<18 or 18+ yr) by treatment group based on the ITT population. Additional descriptive statistics on age distribution are provided in **Table 7**.

Table 7 Baseline Demographics

Baseline Demographics		Active Device (N=31)		Placebo Device (N=32)		P-Value (chi-squared test)
		N	%	N	%	
Gender	Female	21	67.74	26	81.25	0.2182
	Male	10	32.26	6	18.75	
Age (yrs)	< 18	13	41.94	14	43.75	0.8843
	≥18	18	58.06	18	56.25	
Race	Caucasian	11	35.48	16	50.00	0.1478*
	Black	8	25.81	11	34.38	
	Asian	6	19.35	4	12.50	
	Hispanic	6	19.35	1	3.13	
Fitzpatrick Skin type	I	-	-	-	-	0.7852*
	II	4	12.90	5	15.63	
	III	10	32.26	12	37.50	
	IV	8	25.81	4	12.50	
	V	2	6.45	3	9.38	
	VI	7	22.58	8	25.00	

*Fisher's exact test

Table 8 Age at Baseline

At Baseline		Active Device (N=31)	Placebo Device (N=32)	P-Value (t-test)
Age (yrs)	Mean	23.7	23.5	0.9202
	SD	9.71	9.38	
	Min	14.0	13.0	
	Median	19.0	21.5	
	Max	46.0	47.0	

As shown in **Table 7**, there is no statistically significant difference between the treatment groups with regard to gender, age, race or skin type.

Additionally, three of the female subjects were menstruating one in the active treatment group and two in the placebo group.

2.1.3. Baseline Lesions Characteristics

Table 9 presents the distribution of baseline lesions characteristics based on the ITT population. There is no statistically significant difference between treatment groups with regard to the number of lesions, treatment area, global acne assessment, a difference was found between type of lesion (papule / pustule) at baseline but this difference is not meaningful to the outcome of the study.

Table 9 Baseline Lesions Characteristics

Baseline Tumor Characteristics		Active Device (N=31)		Placebo Device (N=32)		P-Value*
		N	%	N	%	
Number of Lesions	<4	-	-	-	-	NR
	4	31	100.00	32	100.00	
Treatment Area (per-lesion)	Right Cheek	28	22.58	25	19.53	0.5386
	Left Cheek	33	26.61	30	23.44	
	Forehead	49	39.52	49	38.28	
	Chin	12	9.68	19	14.84	
	Nose	2	1.61	5	3.91	
Global Acne Assessment	Mild Acne	18	58.06	25	78.13	0.0872
	Moderate Acne	13	41.94	7	21.88	
	Severe Acne	-	-	-	-	
Papule / Pustule (per-lesion)	Papule	68	54.84	95	74.22	0.0012
	Pustule	56	45.16	33	25.78	

*Chi-square or Fisher's exact test.

2.1.4. Number of Treatments

Table 10 presents the total number of treatments patients received based on the ITT population. As can be seen in **Table 10**, there is no statistically significant difference between the treatment groups regarding total number of treatments received.

Table 10 Number of Treatment Sessions

Number of Treatment Sessions	Active Device (N=31)		Placebo Device (N=32)		P-Value
	N	%	N	%	
1	2	6.45	.	.	0.3575
7	13	41.94	12	37.50	
8	16	51.61	20	62.50	

2.1.5. Primary Efficacy Analysis

The primary efficacy analysis is conducted on all evaluable subject data, in this study two patients withdrew prior to collecting efficacy data thus the analysis which is conducted on the ITT patient cohort is actually the per-protocol cohort due to the unavailable data.

These analyses are conducted on a per-lesion basis and not per-subject. The different lesions on a subject are considered to be independent of each other with respect to healing. A total number of 116 lesions are assessed in the active device group and 128 lesions in the placebo treatment group.

The baseline visit is day 1 and thus improvement is relative to day 1 on day 2 which is one day after the first treatment and so on. Therefore on day 5 of the study a total number of 4 days have elapsed since first treatment and is considered the maximal length of follow-up.

