CLINICAL TRIAL

A Randomized, Parallel Group, Open Label, Multicenter Study to Assess the Potential for Adrenal Suppression and Systemic Drug Absorption Following Multiple Dosing with Clobetasol Propionate Cream (Impoyz™), 0.025% versus Clobetasol Propionate (Temovate®) Cream, 0.05% in Subjects with Moderate to Severe Plaque Psoriasis

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ABSTRACT

Importance: Topical corticosteroids continue to play an important role in therapy for individuals with moderate-to-severe psoriasis, particularly in cases where systemic therapy is contraindicated or in which combination topical-systemic therapy is needed to achieve desired results. Although super-high-potency corticosteroids such as clobetasol propionate have the potential to produce desired results, side effects related to systemic absorption may limit their clinical utility. **Objectives:** To evaluate the potential of a new, lower-concentration clobetasol propionate cream 0. 025% (Impoyz Cream, [IMP]) to suppress the hypothalamic-pituitary-adrenal (HPA) axis as compared to clobetasol propionate, 0.05% cream (Temovate Cream, [TMV]) under maximal use conditions in patients with moderate-to-severe plaque psoriasis. To compare the plasma concentrations of clobetasol propionate before and after 2 weeks of topical treatment with either IMP Cream or TMV Cream under maximal use conditions.
Design, Setting, and Participants: Randomized, multi-center, open-label study conducted across 15 clinical sites in the United States. Eligible subjects were males or females, at least 18 years old, with a clinical diagnosis of stable (at least 3 months) plaque-type psoriasis that involved 20% to 50% of the body surface area (BSA). 50 patients with an Investigator Global Assessment (IGA) grade of at least 3 (moderate) at Baseline were randomized (1:1) to twice daily treatment with either IMP Cream or TMV Cream for 15 consecutive days.
Main Outcomes and Measures: Primary safety assessments included hypothalamic-pituitary-adrenal axis suppression (as measured by ACTH stimulation test) and systemic drug absorption (as measured by plasma clobetasol propionate levels drawn at baseline and on Day 15 of treatment at 0, 1, 3, and 6 hours after final study product application). Secondary safety assessments included serum DHEAS at Days 8 and 15 and local cutaneous adverse events. The primary efficacy assessment was Investigator Global Assessment (IGA) score, measured at Days 8 and 15 of treatment. **Results:** Upon conclusion of the treatment period, the mean serum concentration of clobetasol propionate was significantly lower in the IMP Cream group vs the TMV group (56.3 vs 152.5 pg/mL, p=0.014). A lower proportion of subjects in the IMP group experienced HPA-axis suppression compared to the TMV group, although this did not reach statistical significance (12.5% vs 36.4%, p=0.086). In terms of efficacy, the two treatment groups displayed similar marked improvement in psoriasis severity after 15 days of treatment, with 50% of the subjects in each group having an IGA score of 2 (mild) and 16.7% in the IMP group and 18.1% in the TMV group having a score of 0 or 1 (none or minimal). **Conclusions and Relevance:** Subjects with moderate-to-severe plaque psoriasis treated with a 15 day course of IMP Cream demonstrate lower levels of plasma clobetasol propionate than those treated with TMV, suggesting lower levels of systemic corticosteroid exposure with IMP versus those with TMV. Additionally, in this sample, topical therapy with IMP was associated with a trend towards a lower incidence of HPA axis suppression than TMV without comprising efficacy.
Trial Registration: Registered 6 May, 2014.

INTRODUCTION

Topical corticosteroids continue to play an important role in the treatment of moderate-to-severe plaque psoriasis.[1] The side effects of topical corticosteroids can be both local and systemic and play an important determination in their use.[2,3] Systemic exposure, which governs the risk of systemic side effects, can be influenced by variables such as steroid potency, the amount of drug applied, or the duration of use.[4] Although all topical corticosteroids carry a risk of both local and systemic side effects, high-potency topical steroids have higher rates of systemic absorption and thus carry a higher risk of systemic side effects such as hypothalamic-pituitary-adrenal (HPA) axis suppression, hypertension, hyperglycemia, and Cushing's syndrome.[2,5] Thus, a novel formulation of a commonly-prescribed high-potency corticosteroid that offers a lower degree of systemic absorption compared to existing formulations would have significant utility in the treatment of psoriasis, particularly in patients with higher disease severity and greater BSA involvement. To this end, the objectives of this randomized, open-label, multi-center phase II safety study were:

1) To evaluate the potential of clobetasol propionate 0.025% cream (Impoyz [IMP] 0.025% cream) to suppress the HPA axis (a systemic side effect) as compared to clobetasol propionate cream 0.05% cream (Temovate [TMV] 0.05% cream), when applied twice daily for 15 days under maximal use conditions in subjects with moderate-to-severe plaque psoriasis.

