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ANTI ACNE SPOT CREAM IN CONTROLLING FACIAL ACNE : A PROSPECTIVE OPEN LABEL MULTICENTER SAFETY AND EFFICACY TRIAL.

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ABSTRACT
Background: Anti acne spot cream is recommended for treatment of mild to moderate facial acne vulgaris. The safety and efficacy of anti-acne spot cream was evaluated over a period of 60 days. **Aim:** To evaluate the safety and efficacy of anti-acne spot cream in patients with mild to moderate facial acne. **Methods:** Thirty six subjects with mild to moderate facial acne and between the age group of 18 to 50 years were enrolled in the study to receive anti-acne spot cream. The cream was to be applied twice a day on the acne affected area for 60 days. Subjects were instructed to apply the anti-acne formulation daily during the study duration irrespective of their visits to the clinic. Subjects visited the study site during initial Screening and Days 0, 15, 30, 45 and 60. Physical examination, Vitals and Adverse Events (if any) were recorded on all visits. Clinical determinations of disease severity was performed using IGA scale and non-inflammatory and inflammatory lesion counts during initial Screening, Days 0, 15, 30, 45 and Day 60 along with assessment of local cutaneous tolerability and safety. Quality of Life was assessed using Cardiff Acne Disability Index at Baseline and Final Visit. Standardized clinical photographs were captured at baseline, Day 45 and final visit (Day 60). **Results:** The Anti-acne spot cream showed statistically significant difference in all the efficacy parameters at different time points from baseline to end of the study. The percent change in inflammatory and non- inflammatory lesion count was found to be 63.8% and mean change was found to be statistically significant ($p<0.0001$) in total inflammatory and non- inflammatory lesion count as compared to baseline. The quality of life was assessed using Cardiff Acne Disability Index questionnaire. The mean change from day 0 in CADI score was found to be 5.4±3.1 and was statistically highly significant ($p<0.0001$) as compared to day 0. No adverse events were observed during the entire duration of the study. **Conclusions:** We conclude based on the results of the efficacy assessments, the anti-acne spot cream was very effective in treating facial acne. It has shown significant effect in reducing the lesion count without any side effects. Hence the formulation is an effective and safe treatment option in patients with facial acne.

KEYWORDS: Acne, Investigator's Global Assessment, Cardiff Acne Disability Index, Quality of Life.

INTRODUCTION
Acne is an inflammatory follicular, papular, and pustular eruption involving the pilosebaceous apparatus.[1] There are many types of acne with acne vulgaris being the most common. Acne vulgaris is an eruption, predominantly of the face, upper back and chest, composed of comedones, cysts, papules and pustules on an inflammatory base. Acne occurs in almost all individuals at some time or another and is one of the most widespread medical conditions in the world, yet there is no cure. It is reported that there is no single condition that causes more psychic trauma, maladjustment, general insecurity, feelings of inferiority and other psychic suffering than acne vulgaris.[2]

Factors which contribute to the development of acne include hormonal imbalance, bacterial infection, stress, food or cosmetic application.[3]

The development of inflammatory lesions often drives acne patients to seek treatment. According to the severity of acne, there are various treatment modalities. They include both topical and systemic therapy. Topical medicaments used in acne treatment, e.g. tretinoin may primarily cause mild dermatitis. Bleaching of skin and hair is the common side effect of benzoyl peroxide. Although there is no proved documentation regarding systemic absorption of retinoids through skin, they should be avoided during pregnancy and lactation.[4]

Cosmeceuticals and pharmaceuticals are growing areas of interest. With controversy over the use of unsafe ingredients in acne therapy; the development of new active botanical extracts and compounds as anti–acne agents is still a field with great potential.[5]

Antibiotics which suppress *Propionibacterium acnes* are the standard treatment for acne, but are becoming less effective probably because of the emergence of antibiotic-resistant strains.[6, 7, 8]