Error! Reference source not found. presents the VAS score of all the lesions, as assessed by the principal investigator (PI) and by the independent evaluator (IE), and the mean VAS score.

Table 11a VAS Score Assessed by the PI

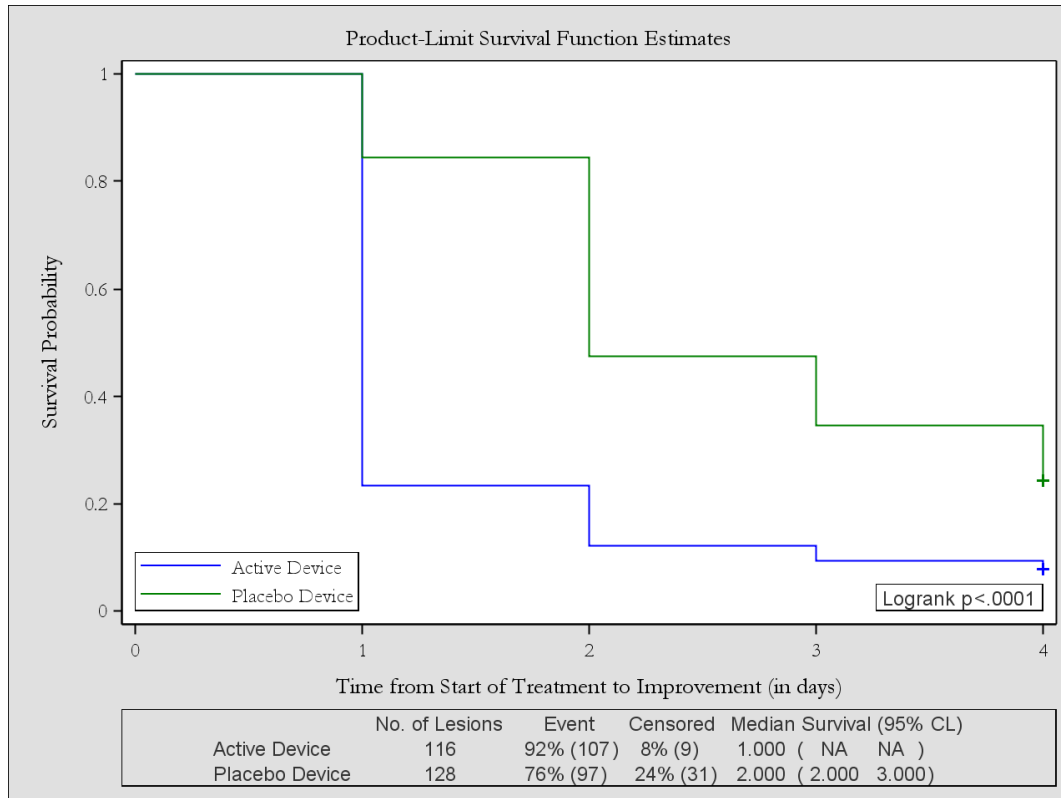
		Visit							
		Day 2		Day 3		Day 4		Day 5	
		N	%	N	%	N	%	N	%
Treatment Group	VAS								
Active Device (N Lesions=116)	Worsening (VAS=1)	2	1.72	2	1.72	2	1.72	2	1.72
	No improvement (VAS=2)	21	18.10	29	25.00	37	31.90	28	24.14
	Improvement (VAS=3)	86	74.14	57	49.14	34	29.31	29	25.00
	Resolution (VAS=4)	7	6.03	28	24.14	43	37.07	57	49.14
Placebo Device (N Lesions=128)	Worsening (VAS=1)	6	4.69	4	3.23	4	3.13	3	2.34
	No improvement (VAS=2)	84	65.63	36	29.03	56	43.75	50	39.06
	Improvement (VAS=3)	32	25.00	68	54.84	45	35.16	37	28.91
	Resolution (VAS=4)	6	4.69	16	12.90	23	17.97	38	29.69