2) To compare the plasma concentrations of clobetasol propionate after multiple uses of TMV Cream to IMP Cream under maximal use conditions.

METHODS

Study Design

This study was a randomized, multicenter, multi-dose, comparator-controlled, open label Phase II clinical trial comparing the safety and efficacy of IMP Cream (clobetasol propionate 0.025%) versus TMV Cream (clobetasol propionate 0.05%) in patients with moderate-to-severe plaque psoriasis. Subjects with 20-50% BSA involvement (representing those with large BSAs and at the greatest risk of systemic side effects) were enrolled across 15 clinical sites in 10 states from May 8, 2014 to August 11, 2015. Subjects were randomized (1:1) to treatment to one of two groups: treatment with IMP Cream or TMV Cream. Subjects were instructed to apply the treatment to all affected areas with the exception of the face, scalp, groin, axillae, and other intertriginous areas twice daily, for a target dose of 5 to 7 grams per day. Chronic medications being used at the time of screening were continued at the discretion of the Investigator (with the exception of agents meeting the criteria for study exclusion). Subjects were scheduled for study visits at Screening, Baseline (Day 1), Day 8, Day 15, and Day 43 (if needed to confirm recovery of HPA axis suppression). Efficacy evaluations were performed on Days 8 and 15, whereas safety evaluations were performed on Days 8, 15, 28 (if HPA axis suppression was noted on the Day 15 visit), and every 28 days thereafter as needed until resolution of HPA axis suppression was noted.

The Institutional Review Board at each participating center reviewed and approved

the study protocol, subject recruiting materials, informed consent form, and all other materials provided to potential subjects for enrollment in the study. The study was conducted in accordance with Good Clinical Practice guidelines and the Consolidated Standards of Reporting Trials (CONSORT) guidelines for clinical trials. The full protocol for the study can be accessed on clinicaltrials.gov.

Inclusion and Exclusion Criteria

In order to be deemed eligible for the study, potential subjects had to be 18 years of age or older with a clinical diagnosis of stable (for a minimum duration of 3 months) plaque-type psoriasis involving 20-50% body surface area (BSA), not including the face, scalp, groin, axillae, or other intertriginous areas. Furthermore, to meet the criteria for inclusion, potential subjects were required to have a minimum BSA involvement of 20% and to have an Investigator's Global Assessment (IGA) grade of at least 3 (moderate) at the baseline visit, as well as a normal ACTH stimulation test and normal DHEAS level at screening.

Subjects with unstable forms of psoriasis (for example, guttate, erythhrodermic, exfoliative, or pustular) were excluded from the study. Subjects deemed to be immunosuppressed or immunocompromised, including those with use of immunosuppressive drugs or systemic psoriasis therapies within 60 days of the baseline visit were deemed ineligible. Subjects who had undergone treatment for any cancer with the exception of skin cancer or cervical cancer *in situ* within 1 year of the baseline visit were excluded. Those who had utilized topical psoriasis therapies (including any use of corticosteroids), phototherapy (PUVA or UVB), or systemic anti-inflammatory agents within 30 days of the baseline visit were excluded from the study. Subjects with a known history of HPA axis abnormalities were deemed ineligible. Further exclusion criteria consisted of use of DHEA or DHEAS-containing products within 30 days of the screening visit, known hypersensitivity to any ingredients of the study or comparator medications, abnormal sleep schedule, previous enrollment in an investigational drug study within 60 days of the baseline visit, inability to comply with study requirements, severe hypertension (SBP > 160 mmHg or DBP > 100 mmHg) at baseline, and pregnancy or current breastfeeding.

Assessments

The primary safety assessments of interest were determination of HPA axis suppression as indicated by the ACTH stimulation test and the level of systemic exposure as measured by plasma concentrations of clobetasol propionate.