In a single-blind, randomized clinical trial performed for the evaluation of tea tree oil in acne vulgaris, the efficacy and skin tolerance of 5% tea tree oil gel in the treatment of mild to moderate acne was compared with 5% benzoyl peroxide lotion in 124 patients. The results showed that both 5% tea tree oil and 5% benzoyl peroxide had a significant effect in ameliorating acne by reducing the number of inflamed and non-inflamed lesions (open and closed comedones), although the onset of action in case of tea tree oil was slower. Encouragingly, patients treated with tea tree oil experienced fewer side-effects.[9]

This novel anti acne spot cream by Sami Labs Limited is a combination of Monolaurin, Ginger SCFE, N-Acetyl Glucosamine, Vitamin E acetate, Olive oil and Jojoba oil. To evaluate the safety and efficacy of topical anti acne spot cream, the present prospective open label multicenter study was undertaken.

METHODS

This prospective study of the efficacy and tolerability of anti-acne spot cream in patients with facial acne was carried out at three centers - Meenakshi Multi-specialty Hospital, Chennai, Vijaya Super Specialty Hospital, Nellore and Kakatiya Hospitals, Hyderabad. A total number of 36 male and female patients aged 18 to 50 years with mild to moderate facial acne vulgaris were included in the study. Subjects with facial inflammatory lesion count > 20 and < 50 (both inclusive), non-inflammatory lesion count of at least 20-100 and Investigators Global assessment score of 3 were included. All patients were included after written informed count. Patients with 2 nodulocystic lesions, prior topical acne treatment or systemic anti-inflammatory agents in past 14 days, patients on systemic corticosteroids, antibacterial, immunosuppressant drugs or abradent facial procedures in the past 30 days, patients with other concurrent facial skin disease and patients who are photosensitive or who are likely to engage in activities that involve excessive or prolonged exposure to sunlight, patients with drug induced acne, patients with menopausal disorders, has a history of significant reactions to topical acne treatments, or a known allergy or hypersensitivity to any listed ingredients and use of oral retinoids within 6 months of Baseline visit were excluded from the study. All patients were included after written informed consent. After recording detailed demographic data (which included age, sex, height, weight and BMI), vital signs (blood pressure, pulse rate, heart rate and respiratory rate), physical examination, medical and medication history, urine pregnancy test were conducted.

Investigator's Global Assessment was calculated as follows –

- Clear skin with no inflammatory or non-inflammatory lesions – 0
- Almost clear; rare non-inflammatory lesions with no more than one small inflammatory lesion – 1
- Mild severity; greater than Grade 1; some non-inflammatory lesions with no more than a few inflammatory lesions (papules/pustules only, no nodular lesions) – 2
- Moderate severity; greater than Grade 2; up to many non-inflammatory lesions and may have some inflammatory lesions, but no more than one small nodular lesion – 3
- Severe; greater than Grade 3; up to many non-inflammatory and inflammatory lesions, but no more than a few nodular lesions – 4

The Cardiff Acne Disability Index consisting of five questions was used. The scoring of each answer was recorded as –
(a) 3 (b) 2 (c) 1 and (d) 0
The CADI score was calculated by summing the score of each question resulting in a possible maximum score of 15 and a minimum score of 0. The higher the score, the more the quality of life was considered to be impaired.

The study was an open label, prospective, multi-center study and was carried out to evaluate the efficacy, safety and tolerability of topical acne formulation. All the 36 subjects enrolled in the study were instructed to apply topical anti-acne spot cream twice a day on the affected area for a period of 60 days. Subjects were followed up at 15 days interval on Day 15, Day 30, Day 45 and Day 60.

All subjects enrolled in the study were evaluated for the effect of investigational product on facial acne during the end of study or at the time of discontinuation of the treatment in comparison with baseline with the Investigator's global assessment rating scale, CADI Score, Total Inflammatory and non-inflammatory lesion count and standardized clinical photographs. The principal Investigator monitored safety data throughout the course of the study. Safety measurements include monitoring of Adverse effects, physical examination results and vital signs.

All statistical testing were planned to be two-sided and performed using in-house software. All analyses were performed on available data from the intent-to-treat (ITT) population, defined as all subjects who received at least one dose of investigational product. Student t test and repeated measure ANOVA were used for assessing the efficacy of anti-acne spot cream. The drop out

patient's data was analyzed on last observation carried forward (LOCF) method.

