



# Efficacy and Safety of Novel Formulation of Clobetasol Propionate 0.025% Cream in Indian Moderate-to-Severe Psoriasis Patients: Phase-2a, Randomized 3-Arm Study

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## ABSTRACT

**Introduction:** Clobetasol propionate (0.05% standard dose formulation), a topical corticosteroid, leads to systemic side-effects like hypothalamic–pituitary–adrenal (HPA) axis

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suppression at doses as low as 2 g/day. The aim of this study was to evaluate HPA axis suppression, efficacy, and safety of clobetasol propionate (0.025%, formulation 5 and 13) versus currently marketed 0.05% cream in Indian patients with moderate-to-severe psoriasis.

**Methods:** In this phase 2a investigator-blinded study, patients aged  $\geq 18$  years with moderate-to-severe psoriasis were randomized 1:1:1 to receive clobetasol propionate 0.025% formulation 5, or 13, or 0.05% cream; twice daily for 28 days. Safety endpoints included adrenocorticotrophic hormone (ACTH) test results at day 28 (primary), and local tolerability at each visit (burning/stinging/pruritus, secondary). Efficacy endpoints included Psoriasis Global Assessment (PGA) score.

**Results:** Overall, 88 patients received clobetasol propionate 0.025% formulation 5 and 13 ( $n = 29$  for both) and 0.05% cream ( $n = 30$ ). At day 28, the proportion of patients with an abnormal ACTH stimulation test (cortisol levels  $\leq 18$   $\mu\text{g}/\text{dl}$ ) was numerically lower in 0.025% formulations: 5 (20.7%) and 13 (17.2%) compared with 0.05% cream (30.0%), ( $p = 0.320$ ). Decrease in burning/stinging /pruritus scores were comparable in all treatment groups and PGA success rates were higher with 0.025% formulations: 5 (38.9%) and 13 (36.8%) compared with 0.05% cream (30.8%).

**Conclusion:** Clobetasol propionate 0.025% could be an effective treatment for moderate-to-severe psoriasis compared with 0.05% cream,

demonstrating comparable efficacy with a better systemic safety profile.

**Trial Registration Number:** REF/2018/01/016779.

**Keywords:** Clobetasol propionate 0.025%; Clobetasol propionate 0.05%; Hypothalamic–pituitary–adrenal axis suppression; Moderate-to-severe psoriasis; Psoriasis Global Assessment; Novel formulation

### Key Summary Points

We aimed to evaluate and compare hypothalamic–pituitary–adrenal (HPA) axis suppression, safety and efficacy of two novel formulations of clobetasol propionate 0.025% cream (formulation 5 [Impoyz<sup>®</sup>] and formulation 13) with the currently marketed clobetasol propionate 0.05% emollient cream (reference formulation) in Indian patients with moderate-to-severe psoriasis.

Two clobetasol formulations, formulation 5 and formulation 13, has similar efficacy and an improved systemic safety profile compared to the clobetasol propionate 0.05% (Temovate E<sup>®</sup>) cream in terms of HPA axis suppression.

Our study findings support the use of novel clobetasol propionate 0.025% cream formulations (formulation 5 and formulation 13) as an effective and safer treatment option for patients with moderate-to-severe psoriasis.

## INTRODUCTION

Psoriasis is a chronic autoimmune skin disorder affecting approximately 0.44–2.8% of the adult population in India [1–3]. The prevalence of psoriasis varies across countries from 0.09–11.43%, leading to a serious global burden with a significant negative impact on patients' quality of life [4]. The symptoms of psoriasis may occur anywhere on the body and are often

characterized by chronic, sharply demarcated, and erythematous scaly plaques that are often painful and severely pruritic [2, 5]. Although not life threatening, these persistent symptoms affect physical, psychological, and social functioning and remain a major challenge to treat in patients with disease complications [6, 7]. The majority of the patients affected with mild [Psoriasis Area Severity Index (PASI)  $\leq 10$ ] to moderate (PASI  $> 10$  but  $\leq 20$ ) psoriasis are generally recommended for treatment with topical therapies such as corticosteroids and vitamin D3 analogs [2, 8, 9]. The systemic therapies including phototherapy, acitretin, methotrexate, cyclosporine, or biologic therapy are recommended for severe psoriasis. However, patients on systemic or phototherapies are adjunctively treated with topical therapies based on the psoriasis severity, body location, lesion thickness, degree of erythema, and amount of scaling [6, 9, 10]. Topical corticosteroids are the most commonly prescribed medication for patients with moderate-to-severe psoriasis and several different types of formulations are currently available [11]. Clobetasol propionate, an ultra-high potent (super potent) topical corticosteroid compared with other corticosteroids, has demonstrated effective and rapid healing of psoriasis [12–16].

The super-high potency of clobetasol propionate 0.05% emollient cream leads to greater systemic absorption, which might result in higher risk of systemic side-effects such as hypothalamic–pituitary–adrenal axis (HPA) suppression, even at the recommended dose as low as 2 g/day. This systemic side-effect has generally limited the clinical use of clobetasol propionate 0.05% cream in patients to small areas and only for a single period not exceeding 2 weeks [15]. Therefore, there is an unmet need to develop novel formulations containing 0.025% concentrations of clobetasol propionate, which would provide a favorable benefit-risk profile. In a recent phase 2, randomized, open-label clinical study conducted in the US, treatment with clobetasol propionate 0.025% (Impoyz<sup>®</sup>) cream had a lower systemic absorption, resulting in lower incidence of HPA axis suppression, with a better safety profile compared with marketed clobetasol propionate

0.05% (Temovate<sup>®</sup>) cream in patients with moderate-to-severe psoriasis [17].