Table 12b VAS Score Assessed by the IE

		Visit							
		Day 2		Day 3		Day 4		Day 5	
		N	%	N	%	N	%	N	%
Treatment Group	VAS								
Active Device (N Lesions=116)	Worsening (VAS=1)	3	2.59	3	2.59	1	0.86	.	.
	No improvement (VAS=2)	18	15.52	15	12.93	24	20.69	16	13.79
	Improvement (VAS=3)	91	78.45	74	63.79	57	49.14	46	39.66
	Resolution (VAS=4)	4	3.45	24	20.69	34	29.31	54	46.55
Placebo Device (N Lesions=128)	Worsening (VAS=1)	6	4.69	4	3.23	3	2.34	4	3.13
	No improvement (VAS=2)	88	68.75	53	42.74	43	33.59	26	20.31
	Improvement (VAS=3)	30	23.44	59	47.58	65	50.78	60	46.88
	Resolution (VAS=4)	4	3.13	8	6.45	17	13.28	38	29.69

Figure 1 presents the survival analysis results for the study patients using the Kaplan-Meier (KM) method for the ITT/PP population.

Figure 1: Primary endpoint - Time to Improvement (mean VAS > 2.5) – ITT/PP



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 versus placebo treated lesions, the difference observed is highly statistically significant ($p < 0.0001$, logrank test). The KM estimate of the improvement rate, at the end of the follow-up, is 92.24% ($se = 2.48\%$) in the active treated lesions whereas in the placebo treated lesions the rate is 75.78% ($se = 3.79\%$). The mean time to improvement as estimated from the KM curve (which is underestimated since the last observation is censored) is 1.45 days ($se = 0.087$) in the active treatment and 2.66 days ($se = 0.099$) in the placebo arm.

The hazard ratio, as calculated from the Cox regression model, is 2.253 (95% CI: [1.686-3.009]) this means that a lesion treated with the active device achieves “improvement” 55.6% sooner than a lesion treated with the placebo device. In other words time to improvement of a lesion treated with an active device is 55.6% shorter than a lesion treated with a placebo device. This result is much better than the hypothesized success criteria of 40%.

Prognostic factors analysis

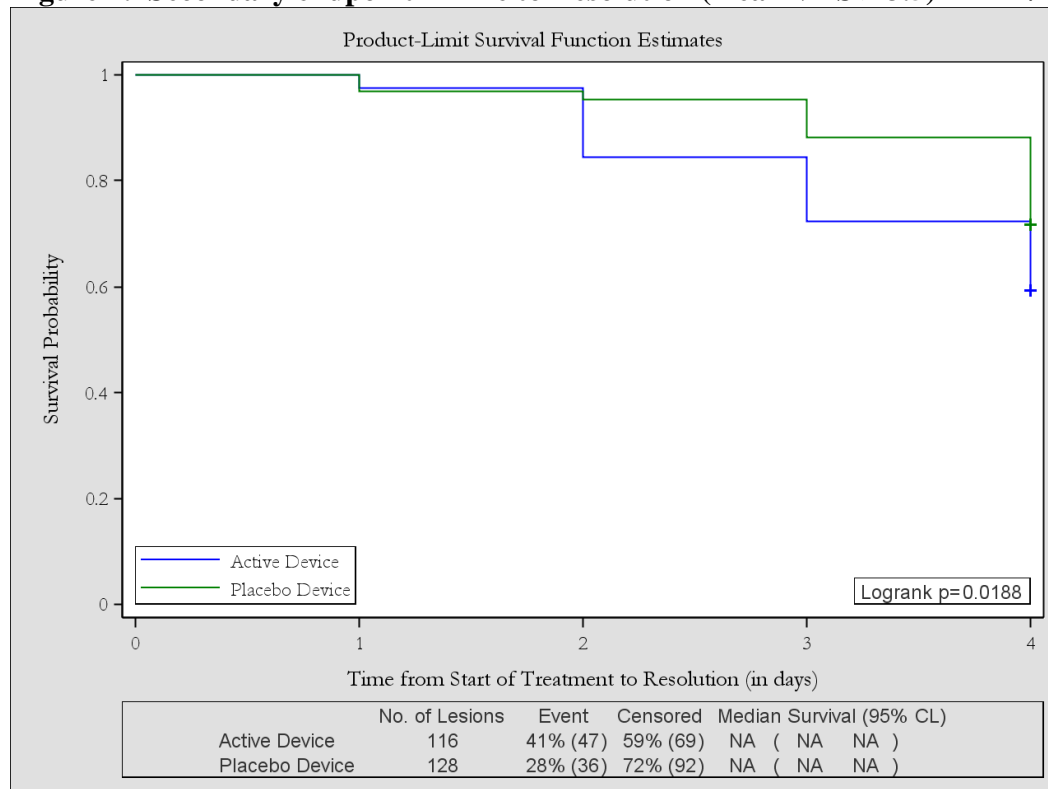
- a. Type of lesion (papule/pustule) at baseline was found to be significantly different between the study groups thus a prognostic factor analysis using a COX regression model was conducted. Time to improvement was modeled as a function of treatment group, lesion type (papule/pustule) and the group*lesion type interaction. The interaction term was not statistically significant ($p=0.5002$) and thus we conclude that lesion type does not affect on the time to improvement.
- b. Number of treatments could also potentially affect time to improvement. Time to improvement was modeled as a function of treatment group, number of treatments (7/8) and the group*number of treatments interaction. The interaction term was not statistically significant ($p=0.0561$) and thus we conclude that lesion type does not affect on the time to improvement.