RESULTS

A total of thirty six (36) subjects were screened and enrolled in the trial after fulfilling inclusion and exclusion criteria with the clinical diagnosis of mild to moderate facial acne vulgaris. The mean age of the subjects was 24.9 years (range 19-36, median 23.5). The demographic data of all the subjects including age, sex, body weight, height and Body Mass Index (BMI) at the beginning of the study is as mentioned in Table 1.

Out of 36 subjects, 34 subjects completed the study. Efficacy analysis was done on Intention to Treat (ITT) population. The missing observation was imputed using LOCF approach (last observation carried forward).

Investigator's Global Assessment scale was evaluated on Day 0, Day 15, Day 30, Day 45 and Day 60 to assess the severity of facial acne. Subjects were included in this study if their IGA score =3. The result of Percent of success of IGA scale is given in Table 2.

The study result showed progressive reduction in IGA score. All the subjects graded the IGA score as moderate in severity at the baseline. After topical application of the anti-acne cream 38.9% of subjects were in the clear category and 55.6% of subjects reported the IGA score as mild and only 5.5% of subjects reported as moderate at the end of the study.

Inflammatory lesion count reflects the severity of acne and was the key element of this study. It was divided into papules, pustules and nodules depending on the severity. The acne severity was assessed by inflammatory lesion count on Day 0, Day 15, Day 30, Day 45 and Day 60. The percent reduction in total inflammatory lesion count is given in Table 3.

The result showed that there were significant differences in inflammatory lesion count over the four time points. The inflammatory lesion count gradually reduced compared to baseline by 63.8% after the application of anti-acne cream.

Non-inflammatory lesion count is also a significant method of measuring the severity of acne. It includes open or closed comedones. The acne severity was assessed by non-inflammatory lesion count on Day 0, Day 15, Day 30, Day 45 and Day 60. The result of percent reduction in total non-inflammatory lesion count is given in Table 4.

The result showed excellent reduction in total non-inflammatory lesion count. It was observed that, after application of topical acne cream, the non-inflammatory lesion count reduced by 63.8% compared to the baseline. Significant changes were observed from Day 15 ($p<0.0001$).

The Mean change in total inflammatory lesion count from baseline shows the effectiveness of the Investigational product and the result is presented in Table 5.

There was significant reduction in the number of inflamed pustules, when compared to the baseline. The overall inflammation, as judged clinically, was also significantly improved when compared to the baseline. The inflammatory lesion count reduced by 16.4±5.2 compared to Visit I. Figure 2 reflects change in the total inflammatory lesion count.

The mean change in total non-inflammatory lesion count from baseline is also an effective parameter to know the effectiveness of the Investigational Product and the result is shown in Table 6.

The result showed significant improvement in acne severity. The change in non-inflammatory lesion count was found to be statistically significant from Day 15. It showed that the non-inflammatory lesion count was reduced by 19.6±7.2 on day 60 in comparison to baseline. Figure 3 reflects change in the total non-inflammatory lesion count.

The Cardiff Acne Disability Index was used to assess acne-related quality of life. Higher the score, more was the quality of life impaired. It was assessed on Baseline visit and Final visit and the result of mean change is given in Table 7.

The result showed remarkable decrease in CADI score and was found to be significantly reduced ($p<0.0001$) by 5.4±3.1 compared to baseline. At the baseline, 7 subjects reported as severe, 12 subjects reported as moderate and 15 subjects as mild, but at the end of the study all 34 subjects reported mild symptoms. Figure 4 reflects change in CADI score.

Photographs were taken on Day 0, Day 45 and Day 60. Figure 5 reflects gradual improvement in patients with facial acnes from baseline to Day 60.

There were no adverse events in the study population. During screening, a physical examination was performed on the subjects, yielding normal findings for all subjects and no changes were observed in the physical examination carried out at the end of the study.