In this study, we aimed to evaluate and compare HPA axis suppression, safety, and efficacy of two formulations of clobetasol propionate 0.025% cream [formulation 5 (Impoyz<sup>®</sup>) and formulation 13] with the currently marketed clobetasol propionate 0.05% emollient cream (reference formulation) in Indian patients with moderate-to-severe psoriasis.

## METHODS

### Patients

The study included adults aged  $\geq 18$  years with a clinical diagnosis of moderate-to-severe psoriasis involving at least 25% body surface area (BSA, excluding scalp, face, groin, axillae, and/or other intertriginous areas involvement, if present). Other inclusion criteria were a Psoriasis Global Assessment (PGA) score of  $\geq 3$  at screening and baseline, and no evidence of abnormal HPA axis function [confirmed by adrenocorticotrophic hormone (ACTH) test] at screening.

Patients who were hypersensitive to clobetasol propionate, or who had a history of psoriasis that was unresponsive to topical corticosteroid therapy, or who had experienced adverse drug reaction to cosyntropin injection (adrenocorticotrophic hormone) were excluded from the study. Patients who had a known history of acute adrenal crisis, Addison's disease, atopic/contact dermatitis, liver disease, renal impairment, heart disease, diabetes, severe respiratory disease, rheumatoid arthritis, malignancies, and immunocompromised conditions were also excluded from the study. Other exclusion criteria were pregnant/lactating women; patients who were treated with radiation therapy or anti-neoplastic agents, or immunosuppressants (within 4 weeks prior to study treatment), antipsoriatics (within 8 weeks of study treatment), biological therapies (within 12 weeks prior to study treatment), and topical corticosteroids (within 2 weeks prior to screening) to ensure complete washout of previously

administered drugs to prevent drug interactions.

### Study Design

This was a phase 2a, randomized, multicenter, active-controlled, investigator-blinded, parallel group, 3-arm study of two formulations of clobetasol propionate 0.025% cream (formulations 5 and 13) and clobetasol propionate 0.05% cream, in patients with moderate-to-severe psoriasis. This study is registered as REF/2018/01/016779. The study was conducted to compare HPA axis suppression, safety, and efficacy of twice daily use of clobetasol propionate 0.025% formulations (formulations 5 and 13; manufactured by Dr. Reddy's Laboratories) with the reference formulation (clobetasol propionate 0.05% cream; manufactured by PharmaDerm). The study comprised a 7-day screening period, a 28-day treatment schedule and a 14-day follow-up period.

The study protocol and informed consent form were reviewed and approved by an Independent Ethics Committee and Institutional Review Board at all six study sites (please see supplementary material for full details). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and per the International Council for Harmonization and Good Clinical Practice guidelines. Informed consent forms were reviewed and approved by all the appropriate Ethics Committees prior to enrolment of the patients into the study.

### Study Assessments

The primary safety endpoint included proportion of patients with abnormal cortisol levels in response to the ACTH test ( $\leq 18$   $\mu\text{g}/100$  ml) at day 28. Secondary safety endpoints included time to abnormal cortisol value and change from baseline in signs of atrophogenicity at days 7, 14, 21, and 28. The local cutaneous atrophogenic activity of the drug was determined by the investigator using visual assessment at planned visits. The effect of the study medication was graded on a scale of 0 (none) to

3 (pronounced) for atrophy and 0 (none) to 4 (pronounced) for telangiectasia. Adverse events (AEs), physical examination, vital signs, clinical laboratory investigations, and local tolerability (rating of burning/stinging and pruritus by the patient) were also recorded. The degree of burning/stinging and pruritus were scored on a scale of 0 (none) to 3 (severe).

Secondary efficacy endpoints included proportion of patients with clear or almost clear skin as assessed by PGA, mean PGA score, and distribution of PGA scores at each time point. Clinical determination of disease severity using the PGA scale was performed by the investigator at planned visits. The PGA was scored with five severity grades on a scale of 0 (clear) to 4 (moderate-to-severe).

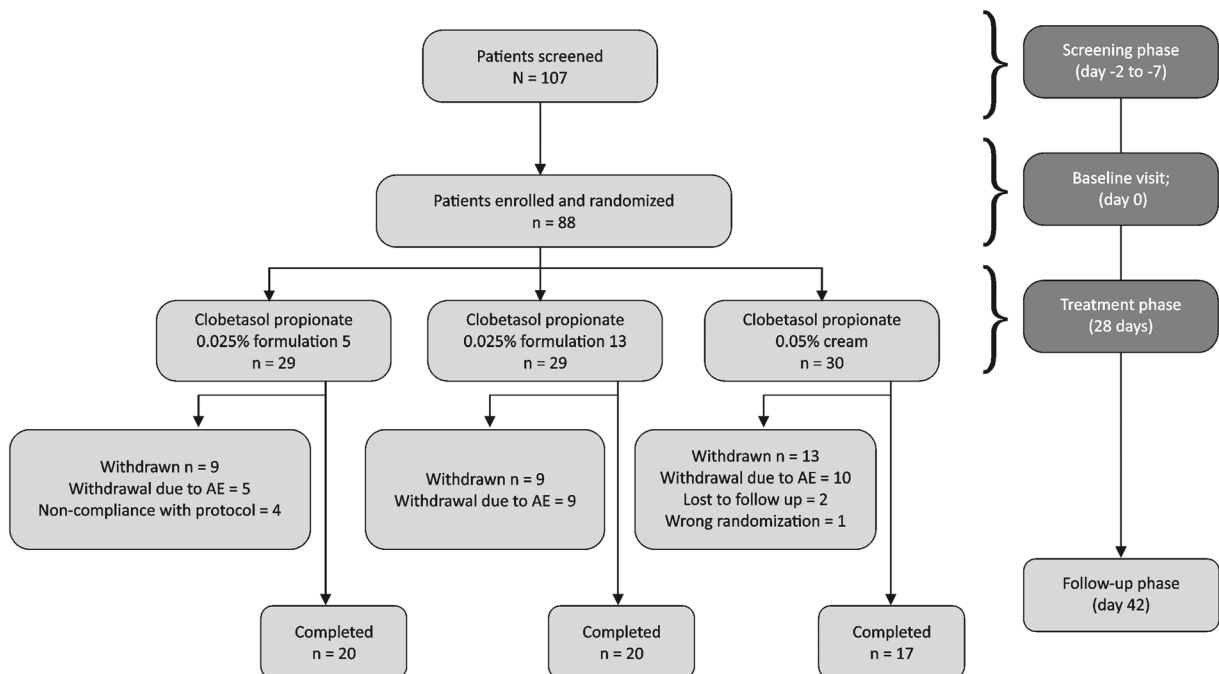
### Treatment, Randomization and Blinding

