

## Original Research Article

# Clinical trial of combination therapy for the efficacy, safety, tolerability and improvements in quality of life in patients with moderate to severe plaque psoriasis

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## ABSTRACT

**Background:** Psoriasis is an autoimmune disorder with clinical manifestations scales, inflammation and dryness. The psoriatic skin behaves differently in concurrence with circadian rhythm. Cell division increases in late night and early morning hours. Enzymatic activity will be more during day time. To balance these variations a 24×7 protection is required. The objective of the present study is to find the improvement in Psoriasis condition with the Combination therapy compared to single drug usage.

**Methods:** A clinical trial for 4 weeks was conducted among psoriasis patients with psorolin oil vs. combination therapy (Dr. JRK's 777 oil, psorolin ointment, psorolin oil and psorolin medicated bathing bar) and the clinical relief was measured among both groups by following parameters like psoriasis area and severity index (PASI), Physician's global assessment (PGA), dermatology life quality index (DLQI), subjective self-assessment questionnaire (SSAQ) and subject investigational product feedback questionnaire (SIPFBQ).

**Results:** Combination therapy (1-3-2 topical therapy) of Dr. JRK's 777 oil, psorolin ointment, psorolin oil and psorolin medicated bathing bar as a treatment regimen was found to be more effective in the treatment of psoriasis.

**Conclusions:** 1-3-2 topical therapy is useful in severe psoriasis conditions and recommended for long term effective treatment of psoriasis.

**Keywords:** Psoriasis, Clinical study, Psorolin, Dr. JRK's 777 oil, Topical therapy

## INTRODUCTION

Psoriasis is a chronic inflammatory disease that is mediated by aberrant immune responses and driven by self-perpetuating cytokine networks.<sup>1</sup> Around 1-3% of adults are being affected by this disease. Plaques, inflammation, dry skin and pruritis are the major clinical symptoms seen in psoriasis conditions. Pruritus has been reported to increase the risk of depression in some patients and can negatively affect patient quality of life.<sup>2,3</sup>

Various surveys on satisfaction of patients currently taking oral/topical medication remains low regarding

efficacy and safety.<sup>4</sup> There is a need for the safe and efficacious medication for the psoriasis patients to improve the quality of life.

The exact cause for psoriasis is not known but environmental, genetic and immune system factors play a major role in psoriasis. Circadian rhythm plays a major role in psoriasis i.e. in keratinocyte proliferation and enzymatic activities. The cell proliferation is high during the early morning hours and late night whereas enzymatic activity was more during day time.<sup>5</sup> To overcome the influence of circadian rhythm, the medication for Psoriasis should consider the effects of Circadian rhythm.

Dr. JRK's 777 oil, Psorolin oil, Psorolin ointment and Psorolin medicated bathing bar combination will help in decreasing the keratinocyte proliferation, enzymes that trigger the psoriasis, soothe the skin and reduce itching and keep the skin moisturized. This combination will give 24x7 protection to the psoriatic skin. The combination will increase the bio-burden and bioavailability of actives on the skin.

The combination of these drugs will help in faster onset of remission and improve the quality of life for psoriatic patients. Present clinical trial was done for this combination therapy to understand the efficacy, safety and improvements in quality of life in psoriatic patients. Findings of the clinical trial were presented in the paper.

**METHODS**

**Study design and participants**

Present study (ref- CTRI/2014/10/005143) is an open label, prospective, randomised, two arm clinical study to evaluate the efficacy, safety and tolerability of standalone therapy of psorolin oil in comparison with the additional

benefits of the combination therapy of Dr. JRK's 777 oil, psorolin medicated bathing bar, psorolin oil and psorolin ointment in adult subjects with moderate to severe psoriasis.

The study had two treatment arms

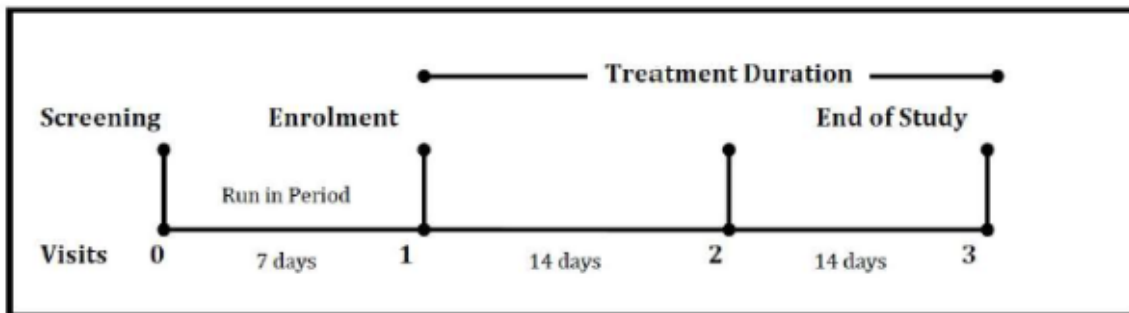
*Treatment arm I:* Mono therapy: Psorolin oil