Table 1: Baseline and Demographic characteristic

Parameter	Statistics	Values
Age (years)	N	36
	Mean (SD)	24.9 (4.6)
	Median	23.5
	Min; Max	19; 36
Gender, n (%)	Male	05 (13.9)
	Female	31 (86.1)
Body weight (kg)	N	36
	Mean (SD)	55.2 (6.3)
	Median	56
	Min; Max	42; 69
Height (cm)	N	36
	Mean (SD)	155.7 (6.6)
	Median	156
	Min; Max	144; 176
BMI (kg/m^2)	N	36
	Mean (SD)	22.8 (2.7)
	Median	23.4
	Min; Max	18; 30

Table 2: Percent of success in Investigator's Global Assessment

Visit	% of subjects with score 3 (%)	% of subjects with score 2 (%)	% of subjects with score 1 (%)
Day 0 (N=36)	100	0	0
Day 15 (N=36)	97.2	2.8	0
Day 30 (N=36)	50	50	0
Day 45 (N=36)	19.4	80.6	0
Day 60 (N=36)	5.5	55.6	38.9

Table 3: Percent reduction in total inflammatory Lesion Count

Visit	Percentage reduction
Day 15 (N=36)	19.8
Day 30 (N=36)	32.8
Day 45 (N=36)	46.7
Day 60 (N=36)	63.8

Table 4: Percent reduction in total non- inflammatory lesion count

Visit	Percentage reduction
Day 15 (N=36)	26.6
Day 30 (N=36)	38.6
Day 45 (N=36)	50.0
Day 60 (N=36)	63.8

Table 5: Mean change in total inflammatory lesion count

Visit	Statistics	Mean change (N=36)	Change from baseline	P Value
I	Mean (SD)	25.7 (4.8)	-	-
	Median	24		
	Min; Max	20; 38		
II	Mean	20.6 (4.9)	5.1 (4.1)	<0.0001*
	Median	21		
	Min; Max	14; 28		
III	Mean	17.3 (2.7)	8.4 (5.1)	<0.0001*
	Median	18		
	Min; Max	10; 21		

IV	Mean	13.7 (3.8)	12 (5.7)	<0.0001*
	Median	14.5		
	Min; Max	4; 20		
V	Mean	09.3 (4.1)	16.4 (5.2)	<0.0001*
	Median	9.5		
	Min; Max	1; 20		

Table 6: Mean change in total non- inflammatory lesion count

Visit	Statistics	Mean change (N=36)	Change from baseline	P Value
I	Mean (SD)	30.6 (7.0)	-	-
	Median	29.5		
	Min; Max	20; 43		
II	Mean	22.5 (4.4)	8.1 (5.9)	<0.0001*
	Median	22		
	Min; Max	16; 35		
III	Mean	18.8 (3.6)	11.8 (6.9)	<0.0001*
	Median	18		
	Min; Max	12; 27		
IV	Mean	15.3 (4.9)	15.3 (7.3)	<0.0001*
	Median	15		
	Min; Max	6; 34		
V	Mean	11.1 (5.6)	19.6 (7.2)	<0.0001*
	Median	9		
	Min; Max	4; 31		

Table 7: Mean change in CADI score

Visit	Statistics	Mean change (N=36)	Change from baseline	P Value
I	Mean (SD)	7.35 (3.4)	-	-
	Median	7.50		
	Min; Max	02; 13		
V	Mean (SD)	1.91 (1.6)	5.4 (3.1)	<0.0001*
	Median	2.00		
	Min; Max	0; 5.0		