2.1.6. Secondary Efficacy Analysis

2.1.6.1. Time to Resolution

Figure 2 presents the survival analysis results for the study patients using the Kaplan-Meier (KM) method for the ITT/PP population.

Figure 2: Secondary endpoint - Time to Resolution (mean VAS > 3.5) – ITT/PP



From the Kaplan-Meier (KM) curves it can be seen that resolution is more frequent and occurs sooner in the course of treatment in the actively treated lesions versus placebo treated lesions, the difference observed is statistically significant ($p=0.0188$, logrank test). The KM estimate of the resolution rate, at the end of the follow-up, is 40.52% ($se=4.56\%$) in the active treated lesions whereas in the placebo treated lesions the rate is 28.13% ($se=3.97\%$). The mean time to improvement as estimated from the KM curve (which is underestimated since the last observation is censored) is 3.54 days ($se=0.076$) in the active treatment and 3.81 days ($se=0.055$) in the placebo arm.

The hazard ratio, as calculated from the Cox regression model, is 1.622 (95% CI:[1.051-2.505]) this means that a lesion treated with the active device achieves “resolution” 38% sooner than a lesion treated with the placebo device. In other words time to resolution of a lesion treated with an active device is 38% shorter than a lesion treated with a placebo device.

2.1.6.2. Time to Resolution as determined by the Patient's assessment

The patient reported a VAS score twice a day once in the morning and once in the evening per lesion on each day of treatment thus the time to resolution includes half days.

Additionally, since the patient report includes the first treatment data set analyzed is the ITT set. But since the two subjects whom are not in the PP are censored before one day in the follow-up there is no difference between the ITT and PP Kaplan-Meier results and thus it presented only once.