Formulation 13 consisted of 0.025% clobetasol propionate with inactive ingredients like stearyl alcohol, cetyl alcohol, glyceryl stearate and PEG-100 stearate, lanolin, mineral oil, sorbitol,

butylated hydroxytoluene, diethylene glycol monoethyl ether, methyl paraben, propyl paraben, and purified water. Formulation 5 consisted of 0.025% clobetasol propionate with inactive ingredients like cetostearyl alcohol, glyceryl stearate and PEG-100 stearate, white wax, butylated hydroxytoluene, isopropyl myristate, cyclomethicone, diethylene glycol monoethyl ether, methyl paraben, propyl paraben, and purified water.

Patients were randomized 1:1:1 (using PROC PLAN in SAS, version 9.2) to clobetasol propionate 0.025% formulation 5, formulation 13 or clobetasol propionate 0.05% cream. Patients were instructed to topically apply the study medication twice daily for 28 days to the target lesion areas (at least 25% BSA), which were identified by the study investigator. The study products were applied in the form of fingertip unit (~ 0.5 g). Patients were asked to apply seven fingertip units in order to cover 25% BSA (3.5 g).

The treatments were blinded by obscuring the commercial labeling of comparator



**Fig. 1** Study design and patient characteristics. *AE*, adverse events

**Table 1** Patient demographic (safety population)

Characteristics	Clobetasol propionate 0.025% cream		Clobetasol propionate 0.05% cream ( <i>N</i> = 30)	All ( <i>N</i> = 88)
	Formulation 5 ( <i>N</i> = 29)	Formulation 13 ( <i>N</i> = 29)		
Age (years)				
Mean (SD)	44.1 (16.88)	47.0 (13.49)	39.1 (10.51)	43.3 (14.06)
Gender				
Women, <i>n</i> (%)	10 (34.5)	11 (37.9)	11 (36.7)	32 (36.4)
Men, <i>n</i> (%)	19 (65.5)	18 (62.1)	19 (63.3)	56 (63.6)
Race				
Asian, <i>n</i> (%)	29 (100.0)	29 (100.0)	30 (100.0)	88 (100.0)
Height (cm)				
Mean (SD)	163.7 (8.37)	164.3 (8.02)	163.0 (6.47)	163.6 (7.58)
Weight (Kg)				
Mean (SD)	59.9 (9.69)	64.8 (11.32)	61.4 (11.49)	62.0 (10.93)

*SD* standard deviation.

products by the study label. The investigator was blinded to the treatment code until database lock.

### Statistical Analysis

A total of 90 patients were planned to be randomized (1:1:1) to clobetasol propionate 0.025% formulation 5, formulation 13, or clobetasol propionate 0.05% cream. Efficacy assessments were analyzed in the per-protocol (PP; defined as all randomized patients who completed both baseline and end of treatment visit and who had no major protocol violations) and modified intention-to-treat (mITT; all randomized patients who received study medication and had at least one post randomization measurement) populations. Safety assessments were conducted in the safety population (all patients randomized at baseline visit who received at least one dose of study medication). The SAS® program (SAS® Institute Inc., USA, and Version 9.2) was used for statistical evaluation. The proportion of patients with abnormal ACTH stimulation and with clear or almost