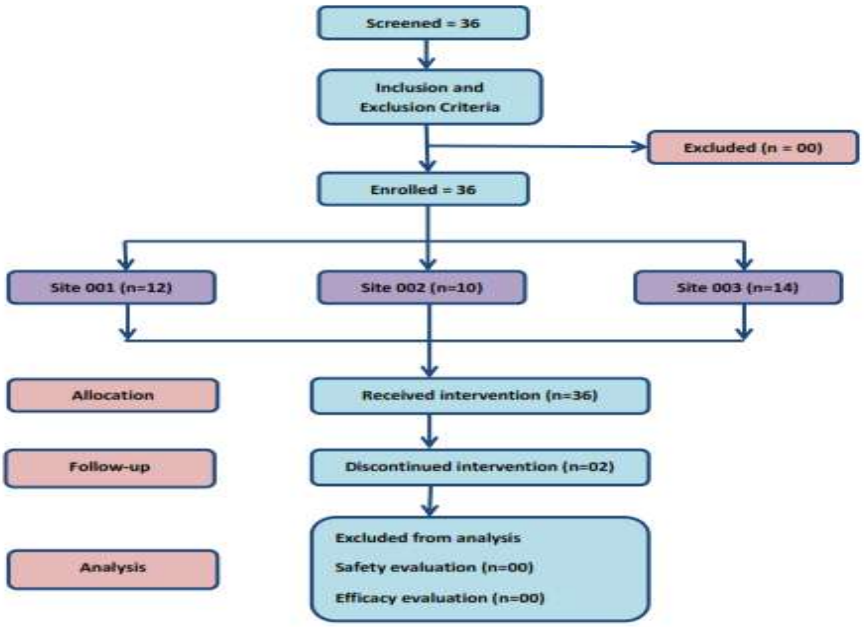


Figure 1: Flowchart of patients participating in the study.