The ACTH stimulation test is the gold standard test for diagnosis of HPA axis suppression. The test measures an individual's ability to mount an appropriate response to pharmacologic stimulation of the HPA axis.[6] Subjects exhibiting signs of HPA axis suppression will not be able to produce a surge of endogenous cortisol in response to administration of cosyntropin (exogenous adrenocorticotropic hormone). The ACTH stimulation test was performed by collecting a 5 mL blood sample from the subject prior to administration of cosyntropin to function as a "control" measurement. The subject was then administered 0.25 mg of IV or IM cosyntropin, followed by repeat collection of 5 mL of blood 30 minutes later. A post-stimulation cortisol level below 18 µg/dL indicated an inadequate response to ACTH stimulation and was taken to be indicative of HPA axis suppression.

Secondary safety assessments included a local cutaneous safety evaluation for atrophy/telangiectasias and a summary of treatment emergent adverse events (TEAEs). The primary efficacy assessment was Investigator's Global Assessment (IGA). Clinical determinations of disease severity using the IGA were performed at each visit from screening through the end of treatment (Box 1)The IGA score is a static assessment of disease severity based on the overall disease severity at the time of the visit.[7] The inclusion criteria for the study required a Baseline IGA of at least 3 (moderate).

Statistical Analysis

All statistical analyses were performed using SAS Version 9.1.3 statistical software (Cary, NC). Significance testing was performed at an α-level of 0.05% using Analysis Of Variance (ANOVA) for continuous variables and Fisher's Exact Test for categorical variables. No imputation was made to account for missing safety data.

RESULTS

Subject Demographics

Eighty-eight subjects were screened for potential inclusion in the study. Of these 88 screened subjects, 50 were randomized, 26 to the IMP group and 24 to the TMV group. Thirty-four of the 38 screen failures were related to the subject not meeting the pre-specified inclusion/exclusion criteria, whereas three were related to withdrawal of consent and one subject was lost to follow-up after the screening visit. Out of the 26 subjects randomized to the IMP group, 2 (7.7%) self-discontinued the medication prior to the completion of the study, compared to 1 (4.2%) in the TMV group. One subject was

Box 1. Investigator's Global Assessment of Disease Severity.

Score	Grade	Definition
0	None	• No plaque elevation above normal skin level • May have residual non-erythematous discoloration • No psoriatic scale • No erythema
1	Minimal or Almost Clear	No more than: • Very slight elevation above normal skin level • Faint light pink coloration • Occasional very fine scale, partially covering some of the lesions
2	Mild	No more than: • Slight but definite elevation of plaque above normal skin level • Light red coloration • Fine scale with some lesions partially covered
3	Moderate	No more than: • Definite elevation with rounded or sloped edges to plaque • Definite red coloration • Somewhat coarse scale with most lesions partially covered
4	Severe/ Very Severe	At least one: • Marked elevation with hard, sharp edges to plaque • Dark red coloration • Coarse, thick scale with virtually all lesions mostly covered and a rough surface

lost to follow-up in each group. Overall, 46 subjects completed the study, 23 (88.5%) in the IMP group versus 22 (91.7%) in the TMV group (Appendix 1). Of note, one subject from the IMP group withdrew from the study but had already undergone a safety evaluation beyond the baseline visit, and thus was included in the analysis of safety outcomes.

Demographic variables were relatively equally distributed between the two treatment groups (Table 1). Overall, roughly two-thirds of subjects were male. All subjects were white, but 58.7% were of Hispanic or Latino descent. The age of included subjects ranged from 18 to 75 years of age. Percent BSA involvement of psoriatic plaques ranged from 20% to 50%. There were no statistically significant differences in measured demographic variables between the two groups, although mean age (43.5 years in the IMP group versus 50.9 years in the TMV group) did approach statistical significance (p = 0.058, Table 1).

Measurement of Extent of Exposure to Treatment Product

Extent of exposure to treatment product was monitored by the number of topical applications. The planned number of applications for the 15 Day treatment period was 29 (two applications per day on Days 1-14 plus one application on Day 15). The actual mean number of applications was 28.3 in the IMP group versus 31.0 in the TMV group (p = 0.200). Overall, 19/24 (79.2%) of subjects in the IMP group and 21/22 (95.5%) of subjects in the TMV group reached a minimum of 26 applications (p = 0.101). The mean amount of product applied was 107.0 grams in the IMP group versus 101.7 grams in the TMV group.