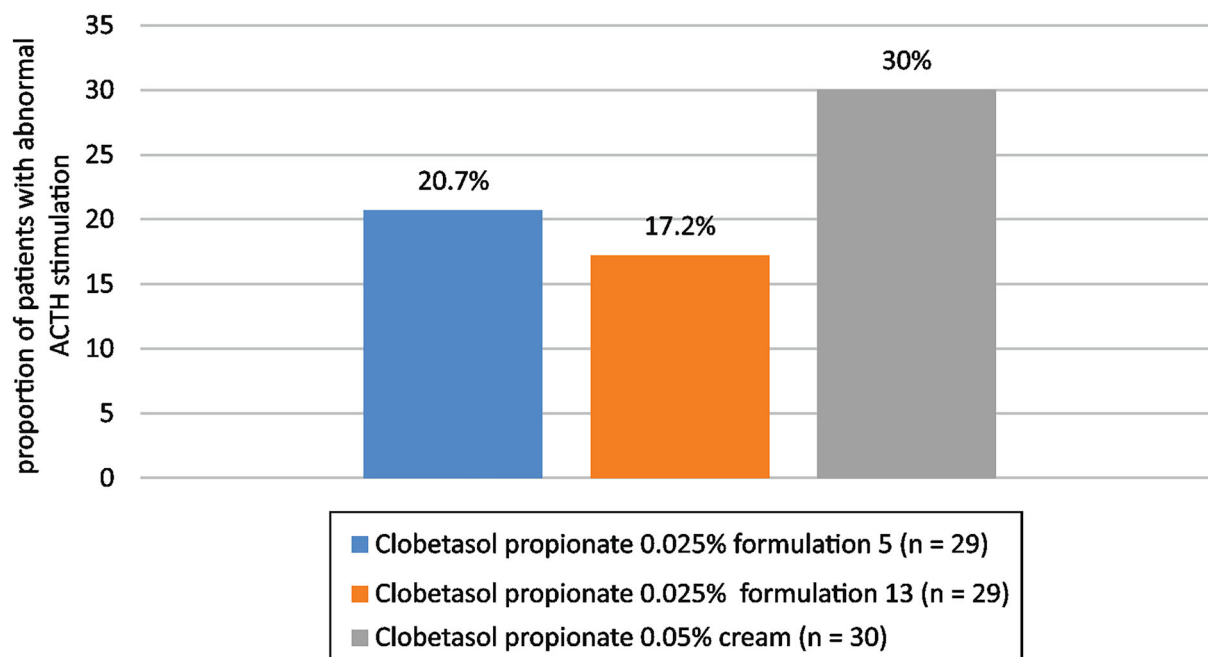
clear PGA at each time point was compared between groups using a chi-square test (Fisher's exact test). The Marascuillo procedure was used for pair-wise comparisons (clobetasol propionate 0.025% formulation 5 vs clobetasol propionate 0.05% cream and clobetasol propionate 0.025% formulation 13 vs clobetasol propionate 0.05% cream).

## RESULTS

### Patient Disposition and Baseline Characteristics

This study was conducted at six centers in India between April 2011 and October 2011. A total of 107 patients were screened, of which 88 were enrolled and randomized to clobetasol propionate 0.025% formulation 5 (*n* = 29), clobetasol propionate 0.025% formulation 13 (*n* = 29) and clobetasol propionate 0.05% cream (*n* = 30), of which 57 (64.8%) patients completed the study (Fig. 1). The major reason for screen failure was patients not meeting the study selection criteria





Visit	ACTH result	Clobetasol propionate 0.025% formulation 5 n = 29	Clobetasol propionate 0.025% formulation 13 n = 29	Clobetasol propionate 0.05% cream n = 30	P-value
Screening	Abnormal	1 (3.4)	0	0	0.320
	Normal	28 (96.6)	29 (100)	30 (100)	
Visit 6 (day 28)	Abnormal	6 (20.7)	5 (17.2)	9 (30.0)	0.320
	Normal	20 (69.0)	24 (82.8)	17 (56.7)	
Time to abnormal cortisol, mean (SE)		23.2 (1.3)	17.5 (1.3)	12.3 (0.7)	0.592

**Fig. 2** Proportion of patients with abnormal ACTH stimulation at day 28 (per protocol population). All values are presented in *n* (%). *ACTH*, adrenocorticotropic hormone; *SE*, standard error

or patients not having appropriate medication-specific washout at the baseline visit. Of the 31 patients (35.2%) who discontinued the study, 77.4% withdrew due to AEs [clobetasol propionate 0.025% formulation 5 (*n* = 5), clobetasol propionate 0.025% formulation 13 (*n* = 9) and clobetasol propionate 0.05% cream (*n* = 10)] (Fig. 1). The baseline demographics and clinical characteristics of all enrolled patients were comparable across treatment groups. The majority of patients were men (63.6%), and all

patients were Asians with a mean age of 43.3 years (Table 1).

### Safety

At day 28, the proportion of patients with an abnormal ACTH stimulation test (cortisol levels  $\leq 18$   $\mu\text{g}/\text{dl}$ ) was numerically lower in the clobetasol propionate 0.025% formulation 5 (20.7%), and formulation 13 (17.2%) groups, compared with the clobetasol propionate 0.05%