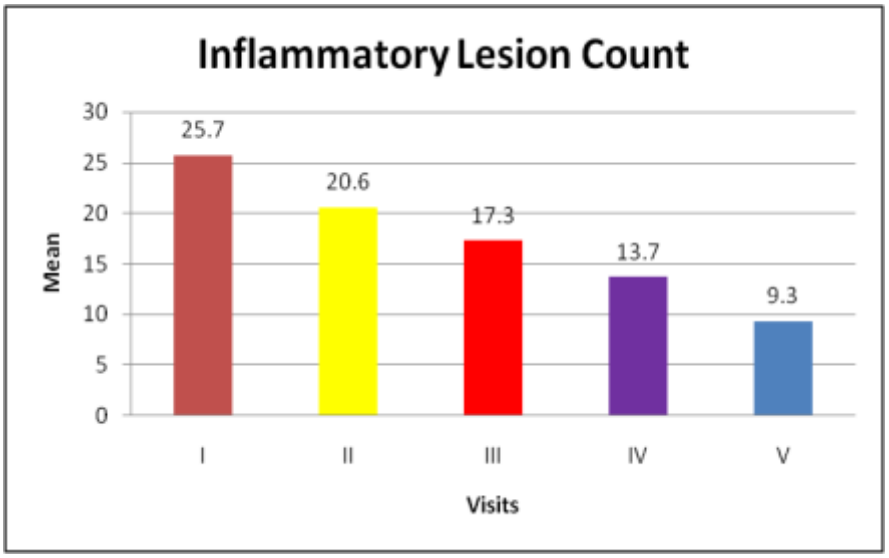


Figure 2: Change in total inflammatory lesion count

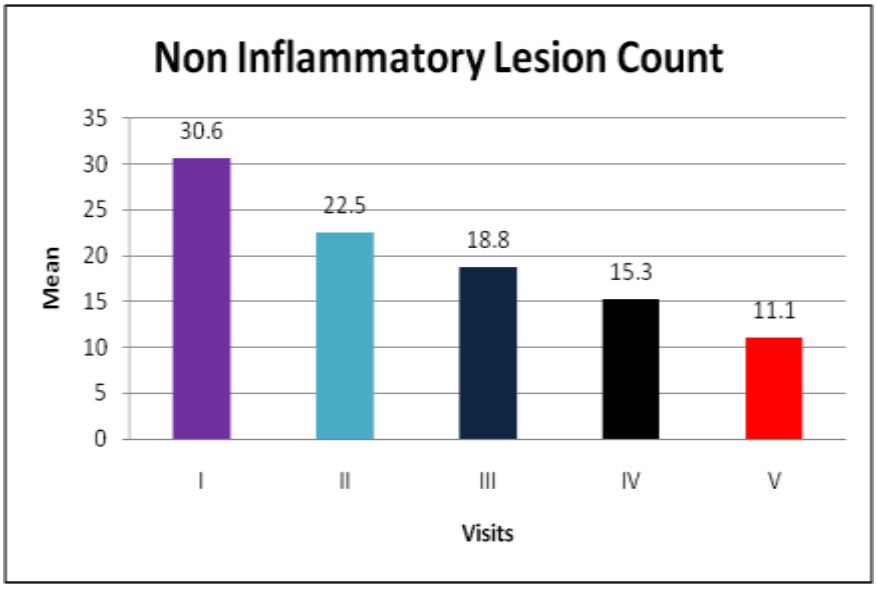


Figure 3: Change in total non inflammatory lesion count

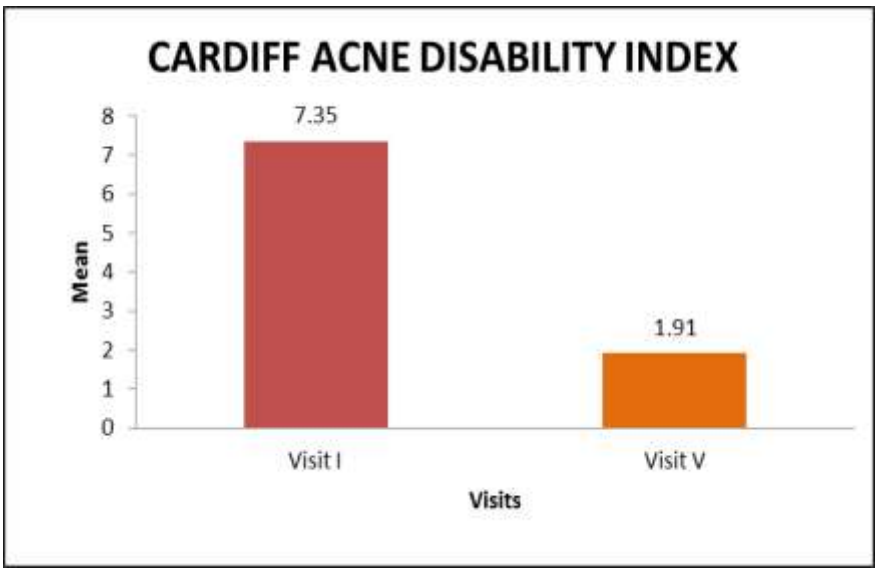
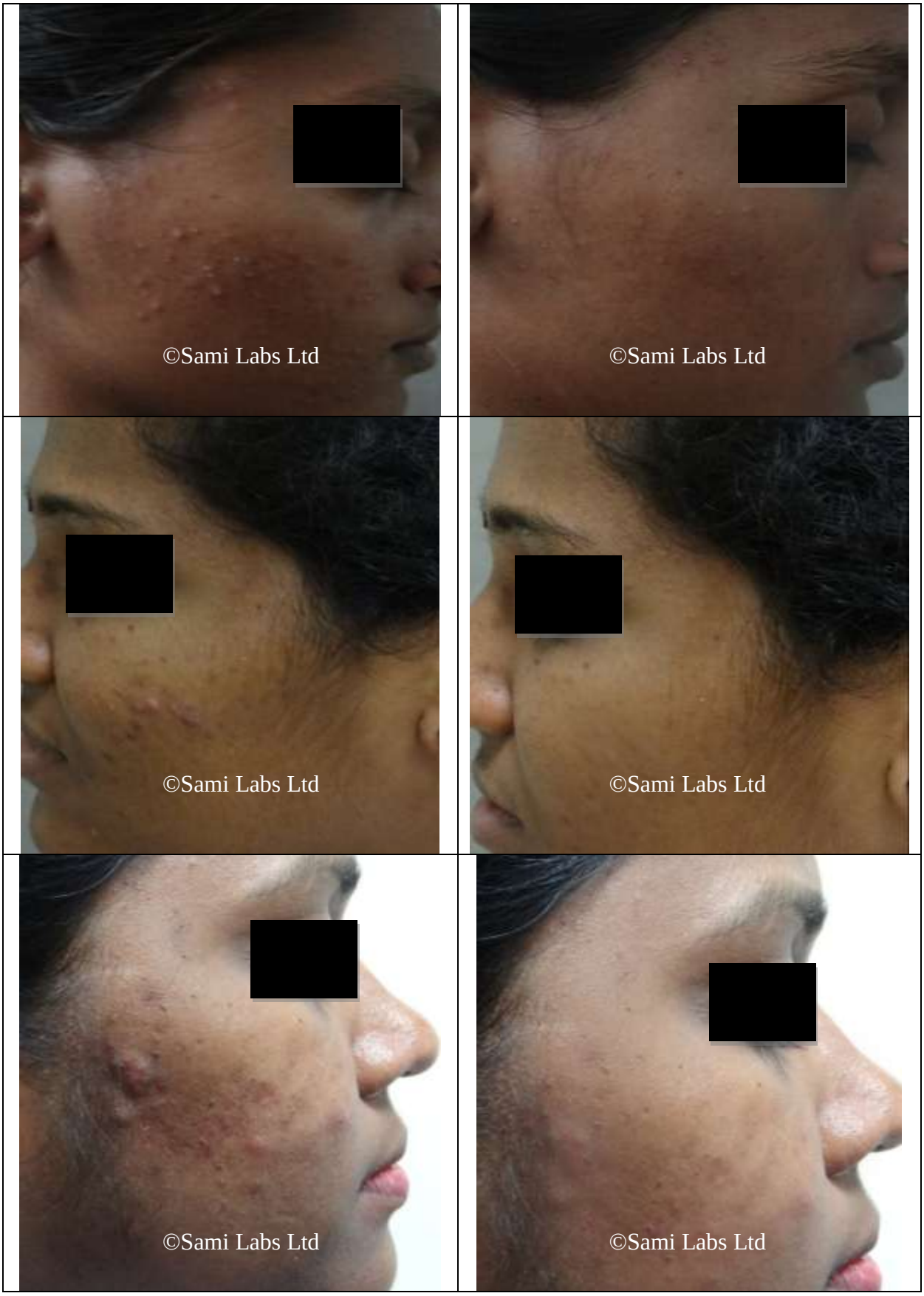