Table 1: Demographic characteristics of subjects included in safety evaluation.

	IMP Cream (n = 24)	TMV Cream (n = 22)	Overall (n = 46)	p-value
Gender				0.603[a]
Female	7 (29.2%)	8 (36.4%)	15 (32.6%)	
Male	17 (70.8%)	14 (63.6%)	31 (67.4%)	
Ethnicity				>0.80[a]
Hispanic/Latino	14 (58.3%)	13 (59.1%)	27 (58.7%)	
Non-Hispanic/Latino	10 (41.7%)	9 (40.9%)	19 (41.3%)	
Race				
White	24 (100%)	22 (100%)	46 (100%)	>0.80[a]
Age				0.16[a]
18-39	10 (41.7%)	2 (9.1%)	12 (26.1%)	
40-63	13 (54.2%)	16 (72.7%)	29 (63.0%)	
64-75	0 (0%)	4 (18.2%)	4 (8.7%)	
≥75	1 (4.2%)	0 (0%)	1 (2.2%)	
Age (Years)				0.058[b]
Mean ± SD	43.5 ± 14.5	50.9 ± 11.2	47.0 ± 13.4	
Median	44.5	50.0	48.5	
Min, Max	18, 75	24, 71	18, 75	
% BSA Involvement				>0.80[b]
Mean ± SD	26.5 ± 8.6	27.0 ± 8.3	26.8 ± 8.4	
Median	22.5	24.0	23.5	
Min, Max	20, 50	20, 48	20, 50	

[a]Fisher's Exact Test, [b]ANOVA
% = percent, ≥ = greater than or equal to, BSA = body surface area

Table 2: Percent reduction in serum DHEAS concentration (µg/mL).

		IMP Cream (n = 23) (%)	TMV Cream (n = 22) (%)	p-value
Percent reduction from Screening to Day 8	Mean ± SD	6.8 ± 28.3	19.7 ± 39.7	0.216[a]
	Median	2.5	24.8	
	Min, Max	-50.4, 100.0	-105.3, 100.0	
Percent reduction from Screening to Day 15	Mean ± SD	11.0 ± 27.0	21.6 ± 46.4	0.353[a]
	Median	16.1	28.4	
	Min, Max	-48.7, 69.0	-122.7, 100.0	

[a] One-way Analysis of Variance (ANOVA)
SD = standard deviation

Table 3: Number and percentage of subjects reporting Treatment-Emergent Adverse Events (TEAEs).

	IMP Cream (n = 24) n, (%)	TMV Cream (n = 22) n, (%)
Subjects reporting any TEAEs	6 (25.0%)	11 (50.0%)
Subjects with TEAEs possibly, probably, or definitely related to study product	5 (20.8%)	10 (45.5%)

Table 4: Local Cutaneous Events at Day 15 of Treatment

	IMP Cream (n = 24) N (%)	TMV Cream (n = 22) N (%)
Telangiectasia	0 (0.0%)	0 (0.0%)
Atrophy	0 (0.0%)	0 (0.0%)
Burning/Stinging	1 (4.2%)	1 (4.5%)
Pain	0 (0.0%)	0 (0.0%)
Itching	6 (25.0%)	7 (31.8%)

Safety of IMP (clobetasol propionate 0.025%) Cream versus TMV (clobetasol propionate 0.05%) Cream

At Day 15 of the study, 3 (12.5%) subjects in the IMP group had an abnormal ACTH stimulation test result (indicative of HPA axis suppression), versus 8 (36.4%) subjects in the TMV group (p=0.086, Figure 1).

When assessing systemic exposure, the mean plasma concentration representing the average of all post-treatment concentrations was 56.3 pg/mL (95% CI 9.9 pg/mL to 102.7 pg/mL) for IMP Cream versus 152.5 pg/mL (95% CI 90.0 pg/mL to 214.9 pg/mL) for TMV Cream (p=0.014, Figure 2). The mean post-treatment plasma concentrations of clobetasol propionate were significantly greater in subjects with HPA axis suppression (determined by abnormal ACTH stimulation test results) versus those without HPA axis suppression (217.1 pg/mL vs. 71.2 pg/mL, respectively).