**Table 2** Incidence of treatment-emergent adverse events (safety population)

TEAEs, <i>n</i> (%)	Clobetasol propionate 0.025% cream						Clobetasol propionate 0.05% cream			
	Formulation 5 ( <i>N</i> = 29)			Formulation 13 ( <i>N</i> = 29)			<i>N</i> = 30			
	Total	Treatment related	Probably related	Total	Treatment related	Probably related	Total	Treatment related	Probably related	
Patients with at least 1 TEAE	13 (44.8)	0	12 (41.4)	15 (50.0)	0	10 (34.5)	15 (50.0)	0	11 (36.7)	
TEAEs in > 3% of patients	0	0	0	0	0	0	2 (6.7)	0	0	
Pain	0	0	0	0	0	0	1 (3.3)	0	0	
Pyrexia	0	0	0	0	0	0	1 (3.3)	0	0	
Gastroenteritis	0	0	0	0	0	0	1 (3.3)	0	0	
Nasopharyngitis	0	0	0	0	0	0	2 (6.7)	0	0	
Tinea cruris	0	0	0	0	0	0	1 (3.3)	0	0	
Blood cortisol decrease	13 (44.8)	0	12 (41.4)	11 (37.9)	0	10 (34.5)	11 (36.7)	0	11 (36.7)	
Cough	0	0	0	0	0	0	2 (6.7)	0	0	
Pruritus	1 (3.4)	0	0	0	0	0	1 (3.3)	0	0	
Telangiectasia	0	0	0	0	0	0	1 (3.3)	0	1 (3.3)	
		<b>Mild</b>	<b>Moderate</b>	<b>Severe</b>	<b>Mild</b>	<b>Moderate</b>	<b>Severe</b>	<b>Mild</b>	<b>Moderate</b>	<b>Severe</b>
Proportion of patients with mild, moderate, and severe										
Patients with at least 1 TEAE	11 (37.9)	2 (6.9)	1 (3.4)	7 (24.1)	3 (10.3)	1 (3.4)	9 (30.0)	6 (20.0)	3 (10.0)	
Pain	0	0	0	0	0	0	0	0	1 (3.3)	
Pyrexia	0	0	0	0	0	0	1 (3.3)	0	0	
Gastroenteritis	0	0	0	0	0	0	1 (3.3)	0	0	
Nasopharyngitis	0	0	0	0	0	0	0	2 (6.7)	0	
Tinea cruris	0	0	0	0	0	0	1 (3.3)	0	0	
Blood cortisol decrease	10 (34.5)	2 (6.9)	1 (3.4)	7 (24.1)	3 (10.3)	1 (3.4)	6 (20.0)	4 (13.3)	1 (3.3)	
Hyperglycemia	1 (3.4)	0	0	0	0	0	0	0	0	
Cough	0	0	0	0	0	0	2 (6.7)	0	0	
Pruritus	1 (3.4)	0	0	0	0	0	0	0	1 (3.3)	
Telangiectasia	0	0	0	0	0	0	1 (3.3)	0	0	

TEAEs treatment-emergent adverse events.

**Table 3** Change from baseline in signs of atrophogenicity by visit (safety population)

Treatment	Baseline atrophy score	Change from baseline in signs of atrophogenicity by visit: Atrophy score								
		Visit 3 (day 7), n (%)			Visit 4 (day 14), n (%)			Visit 5 (day 21), n (%)		
		0	1	2	0	1	2	0	1	2
Clobetasol propionate 0.025% formulation 5	0 ( <i>n</i> = 26)	25 (96.2)	0	0	20 (76.9)	1 (3.8)	0	17 (65.4)	2 (7.7)	0
	1 ( <i>n</i> = 3)	0	3 (100)	0	0	3 (100.0)	0	1 (33.3)	2 (66.7)	0
Clobetasol propionate 0.025% formulation 13	0 ( <i>n</i> = 23)	22 (95.7)	0	0	15 (65.2)	2 (8.7)	0	12 (52.2)	3 (13.0)	0
	1 ( <i>n</i> = 5)	1 (20.0)	4 (80.0)	0	4 (80.0)	1 (20.0)	0	4 (80.0)	1 (20.0)	0
	2 ( <i>n</i> = 1)	0	0	1 (100)	1 (100)	0	0	1 (100)	0	0
Clobetasol propionate 0.05% cream	0 ( <i>n</i> = 26)	22 (84.6)	0	0	16 (61.5)	1 (3.8)	0	11 (42.3)	2 (7.7)	1 (3.8)
	1 ( <i>n</i> = 4)	1 (25.0)	3 (75.0)	0	2 (50)	2 (50.0)	0	4 (100)	0	0

Treatment	Baseline telangiectasia score	Change from baseline in signs of atrophogenicity by visit: Telangiectasia score								
		Visit 3 (day 7), n (%)			Visit 4 (day 14), n (%)			Visit 5 (day 21), n (%)		
		0	1	2	0	1	2	0	1	2
Clobetasol propionate 0.025% formulation 5	0 ( <i>n</i> = 29)	28 (96.6)	0	0	24 (82.8)	0	0	20 (69.0)	2 (6.9)	0
Clobetasol propionate 0.025% formulation 13	0 ( <i>n</i> = 28)	27 (96.4)	0	0	21 (75.0)	1 (3.6)	0	17 (60.7)	3 (10.7)	0
	2 ( <i>n</i> = 1)	0	0	1 (100)	1 (100)	0	0	1 (100)	0	0
TMV cream	0 ( <i>n</i> = 30)	26 (86.7)	0	0	21 (70.0)	0	0	16 (53.3)	2 (6.7)	0

0, none; 1, slight; 2, moderate; 3, pronounced; 4, very pronounced.

cream (30.0%) group, though the differences were not statistically significant ( $p = 0.320$ ) (Fig. 2). The mean (SE) time to abnormal cortisol value was longer in the clobetasol propionate 0.025% formulation 5 group [23.2 (1.3) days] and formulation 13 group [17.5 (1.3) days] when compared with the clobetasol propionate 0.05% cream group [12.3 (0.7) days], though the differences were not statistically significant ( $p = 0.592$ ). Overall, 44.8% (13/29) of patients in the clobetasol propionate 0.025% formulation 5 group, 50.0% (15/29) in the formulation 13 group, and 50% (15/30) of patients in clobetasol propionate 0.05% cream group experienced at least 1 treatment-emergent adverse event (TEAE) (Table 2). None of the AEs were

considered by the investigator as definitely related to the treatment. Decreased blood cortisol was the common AE reported in both the clobetasol propionate 0.025% formulation 5 (44.8%) and formulation 13 (37.9%) groups, and also in the clobetasol propionate 0.05% cream group (36.7%). Most of the AEs reported were mild in severity (37.9% in the clobetasol propionate 0.025% formulation 5 group, 24.1% in the clobetasol propionate 0.025% formulation 13 group, and 30.0% in the clobetasol propionate 0.05% cream group). Severe AEs were reported in 3.4% of patients in both the clobetasol propionate 0.025% formulation 5 and 13 groups, and 10% of patients in the clobetasol propionate 0.05% cream group. Overall,