Figure 4: Change in CARDIFF acne disability index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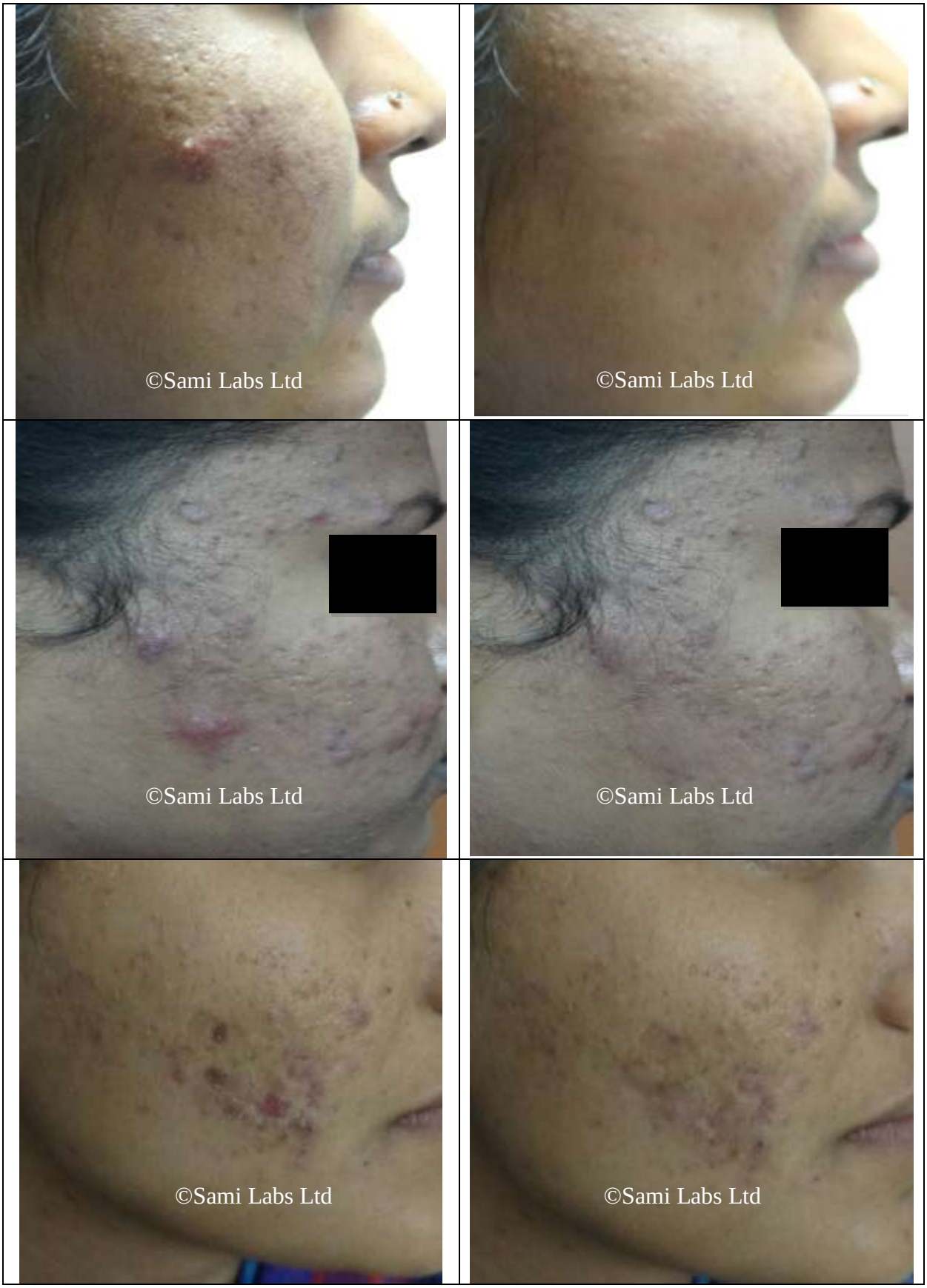