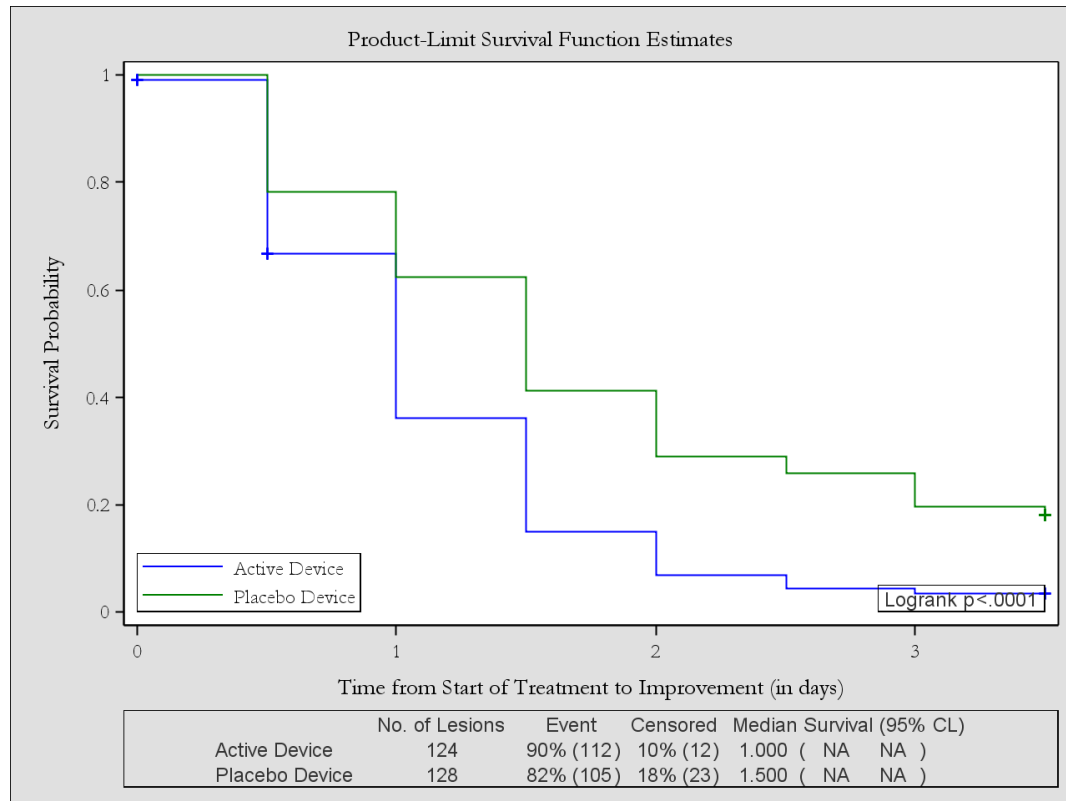
Table 12 presents the patient score of all the lesions, as assessed by the patient - ITT

Table 13 VAS Score Assessed by the patient - ITT

		Time from Start of Treatment (in days)																	
		0		0.5		1		1.5		2		2.5		3		3.5		4	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Treatment Group	Patient Assessment Score																		
Active Device (N Lesions=124)	Worse	.	.	2	0.82	3	1.24	1	0.41	1	0.43	1	0.42	1	0.42
	No change	123	48.81	75	30.74	48	19.83	33	13.52	17	7.33	16	6.67	21	8.79	15	6.15	.	.
	Improvement	1	0.40	39	15.98	60	24.79	75	30.74	80	34.48	81	33.75	71	29.71	70	28.69	4	50.00
	Resolution	3	1.24	7	2.87	14	6.03	18	7.50	22	9.21	31	12.70	.	.
Placebo Device (N Lesions=128)	Worse	.	.	1	0.41	4	1.65	3	1.23	.	.	4	1.67	5	2.09	5	2.05	.	.
	No change	128	50.79	99	40.57	84	34.71	68	27.87	51	21.98	62	25.83	44	18.41	45	18.44	.	.
	Improvement	.	.	28	11.48	39	16.12	56	22.95	64	27.59	46	19.17	57	23.85	57	23.36	4	50.00
	Resolution	1	0.41	1	0.41	5	2.16	12	5.00	18	7.53	21	8.61	.	.

Figure 3 presents the survival analysis results for the study patients per lesion using the Kaplan-Meier (KM) method for the ITT population.