**Table 4** Proportion of patients with burning/stinging and pruritus scores by visit (safety population)

Burning/stinging, <i>n</i> (%)	Clobetasol propionate 0.025% cream		Clobetasol propionate 0.05% cream ( <i>N</i> = 30)
	Formulation 5 ( <i>N</i> = 29)	Formulation 13 ( <i>N</i> = 29)	
Visit 3 (day 7)			
0	10 (34.5)	12 (41.4)	9 (30.0)
1	11 (37.9)	13 (44.8)	14 (46.7)
2	5 (17.2)	3 (10.3)	2 (6.7)
3	2 (6.9)	0	1 (3.3)
Visit 4 (day 14)			
0	9 (31.0)	13 (44.8)	11 (36.7)
1	13 (44.8)	9 (31.0)	10 (33.3)
2	2 (6.9)	1 (3.4)	0
Visit 5 (day 21)			
0	9 (31.0)	16 (55.2)	12 (40.0)
1	12 (41.4)	5 (17.2)	6 (20.0)
2	1 (3.4)	0	0
Visit 6 (day 28)			
0	15 (51.7)	20 (69.0)	21 (70.0)
1	10 (34.5)	7 (24.1)	6 (20.0)
2	1 (3.4)	2 (6.9)	0
Pruritus, <i>n</i> (%)	Clobetasol propionate 0.025% cream		Clobetasol propionate 0.05% cream ( <i>N</i> = 30)
	Formulation 5 ( <i>N</i> = 29)	Formulation 13 ( <i>N</i> = 29)	
Visit 3 (day 7)			
0	6 (20.7)	8 (27.6)	5 (16.7)
1	10 (34.5)	12 (41.4)	11 (36.7)
2	10 (34.5)	8 (27.6)	10 (33.3)
3	2 (6.9)	0	0
Visit 4 (day 14)			
0	6 (20.7)	7 (24.1)	7 (23.3)
1	16 (55.2)	15 (51.7)	12 (40.0)
2	2 (6.9)	1 (3.4)	1 (3.3)
3	0	0	1 (3.3)
Visit 5 (day 21)			

**Table 4** continued

Pruritus, <i>n</i> (%)	Clobetasol propionate 0.025% cream		Clobetasol propionate 0.05% cream ( <i>N</i> = 30)
	Formulation 5 ( <i>N</i> = 29)	Formulation 13 ( <i>N</i> = 29)	
0	8 (27.6)	12 (41.1)	10 (33.3)
1	11 (37.9)	9 (31.0)	6 (20.0)
2	3 (10.3)	0	1 (3.3)
3	0	0	1 (3.3)
Visit 6 (day 28)			
0	11 (37.9)	15 (51.7)	14 (46.7)
1	13 (44.8)	11 (37.9)	11 (36.7)
2	2 (6.9)	3 (10.3)	2 (6.7)

0, none; 3, severe.

5 patients in the clobetasol propionate 0.025% formulation 5 group, 9 patients in the clobetasol propionate 0.025% formulation 13 group, and 10 patients in the clobetasol propionate 0.05% cream group withdrew from the study due to decreased blood cortisol. No serious AEs or deaths were reported during the study.

No shift in atrophy scores from baseline to day 7 was observed in the clobetasol propionate 0.025% formulation 5 group; however, a shift in atrophy score from 1 to 0 from baseline to visit 3 for 1 patient each in the clobetasol propionate 0.025% formulation 13 group and the clobetasol propionate 0.05% cream group (Table 3) was noted. No change in telangiectasia score from baseline to visit 3 in any of the treatment groups was observed. A shift in telangiectasia score from 2 to 0 ( $n = 1$ ) and 0 to 1 ( $n = 1$ ) from baseline to visit 4 in the clobetasol propionate 0.025% formulation 13 group was observed. Additionally, a shift from baseline to visit 5 in telangiectasia score of 0 to 1 ( $n = 2$ ) in the clobetasol propionate 0.025% formulation 5 group, a shift of 0 to 1 ( $n = 3$ ) and 2 to 0 ( $n = 1$ ) in the clobetasol propionate 0.025% formulation 13 group, and a shift from 0 to 1 ( $n = 2$ ) in the clobetasol propionate 0.05% cream group was observed (Table 3).

A gradual decrease in the scores of burning/stinging in all three groups was observed by day 28 (clobetasol propionate 0.025% formulation 5 vs clobetasol propionate 0.025% formulation 13 vs clobetasol propionate 0.05% cream groups, score 0: 51.7%, 69.0%, and 70.0%; score 1: 34.5%, 24.1%, and 20%; score 2: 3.4%, 6.9%, and none). The treatment groups were comparable with respect to burning/stinging scores at all visits. Similarly, a reduction in the pruritus score was noted at visit 6 (clobetasol propionate 0.025% formulation 5 vs clobetasol propionate 0.025% formulation 13 vs clobetasol propionate 0.05% cream groups, score 0: 37.9%, 51.7%, and 46.7%; score 1: 44.8%, 37.9%, and 36.7%; score 2: 6.9%, 10.3%, and 6.7%). The three groups were comparable with respect to pruritus scores at all visits (Table 4).