Secondary safety assessments included serum DHEAS concentration, local cutaneous adverse events, and TEAEs. Reduction in serum concentration of DHEAS (which represents an indirect measure of HPA axis suppression) was measured twice during the duration of the study, on treatment Day 8 and treatment Day 15, both versus the baseline blood sample taken during the screening visit. On Day 8, the mean reduction in serum DHEAS concentration seen in the group treated with IMP Cream was of lower magnitude than that noted in the group treated with TMV Cream, although the difference was not statistically significant (6.8% vs. 19.7%, p = 0.216, Table 2). Likewise, at Day 15, this same trend was noted, but again the difference was not

Figure 1: Percentage of subjects with abnormal ACTH stimulation test at Day 15, stratified by treatment group.

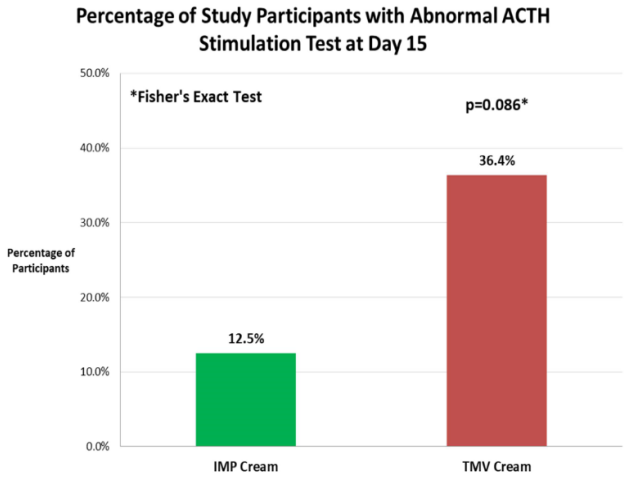
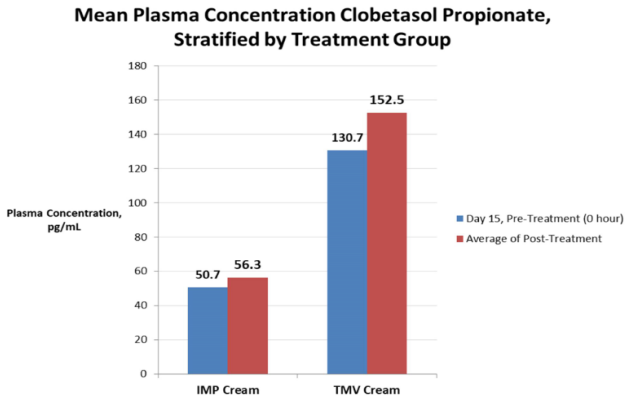


Figure 2: Mean plasma concentration of clobetasol propionate, stratified by treatment group.



statistically significant (11.0% for the IMP Group vs. 21.6% for the TMV Group, p=0.353, Table 2).

Local cutaneous effects, including development of clinically significant telangiectasia, atrophy, burning or stinging, itch, and pain were evaluated at Baseline (Day 1 of treatment), Day 8, and Day 15. No clinically significant telangiectasia or atrophy was noted in any participants in either treatment group throughout the duration of the study. Two (8.3%) subjects in the IMP group noted clinically significant burning/stinging at Baseline (prior to first application of study product) with symptoms resolving in one of the two subjects by Day 8 of treatment, whereas the symptoms persisted in the other subject throughout the duration of treatment. In the TMV Group, 5 (22.7%) subjects noted clinically significant burning/stinging at Baseline (prior to first application of study product), with symptoms persisting to Day 8 in 2 (9.1%) of the subjects and throughout the treatment period in 1 (4.5%) subject (Figure 3). Clinically significant pruritus was reported by 79.2% of subjects in the IMP group at Baseline, falling to 25% of subjects by the Day 15 visit, compared to 81.8% and 31.8% of the TMV group at Baseline and Day 15, respectively. Clinically significant pain was noted in 1 (4.2%) subject in the IMP group and 2 (9.1%) subjects in the TMV group at Baseline; these symptoms resolved in all 3 subjects by Day 8 of treatment.

TEAEs were seen in 6 (25.0%) subjects in the IMP treatment group versus 11 (50.0%) in the group treated with TMV Cream (Table 3). The most common adverse events (other than HPA axis suppression) were local cutaneous symptoms, which were similar in both treatment groups (Table 4).