Figure 3 Secondary endpoint: Time to Improvement (VAS = 3) – ITT



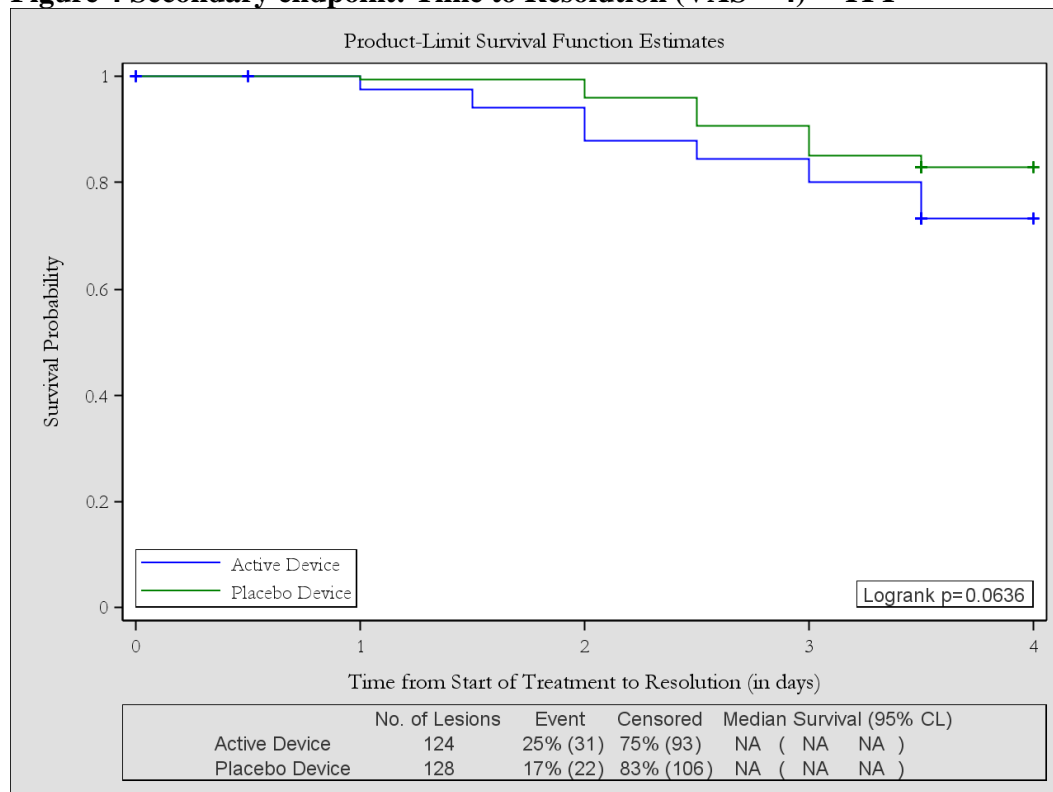
From the KM curves it can be seen that improvement is more frequent and occurs sooner in the course of treatment in the actively treated lesions versus placebo treated lesions, the difference observed is highly statistically significant ($p < 0.0001$, logrank test). The KM estimate of the improvement rate, at the end of the follow-up, is 96.49% ($se = 1.72\%$) in the active treated lesions whereas in the placebo treated lesions the rate is 82.03% ($se = 3.39\%$). The mean time to improvement as estimated from the KM curve (which is underestimated since the last observation is censored) is 1.14 days ($se = 0.061$) in the active treatment and 1.78 days ($se = 0.096$) in the placebo arm.

The hazard ratio, as calculated from the Cox regression model, is 1.789 (95% CI:[1.360-2.353]) this means that a lesion treated with the active device achieves “improvement” 44.1% sooner than a lesion treated with the placebo device. In other words time to

improvement of a lesion treated with an active device is 44.1% shorter than a lesion treated with a placebo device using the patient assessment of improvement.

Figure 4 presents the survival analysis results for the study patients per lesion using the Kaplan-Meier (KM) method for the ITT population.

Figure 4 Secondary endpoint: Time to Resolution (VAS = 4) – ITT



From the Kaplan-Meier (KM) curves it can be seen that resolution is more frequent and occurs a bit sooner in the course of treatment than in the actively treated lesions versus placebo treated lesions, the difference observed is not statistically significant (p=0.0636, logrank test).

2.1.6.3. The change from baseline in the five-grade reference photographic scale

Error! Reference source not found. presents the grade of all the lesions, as assessed by the principal investigator (PI) and by the independent evaluator (IE).