### Efficacy

In the PP population, at the baseline visit the proportion of patients with a PGA score of 3 were 61.1%, 63.2%, and 53.8% and those with a PGA score of 4 were 38.9%, 36.8%, and 46.2% in clobetasol propionate 0.025% formulation 5, clobetasol propionate 0.025% formulation 13, and clobetasol propionate 0.05% cream groups, respectively. The mean PGA score gradually

**Table 5** Proportion of patients with PGA score by visit (per protocol population)

PGA score by visit	Clobetasol propionate 0.025% cream		Clobetasol propionate 0.05% cream (N = 13)
	Formulation 5 (N = 18)	Formulation 13 (N = 19)	
Baseline visit			
0	0	0	0
1	0	0	0
2	0	0	0
3	11 (61.1)	12 (63.2)	7 (53.8)
4	7 (38.9)	7 (36.8)	6 (46.2)
Mean (SD)	3.4 (0.50)	3.4 (0.50)	3.5 (0.52)
Success	0	0	0
Visit 3 (day 7)			
0	0	0	0
1	0	0	0
2	0	3 (15.8)	1 (7.7)
3	14 (77.8)	13 (68.4)	9 (69.2)
4	4 (22.2)	3 (15.8)	3 (23.1)
Mean (SD)	3.2 (0.43)	3.0 (0.58)	3.2 (0.55)
Success	0	0	0
Visit 4 (day 14)			
0	0	0	0
1	0	1 (5.3)	1 (7.7)
2	8 (44.4)	9 (47.4)	5 (38.5)
3	10 (55.6)	7 (36.8)	7 (53.8)
4	0	2 (10.5)	0
Mean (SD)	2.6 (0.51)	2.5 (0.77)	2.5 (0.66)
Success <sup>a</sup>	0	1 (5.3)	1 (7.7)
Visit 5 (day 21)			
0	0	1 (5.3)	1 (7.7)
1	2 (11.1)	1 (5.3)	0
2	13 (72.2)	13 (68.4)	10 (76.9)
3	3 (16.7)	4 (21.1)	2 (15.4)
4	0	0	0
Mean (SD)	2.1 (0.54)	2.1 (0.71)	2.0 (0.71)

**Table 5** continued

PGA score by visit	Clobetasol propionate 0.025% cream		Clobetasol propionate 0.05% cream ( <i>N</i> = 13)
	Formulation 5 ( <i>N</i> = 18)	Formulation 13 ( <i>N</i> = 19)	
Success <sup>b</sup>	2 (11.1)	2 (10.5)	1 (7.7)
Visit 6 (day 28)			
0	0	1 (5.3)	1 (7.7)
1	7 (38.9)	6 (31.6)	3 (23.1)
2	11 (61.1)	10 (52.6)	8 (61.5)
3	0	2 (10.5)	1 (7.7)
4	0	0	0
Mean (SD)	1.6 (0.50)	1.7 (0.75)	1.7 (0.75)
Success <sup>c</sup>	7 (38.9)	7 (36.8)	4 (30.8)

All values are presented as n (%) unless specified. *SD*, standard deviation.

0, clear; 1, almost clear; 2, mild; 3, moderate; 4, moderate to severe.

<sup>a</sup> *p* value 0.5245

<sup>b</sup> *p* value 0.9477

<sup>c</sup> *p* value 0.8934

reduced from baseline visit to end of treatment (day 28) in all three treatment groups, with no significant differences between the groups [clobetasol propionate 0.025% formulation 5 (baseline to day 28: 3.4 to 1.6), clobetasol propionate 0.025% formulation 13 (baseline to day 28: 3.4 to 1.7), and clobetasol propionate 0.05% cream (baseline to day 28: 3.5 to 1.7)] (Table 5). The PGA success rates (clear or almost clear) at the end of the study were 38.9%, 36.8%, and 30.8% in patients treated with clobetasol propionate 0.025% formulation 5, clobetasol propionate 0.025% formulation 13, and clobetasol propionate 0.05% cream, respectively. The PGA success rates were comparable across the three treatment groups with no significant differences ( $p = 0.893$ ).

## DISCUSSION

This comparative phase 2a study aimed to evaluate HPA axis suppression, safety, and efficacy of novel formulations of 0.025% clobetasol

propionate test creams (clobetasol propionate 0.025% formulations 5 and 13) with the currently marketed 0.05% formulation of clobetasol propionate cream in patients with moderate-to-severe psoriasis. The results of the present study demonstrated that both the new formulations, with half the concentration (0.025%) of currently marketed clobetasol propionate 0.05% formulation, had a numerically lower risk of causing HPA axis suppression, while showing similar efficacy to the currently marketed full strength clobetasol propionate 0.05% product. There was a trend towards lower HPA axis suppression in the lower strength formulations compared with the higher strengths, but the study results lacked statistical significance. Also, the lower strength formulations caused a more delayed reduction in the endogenous cortisol levels: together, these aspects make for a better risk-benefit profile compared with the higher strength product. Formulation 5, which was selected for further studies, had a higher trend for mean (SE) time to abnormal cortisol value [23.2 (1.3) days] compared with clobetasol

propionate 0.05% cream [12.3 (0.7) days], though the differences were not statistically significant ( $p = 0.592$ ).

No patient had a PGA score of 4 after 3 weeks of treatment in any of the groups, demonstrating similar efficacy of the novel clobetasol propionate formulations (0.025%) to that of clobetasol propionate 0.05% cream. The treatments with both test and reference formulations were effective, with PGA success rates achieved in  $\sim 37.9\%$  of patients in the clobetasol propionate 0.025% formulation groups, which was comparable with the reference clobetasol propionate 0.05% cream group (30.8%) at the end of treatment. Though not significant ( $p$ -value, 0.893), the proportion of patients with PGA success rates at day 28 were numerically higher in the clobetasol propionate 0.025% formulation groups compared with the clobetasol propionate 0.05% formulation group. The mean (SD) PGA score in patients with chronic psoriasis treated with once daily clobetasol propionate 0.05% cream was 2.46 (0.92) [18], while in our study the twice daily application of both clobetasol propionate 0.05% cream and clobetasol propionate 0.025% formulations for 4 weeks showed a numerically greater reduction in mean (SD) PGA scores at the end of the study favoring twice daily application of clobetasol propionate creams.