*Treatment arm II:* Combination therapy:

- Dr. JRK's 777 oil
- Psorolin medicated bathing bar
- Psorolin oil
- Psorolin ointment

Study was initiated on 26<sup>th</sup> January 2015 and completed on 06<sup>th</sup> June 2015. 48 subjects were enrolled into the study and randomized into two treatment arms in a 2:1 ratio. 32 subjects were randomized into treatment arm I and 16 subjects were randomized into treatment arm II.

The study was designed to have duration of 5 weeks comprising of 4 weeks of treatment period. The treatment duration was divided into 4 visits with objective and subjective assessments at every visit.



**Figure 1: Study design.**

**Visit 0 - Screening visit**

Informed consent process was undertaken for patients with moderate to severe psoriasis before screening procedures. The informed consent document was also made available in vernacular language for the ease and convenience of the subject. The investigator and the study team also explained the procedures of clinical study to the subject. Each participant was given ample time to read, understand and clarify their doubts, before agreeing to participate in the clinical study by signing the informed consent document.

All screening procedures were initiated only after the written informed consent was obtained. Demographic details and vital signs were recorded. PASI (Psoriasis Area and Severity Index) was recorded by the investigator upon physical examination of the subjects. Based on the PASI score, the subject was selected to be enrolled into study. Subjects were instructed to refrain from use of any products meant for the

management/treatment of psoriasis during the run-in period.

**Visit 1 - Enrolment and randomization visit**

After verification of the study criteria, subjects were enrolled. Enrolled subjects were randomized to either of the two treatment arms in a 2:1 ratio. Objective assessment such as PASI and PGA (Physician's Global Assessment) were undertaken. Subjective assessment such as DLQI (Dermatology life quality index) and SSAQ (Subjective self-assessment questionnaire) were undertaken. Investigational product was dispensed along with the IPCC (Investigational product compliance card) as per the randomization schedule.

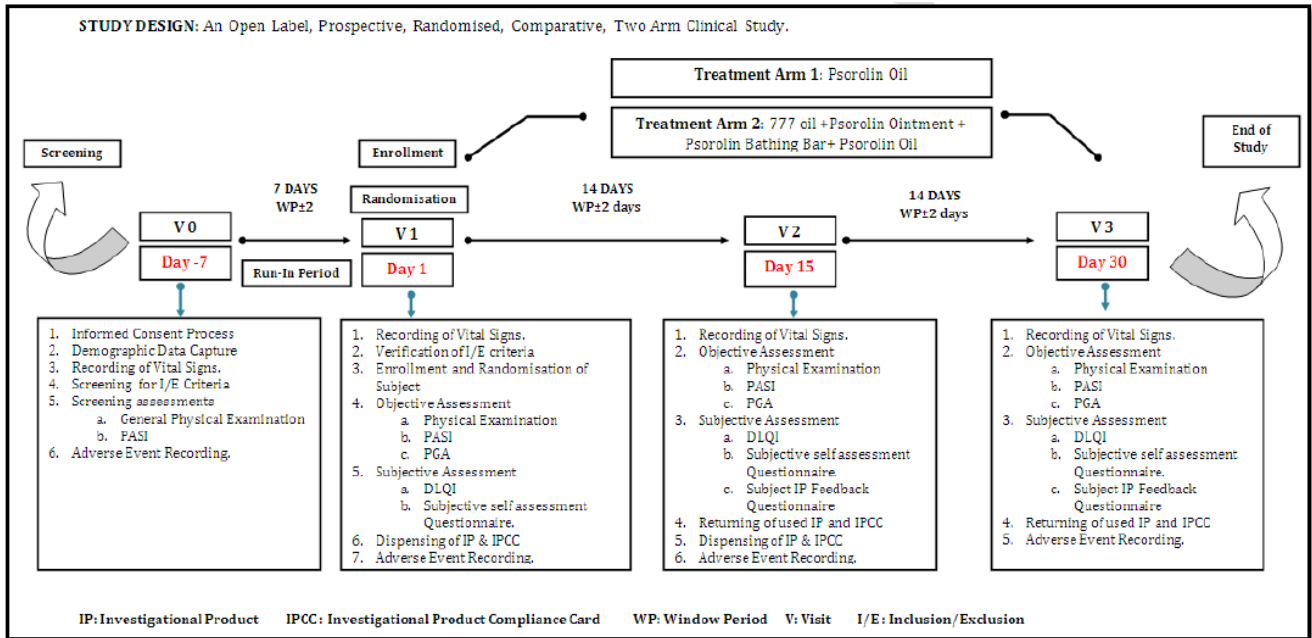
**Visit 2 - Improvement metrics<sup>6-8</sup>**