Analysis of Treatment Efficacy

Efficacy results, as measured by the IGA scale at Baseline and on Days 8 and 15, were similar between the two treatment groups, although the study was not powered to demonstrate a significant efficacy difference between the groups (Figure 4). At Baseline, all subjects had an IGA score of 3 or 4 (as required by the criteria for inclusion in the study). At Day 15 of treatment, 50% of subjects in each treatment group had an IGA score of 2 (mild), and 16.7% of subjects in the IMP group and 18.1% in the TMV group had a score of 0 or 1 (null or minimal, respectively).

Figure 3: Percentage of subjects with clinically significant application site burning or stinging, stratified by treatment group.

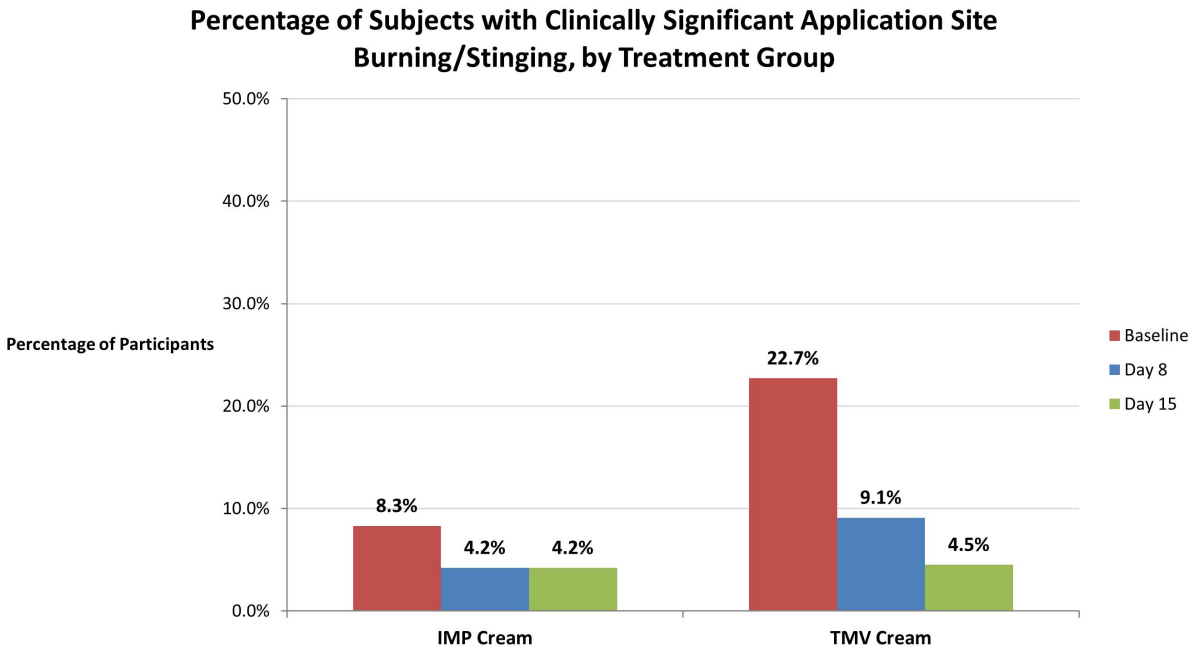
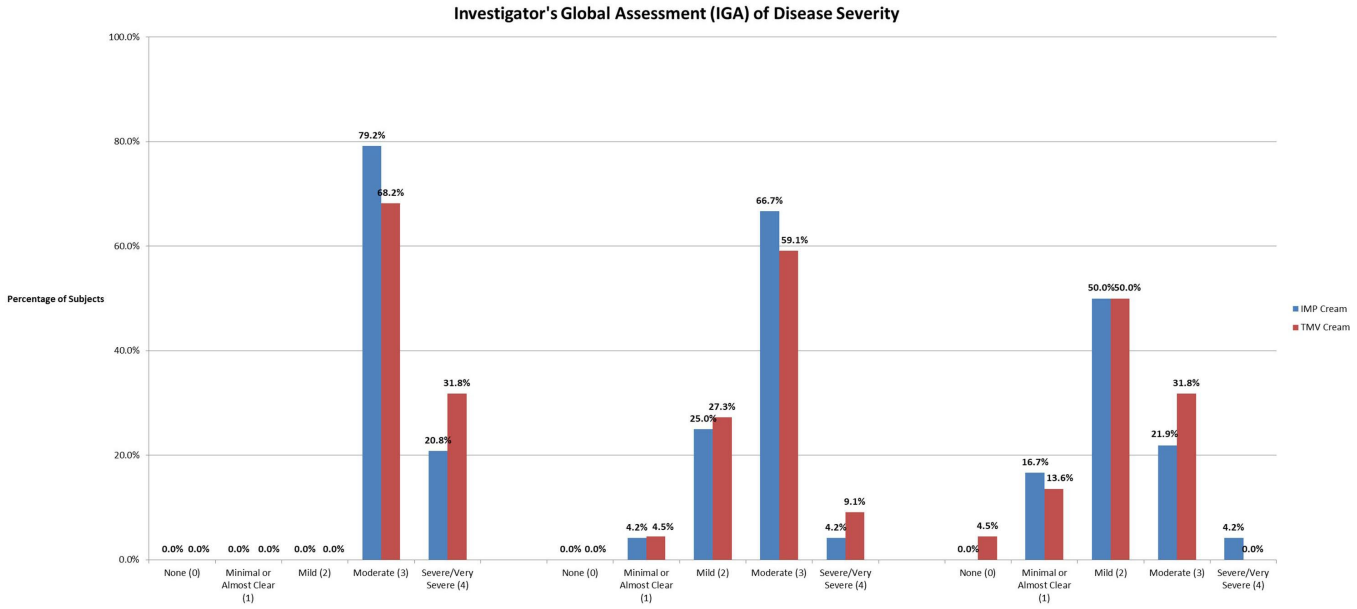