The topical use of clobetasol propionate at a dose as low as 2 g/day (0.05% cream) can cause HPA suppression within a few days. In a previous study, the frequency of HPA axis suppression was  $\sim 40\%$  in patients using 0.05% clobetasol propionate for 2–3 weeks [19, 20]. The novel formulation containing half the strength of clobetasol propionate, which is associated with decreased systemic absorption, could be a safer alternative to the currently marketed clobetasol propionate 0.05% cream. In a recent phase 2 study, which was mandated by USFDA for the approval of the novel formulation containing half the strength of clobetasol propionate cream (clobetasol propionate 0.025%), the proportion of patients with abnormal ACTH stimulation (indicating HPA suppression) was lower in the clobetasol propionate 0.025% group (12.5%) compared with the clobetasol propionate 0.05% cream

group (36.4%) after twice-daily treatment for 15 days [17]. In the present study, the proportion of patients with abnormal ACTH stimulation after 28 days of treatment was numerically lower in the clobetasol propionate 0.025% formulation groups compared with the clobetasol propionate 0.05% formulation group ( $p$ -value, 0.320). Additionally, although not statistically significant, time to abnormal cortisol value was also longer in the clobetasol propionate 0.025% formulation groups compared with the 0.05% cream group, indicating that the reference product with double strength causes abnormality in cortisol homeostasis at a much earlier time point. These results should be interpreted cautiously as the present study had a small sample size; larger studies may be required to further validate these results. Further, our study is limited as the pharmacokinetics of the drug were not analyzed, which may limit the interpretation of plasma drug concentration correlation with HPA axis suppression. In a recent phase 2 comparative study in the US, it was reported that after 15 days of treatment, the plasma drug concentration of clobetasol propionate 0.025% was significantly less than that of clobetasol propionate 0.05% (56.3 pg/ml vs 152.5 pg/ml;  $p = 0.014$ ) [17]. A correlation between lower systemic exposure and lower HPA axis suppression was also seen in this study, indicating a better risk-benefit profile for the clobetasol propionate 0.025% cream, compared with the currently marketed clobetasol propionate 0.05% cream.

The data demonstrated comparable results with respect to the safety profile of clobetasol propionate 0.05% cream. A decrease in blood cortisol concentration was the commonly reported AE responsible for patient withdrawal in all the treatment groups. Most of the AEs reported in the study were mild in severity and none of the AEs were considered to be definitely related to treatment by the investigator. No serious AEs or deaths were reported in this study. It is noteworthy that this study had a longer treatment duration of 4 weeks in comparison to other clinical studies of clobetasol propionate with recommended 2-week treatment duration in patients with psoriasis [14, 16, 21, 22]. Despite the longer treatment

duration, there were no new safety findings observed in any of the treatment groups.

An interesting observation was that the results pertaining to HPA axis suppression using clobetasol propionate 0.025% cream in this Indian study are not, in fact, statistically significant but showed similar efficacy to that of 0.05% strength. And because systemic exposure to steroids depends upon their potency, the novel half-strength formulation (0.025%) offered a lower degree of systemic absorption of this potent topical corticosteroid without compromising on efficacy [17]. Additionally, no significant difference in baseline BSA between the groups was observed and the amount of formulation applied was calculated based on BSA to ensure that there was no inter-subject variability. The BSA and the amount of drug applied were not significantly different between the groups, which avoided bias. In line with Draelos et al.'s study, our study results confirmed that the half-strength (compared with marketed propionate cream) novel formulations (0.025%, formulation 5 and 13) had similar efficacy to that of the 0.05% formulation. Hence, these reduced strength clobetasol propionate 0.025% formulations could serve as a better treatment option for patients with moderate-to-severe psoriasis, while avoiding exposure to higher concentrations of the drug that may result in long-term toxicities.

### Limitations

The present study had a small sample size and further studies with a higher sample number may be required to validate these results. The pharmacokinetics of the drug were not analyzed in the present study, which may restrict the interpretation of plasma drug concentration correlation with HPA axis suppression.

### CONCLUSIONS

The novel formulations of clobetasol propionate (formulations 5 and 13) had numerically, yet not significantly, lesser HPA axis suppression than the full-strength marketed product, while showing similar efficacy. Cortisol

homeostasis seemed to be impacted earlier by the clobetasol propionate 0.05% cream compared with the clobetasol propionate 0.025% formulations as shown by 'Time to Abnormal Cortisol'. Overall, our study findings support the use of the novel clobetasol propionate 0.025% cream formulations (formulation 5 and formulation 13) as an effective and safer treatment option for patients with moderate-to-severe psoriasis. The novel formulations of clobetasol propionate 0.025% have similar efficacy and an improved safety profile compared with the currently marketed clobetasol propionate 0.05% formulation.

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**Compliance with Ethics Guidelines.** The study protocol and informed consent form were reviewed and approved by an Independent Ethics Committee and Institutional Review Board at all six study sites (please see supplementary material for full details). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and per the International Council for Harmonization and Good Clinical Practice guidelines. Informed consent forms were reviewed and approved by all the appropriate Ethics Committees prior to enrolment of the patients into the study.

**Data Availability.** The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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