Figures 5: In the left column samples of "before treatment" and in right column the respective samples of "after treatment".

DISCUSSION

Acne vulgaris (acne) remains common in dermatology practice. Lifetime prevalence estimates range from 73.3% to almost 100%. Although acne most frequently occurs in adolescence, over 40% of men and women experience acne in their 20s and a significant percentage of patients, especially women continue to be affected well into adulthood.[10]

A number of factors need to be considered when selecting therapy, including severity of lesions, duration of disease, past and present response to treatment and any tendency for scarring or post inflammatory pigmentation.

Many Allopathic drugs and their combination therapies are used in the treatment of acne vulgaris like Adapalene, Retinoic acid containing drugs, Clindamycin, Benzoyl peroxide and many more are used in suitable formulations. But the problem with these drugs and their combination therapies is that they have recorded side effects.[11]

The introduction of novel formulations for the treatment of acne may produce many advantages over previously used therapies. The current study conducted for Anti-acne spot cream in patients with mild to moderate facial acne showed remarkable results.

All the efficacy endpoints - percent of change as per IGA scale, the percent change in inflammatory and non-inflammatory lesion count, mean change in CADI score and standardized clinical photography assessment showed positive results.

On Day 0 the Principal Investigator graded the IGA scale for all subjects on severity as moderate whereas at the end of the study only 8.6% subjects were graded moderate severity, 55.6% of subjects in mild severity and 38.9% subjects were graded as clear.

The percent change in inflammatory and non-inflammatory lesion count was found to be 63.8% and mean change was found to be statistically significant ($p<0.0001$) in total inflammatory and non-inflammatory lesion count as compared to baseline.

The quality of life was assessed using Cardiff Acne Disability Index questionnaire. The mean change from Day 0 in CADI score was found to be 5.4±3.1. The mean change in CADI score was statistically highly significant ($p<0.0001$) as compared to Day 0.

Out of 36 subjects, none reported any adverse event during the study tenure. There was no significant difference in vital signs from baseline till the end of the study. Hence it can be concluded that the anti-acne formulation was very effective in treating facial acne. It has shown significant effect in reducing the lesion counts without any side effects. Hence the formulation was safe for use.

The pathogenesis of acne vulgaris is multi factorial and hence this anti-acne spot cream can be beneficial in treating acne patients with mild to moderate facial acne.

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