Table 14a Grade Score Assessed by the PI

		Visit									
		Day 1		Day 2		Day 3		Day 4		Day 5	
		N	%	N	%	N	%	N	%	N	%
Treatment Group	Reference Scale										
Active Device	Fully Resolved	.	.	5	4.31	26	22.41	39	33.62	57	49.14
	Almost Resolved	.	.	15	12.93	35	30.17	34	29.31	25	21.55
	Papule	64	53.33	77	66.38	47	40.52	40	34.48	29	25.00
	Pustule	55	45.83	19	16.38	8	6.90	2	1.72	3	2.59
	Nodule	1	0.83	1	0.86	2	1.72
Placebo Device	Fully Resolved	.	.	5	3.91	12	9.68	18	14.06	37	28.91
	Almost Resolved	.	.	16	12.50	49	39.52	43	33.59	30	23.44
	Papule	93	72.66	84	65.63	50	40.32	51	39.84	49	38.28
	Pustule	33	25.78	19	14.84	9	7.26	5	3.91	4	3.13
	Nodule	2	1.56	4	3.13	4	3.23	11	8.59	8	6.25

Table 15 Grade Assessed by the IE

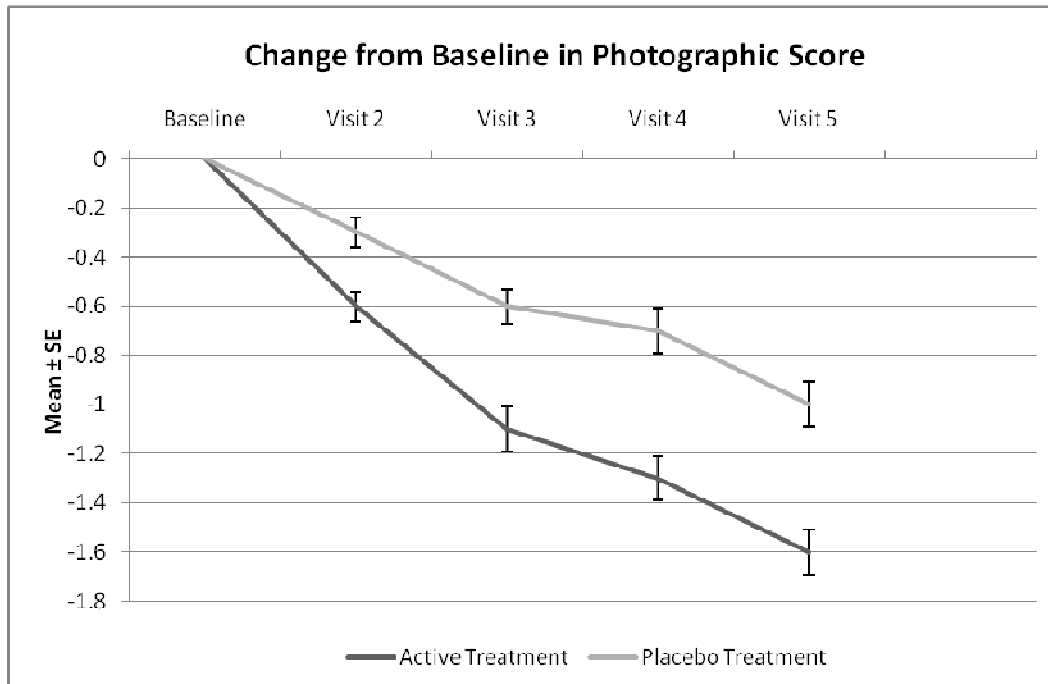
		Visit									
		Day 1		Day 2		Day 3		Day 4		Day 5	
		N	%	N	%	N	%	N	%	N	%
Treatment Group	Reference Scale										
Active Device	Fully Resolved	.	.	5	4.31	21	18.10	28	24.14	49	42.24
	Almost Resolved	.	.	19	16.38	30	25.86	37	31.90	30	25.86
	Papule	52	43.33	69	59.48	50	43.10	36	31.03	25	21.55
	Pustule	68	56.67	22	18.97	13	11.21	13	11.21	10	8.62
	Nodule	.	.	1	0.86	2	1.72	2	1.72	2	1.72

		Visit									
		Day 1		Day 2		Day 3		Day 4		Day 5	
		N	%	N	%	N	%	N	%	N	%
Placebo Device	Fully Resolved	.	.	4	3.13	4	3.23	10	7.81	32	25.00
	Almost Resolved	.	.	11	8.59	33	26.61	44	34.38	40	31.25
	Papule	83	64.84	80	62.50	59	47.58	50	39.06	33	25.78
	Pustule	41	32.03	26	20.31	21	16.94	17	13.28	18	14.06
	Nodule	4	3.13	7	5.47	7	5.65	7	5.47	5	3.91

The photographic scale scores of the two evaluators are averaged in order to obtain a single daily photographic score per lesion of each subject. The change from baseline in this score is compared between the study groups on a per lesion basis (Figure 5).