Improvement metrics using the same assessments as in visit 1 were undertaken— objective assessment such as PASI, PGA and subjective assessment such as DLQI,

SSAQ along with SIPFBQ (Subject IP feedback questionnaire) were undertaken. Used IP containers were collected along with filled IPCC and IP was dispensed for the next 14 days.

**Visit 3 - End of study visit**

Same assessments as in visit 2 were undertaken- objective assessment such as PASI, PGA and subjective assessment such as DLQI, SSAQ, SIPFBQ were undertaken. Used IP containers were collected along with filled IPCC. This visit marked the end of the study and no investigational product was dispensed.



**Figure 2: Schematic representation of study design.**

**Criteria for evaluation**

**Primary end points**

**Objective assessments**

- Psoriasis area and severity index (PASI): PASI 75 or 75% improvement from visit 1 to end of study.
- Physician’s global assessment (PGA): Score of 2 or less from visit 1 by end of study.

**Subjective assessments**

- Dermatology life quality index (DLQI): Score 0-8 by end of study.
- Subjective self - assessment questionnaire: Increase of ≥12 scores from Visit 1 to end of study.
- Subject IP feedback questionnaire: Score ≥12 by end of study.

**Secondary end points**

**Objective assessments**

- Psoriasis area and severity index (PASI): PASI 50 or 50% improvement from visit 1 to end of study.

- Physician’s global assessment (PGA)): Score of 3 or 4 from visit 1 to end of study.

**Subjective assessments**

- Dermatology life quality index (DLQI): Score 9-16 by end of study.
- Subjective self- assessment questionnaire: Increase in score of 8-11 by end of study.
- Subject IP feedback questionnaire: Score 8-11 by end of study.

**Statistical analysis**

Statistical tests were carried out at 5% level of significance with a two-sided hypothesis. Descriptive measures such as mean, standard deviation and proportions were used to model the basic characteristics of the subject/sample. Socio-demographic balance of the sample was considered at this stage. The statistical software SAS V-9.1.3 was used to analyze both parametric and non-parametric tests. Repeated measures ANOVA and ANCOVA were used, 95% confidence intervals were provided for the estimated parameters.

All patients provided written informed consent. The protocol and consent were approved by institutional

review boards/ethics committees (*Universal Ethics*) at all investigational sites.

The study was conducted in accordance with the ethical principles as laid out in the current version of the Declaration of Helsinki, ICH harmonised tripartite guideline – guideline for good clinical practice E6 (R1) and ICMR (Indian Council for Medical Research) ethical

Guidelines for biomedical research on human participants and schedule Y of drugs and cosmetics rules, (V Amendment), 2014. The study was registered in CTRI (clinical trial registry of India).

## RESULTS

48 subjects with moderate to severe psoriasis (PASI score: 31-45) was considered for the study and 4 weeks of treatment was given. The improvement in the condition of psoriasis was measured using tools such as PASI (Psoriasis Area and Severity Index), PGA (Physician's global assessment, DLQI (Dermatology life quality of index). Such assessment criteria have been validated as the gold standard for evaluating the improvement in psoriatic condition.

Improvements in various conditions are as follows.

**Table 1: Improvement in PASI (%).**

Visits	Mono therapy		Combination therapy	
	Improvement	Standard deviation	Improvement	Standard deviation
1-2	57.74	1.189	64.28	1.61
2-3	62.05	1.882	65.23	4.39
1-3	83.93	1.055	87.61	1.39

There is 87.61% improvement in PASI score with combination therapy in third visit.