Figure 4: Investigator's Global Assessment (IGA) of disease severity.



DISCUSSION

The results of this Phase II trial, mandated by the FDA as part of the approval process for IMP Cream, suggest that IMP Cream is a safer alternative to TMV based on reduced HPA axis suppression and reduced systemic exposure to clobetasol propionate. This is an important study as it investigates a key safety outcome: HPA axis suppression, a marker of degree of systemic absorption. Although degree of systemic exposure to topical steroids is one of the key concerns with these agents, safety evaluations measuring HPA axis suppression were historically not required for many of the older high-potency topical corticosteroid formulations. For these agents, most information regarding HPA axis suppression was obtained through post-market reports.[9]

The present results indicated a 3-fold reduction in HPA axis suppression (with a trend toward statistical significance), and a statistically significant >2.5-fold reduction in circulating plasma clobetasol propionate levels in the group treated with IMP, compared to the group treated with TMV. Furthermore, in all cases, HPA axis suppression secondary to use of IMP Cream was reversible. Importantly, these findings were observed despite the significant amount of product required in this population with significant BSA involvement. Equally important, this was demonstrated in the context of preserved efficacy, as measured by the IGA scale. These results, taken together, indicate the potential of IMP cream to be used more safely in patients with moderate-to-severe psoriasis who require an adjunct to systemic therapy or in those who are not candidates for systemic therapy. The finding of a lesser degree of HPA axis suppression in patients treated with IMP versus TMV is particularly noteworthy as this study was carried out under maximal use conditions in patients with moderate-to-severe disease affecting a significant percentage of the body surface area (20-50%).

LIMITATIONS

Although the proportion of subjects with abnormal ACTH stimulation test results and the degree of reduction in serum DHEAS concentration were both numerically lower for subjects treated with IMP, the differences were not statistically significant. No statistical justification was made for the sample size of 50 subjects and the study was not powered to detect a statistically significant difference between treatment groups when measuring HPA axis suppression or efficacy.

CONCLUSION

The results of this Phase 2 open label clinical study indicate that IMP Cream (clobetasol propionate 0.025%) is associated with a lower incidence of HPA axis suppression and reduced systemic exposure compared to TMV Cream (clobetasol propionate 0.05%) under maximal use conditions in patients with moderate-to-severe plaque psoriasis. This data suggests that compared to traditional dose formulations of clobetasol propionate (0.05%), IMP may provide a better safety profile without compromising efficacy. Therefore, the use of IMP may allow for safer treatment of patients with moderate-to-severe plaque psoriasis who are not candidates for systemic therapy or who would benefit from adjuvant topical therapy in combination with systemic therapy.

Conflict of Interest Disclosures: ZDD, JFF and RC have received honoraria for consulting services from Encore Dermatology. All authors serve as investigators for Encore Dermatology.

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Appendix 1: Participant flow through the study.