The repeated measures analysis of variance model shows a significant day*treatment group interaction ($F(1,910)=6.25$, $p=0.0126$). This means that the rate of change (reduction) in the scores is significantly different between the active treatment group and the placebo treatment group, where the mean overall reduction in the scores of the active treated lesions is 1.3017 ($se=0.1184$) points and in the placebo treatment lesions is 0.8929 ($se=0.1138$).

Figure 5: Mean Change from baseline Photographic scale



2.2. Safety Analysis

Other than the side effects tabulated below no adverse events were observed throughout the entire treatment regimen in both treatment arms.

Table 1 displays the side effects observed in the study.

Table 14 Side effects tabulation

Treatment Group	Subject Id	Visit #	Event	Reported by	Start Date	End Date	Ongoing	Severity	Treatment Discontinued
Active Device	Israel-IL-028	3	BURNING SENSATION	Subject	29APR2008	29APR2008	No	Minor side effects	.
Active Device	USA-US-002	2	CHEST CONGESTION	Subject	20MAY2008	20MAY2008	No	No side effects	No
Active Device	USA-US-006	2	SEVERE HEADACHE	Subject	20MAY2008	20MAY2008	No	Minor side effects	No

2.3. Pooling of Patient Data

Table 15 displays the number of patients enrolled in the study according to clinical centers.

Table 15 Clinical Centers

Clinical Center	Active Device (N=31)		Placebo Device (N=32)	
	N	%	N	%
USA	16	51.61	17	53.13
IL	15	48.39	15	46.88

In randomized clinical trials, it is common to pool the results across clinical centers, especially where all centers follow a common protocol. This is done even if differences in the distribution of baseline prognostic factors exist between centers. However, it is important to ensure that the treatment effect is consistent across centers before pooling the results.

The Cox regression model was used to test for interaction between treatment group and center to determine whether the treatment difference was consistent across centers. The data presented in this section is for the ITT/PP population.

The Cox regression model show a significant difference between the treatment groups ($p=0.0001$) as seen in the primary efficacy analysis but no center difference ($p=0.1530$) or center by treatment interaction ($p=0.8946$) was found thus the poolability of the centers is not questionable.

3. SUMMARY AND CONCLUSIONS

There were no differences found between the treatment groups regarding baseline demographic parameters. In addition except for the distribution of lesion type (pustule/papule) the distribution of baseline lesion characteristics were similar between the study groups.

No center by treatment group interaction was found.

No adverse events occurred throughout the treatment regimen. Side effects observed chest congestion and headache were not treatment related. One subject in the treatment group felt a burning sensation at the third visit.

- Time to improvement of a lesion treated with an active device is 55.6% shorter than a lesion treated with a placebo device. This result is much better than the hypothesized success criteria of 40%.
 - ❖ The number of treatments (7 or 8) applied did not affect the time to improvement.
 - ❖ The type of lesion ((pustule/papule) did not affect the time to improvement.
- Time to resolution of a lesion treated with an active device is 38% shorter than a lesion treated with a placebo device.
- The subjects (from the patient diaries) reported improvement rate in the active treated lesions is 44.1% shorter than the placebo treated lesions.
- The subjects (from the patient diaries) reported resolution rate in the active treated lesions is not statistically significantly different from the placebo treated lesions.
- The rate of change of the in the Photographic score is significantly different between lesions treated with an active device compared with lesions treated with a placebo device.

In conclusion this study has succeeded in proving that the *no!no! skin*TM Acne Clearance System is safe and effective, reducing the time to improvement by 56% in actively treated lesions versus placebo treated lesions.