**Table 2: Improvement in PGA.**

Visits	Mono therapy		Combination therapy	
	Improvement	Standard deviation	Improvement	Standard deviation
1-2	1.66	0.97	1.81	0.75
2-3	1.34	0.48	2.31	0.48
1-3	3	0.84	4.13	0.62

There is 4.13 improvement in PGA index in third week.

**Table 3: Improvement in DLQI.**

Visits	Mono therapy		Combination therapy	
	Improvement	Standard deviation	Improvement	Standard deviation
1	19.44	1.61	19.50	1.67
2	14.72	2.26	12.44	1.86
3	6.25	1.14	4.94	0.93
1-3	13.19	1.96	14.56	1.21

**Table 4: Improvement in SSAQ.**

Visits	Mono therapy		Combination therapy	
	Improvement	Standard deviation	Improvement	Standard deviation
1	2.97	0.86	3.13	0.96
2	10.34	1.38	11.38	0.89
3	15.84	1.27	17.13	1.02
1-2	7.38	1.54	8.25	1
2-3	5.50	1.08	5.75	1.06
1-3	12.88	1.18	14	0.82

**Table 5: Improvement in SSIPFBQ.**

Visits	Mono therapy		Combination therapy	
	Improvement	Standard deviation	Improvement	Standard deviation
2	9.41	1.13	9.50	1.15
3	14.56	2.40	17	1.03
2-3	5.16	1.90	7.50	0.52

There is a great improvement in DLQI, SSAQ and SSIPFBQ in combination therapy compared to mono therapy.

Statistical analysis of clinical data for Combination Therapy - Dr. JRK's 777 oil, psorolin ointment, psorolin oil, psorolin MBB vs mono therapy - psorolin oil.

**Table 6: Statistical analysis of clinical data.**

Measurement parameters	Z value	P value
PASI	5.60	<0.05
PGA	-6.30	<0.05
DLQI	0.00	1
SSAQ	0.00	1
SSIPFBQ	0.00	1

## DISCUSSION

In the present clinical trial, the combination therapy of Dr. JRK's 777 oil, Psorolin ointment, Psorolin oil and Psorolin medicated bathing bar was evaluated for treatment benefit in psoriasis conditions. Psoriasis is a chronic and complex condition and medication for the same should be able to address various factors in psoriasis.

Faster and significant improvement was observed in 4 weeks' treatment with combination therapy. Even though the significant improvement was seen in monotherapy the patient satisfaction was more with combination therapy.

The combination therapy we evolved based on circadian rhythm. Psoriasis problem is linked with circadian rhythm. Therefore, circadian rhythm has to be corrected to treat the psoriasis.

Psoriasis is an autoimmune disorder that has deposition of immature, non-functioning hyper proliferated keratinocytes. In psoriasis normal keratinocytes cell cycle will reduce from 28 days to 3 days. Keratinocytes proliferation does vary in day and night which shows the influence of circadian rhythm on keratinocytes. If the treatment is able to link with the proliferating time of keratinocytes, then the treatment success will be more in controlling the keratinocytes proliferation and enzymatic activities.

In psoriasis, inflammation occurs in the skin, leading to the red, itchy and scaly patches known as plaques.<sup>9</sup> This attack is carried out by cytokines, which are proteins that help control the immune system's inflammatory response. Cytokines trigger inflammation, causing the blood vessels to expand and send more immune cells to different parts of the body.

Certain enzymes like elastase are also involved in psoriasis that causes aging and play a significant role in cell damage and other barrier functioning of the skin.

These enzymes also trigger the inflammation reactions and thus elastase inhibition is required in psoriasis condition. These enzymes release differ significantly in day and night. The treatment products combination should have potential to address various factors that affect psoriatic conditions.

The combination drugs such as Dr. JRK's 777 oil, Psorolin ointment, Psorolin oil and Psorolin medicated bathing bar are proprietary Siddha formulations of Dr. JRK's Research and Pharmaceuticals Pvt., Ltd., Chennai. The Dr. JRK's 777 oil is composed of oil extracts of *Wrightia tinctoria*. Psorolin oil is composed of extracts of *Wrightia tinctoria*, *Indigofera tinctoria* and *Indigofera asphalathoids*. The Psorolin ointment is composed of *Wrightia tinctoria* and *Cynodon dactylon*. Psorolin medicated bathing bar is a super fatted bar with 10% each of *Wrightia tinctoria* and *Aloe vera* thailam.

Each product in combination has significant role in reducing the effects of psoriasis condition. The combination will help to overcome the influence of circadian rhythm in psoriasis. The usage of the combination is according to the response of body to circadian rhythm.

Dr. JRK's 777 oil has to be used as a pre-bath oil. This will remove the dead deposited keratinocytes on the skin caused due to high proliferation during late night and early morning hours. It also reduces the keratinocyte proliferation.

Bathing with Psorolin medicated bathing bar will exfoliate the scales and opens up the pores for further treatment. Herbal actives present in it will help in reducing the proliferation and soothing of skin.

After bath, Psorolin oil followed by Psorolin ointment has to be applied. Psorolin oil is reduces the keratinocytes proliferation and Psorolin ointment significantly reduces the elastase enzyme activity.<sup>10</sup>

Thus this combination will give complete day protection to the psoriatic skin and this will help in limiting the circadian rhythm influence in psoriasis treatment.

In current clinical trial in 30 days, the combination therapy shows great improvement of 87.61% in PASI score with a standard deviation of 1.39 whereas with monotherapy its 83% improvement with a standard deviation of 1.05. PGA score, which is the overall improvement in psoriasis conditions shows 4.13 for combination therapy with a standard deviation of 0.62 and for monotherapy its 3 with a standard deviation of 0.84.

The subjective feedback from all the subjects shows that DLQI, SSAQ and SSIPFBQ with combination therapy is 14.15, 14 and 7.50 with a standard deviation of 1.21, 0.82 and 0.52 respectively. With monotherapy DLQI, SSAQ

and SSIPFBQ is 13.19, 12.88 and 5.16 with a standard deviation of 1.96, 1.18 and 1.90.

The statistical analysis shows that combination therapy was found to be more effective than mono therapy, showing statistical significance in PASI and PGA parameters.

Where as in parameters such as DLQI, SSAQ and SSIPFBQ it shows there is no statistical difference between the two therapies however effectiveness of combination therapy was found to be considerably higher than monotherapy.

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*Ethical approval: The study was approved by the Institutional Ethics Committee*

## REFERENCES

1. Sobell JM1, Foley P, Toth D, Mrowietz U, Girolomoni G, Goncalves J, et al. Effects of Apremilast on Pruritus and Skin Discomfort/Pain Correlate with Improvements in Quality of Life in Patients with Moderate to Severe Plaque Psoriasis. *Acta Derm Venereol*. 2016;96:514–20.
2. Lebwohl MG, Bachelez H, Barker J, Girolomoni G, Kavanaugh A, Langley RG, et al. Patient perspectives in the management of psoriasis: results from the population based Multinational Assessment of Psoriasis and Psoriatic Arthritis Survey. *J Am Acad Dermatol*. 2014;70:871–81.
3. Reich A, Hrehorow E, Szepietowski JC. Pruritus is an important factor negatively influencing the well-being of psoriatic patients. *Acta Derm Venereol*. 2010;90:257–63.
4. Parisi R, Symmons DP, Griffiths CE, Ashcroft DM. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. *J Invest Dermatol*. 2013;133:377–85.
5. Gelfant S, Ozawa A, Chalker DK, Smith JG. Circadian rhythms and differences in epidermal and dermal cell proliferation in uninvolved and involved psoriatic skin in vivo. *J Invest Dermatol*. 1982;78:58-62.
6. Schafer I, Hacker J, Rustenbach SJ, Radtke M, Franzke N, Augustin M. Concordance of the Psoriasis Area and Severity Index (PASI) and patient-reported outcomes in psoriasis treatment. *Eur J Dermatol* 2010;20:62–7.
7. Basra MK, Salek MS, Camilleri L, Sturkey R, Finlay AY. Determining the minimal clinically important difference and responsiveness of the Dermatology Life Quality Index (DLQI): further data. *Dermatology*. 2015;230:27–33.
8. Hongbo Y, Thomas CL, Harrison MA, Salek MS, Finlay AY. Translating the science of quality of life into practice: What do dermatology life quality index scores mean? *J Invest Dermatol*. 2005;125:659–64.
9. Kuchekar AB, Pujari RR, Kuchekar SB, Dhole SN, Mule PM. Psoriasis: A comprehensive review. *Int J Pharmacy Life Sci*. 2011;2(6):857-77.
10. Amruthavalli GV, Rajagopal G. Reference of Circadian Rhythm in the Treatment of Psoriasis – A Novel Insight. *Res Rev: A J Unani, Siddha Homeopathy*. 2015;2(2):1–7.

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