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APPLICATION NUMBER:

209483Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology Review

NDA #: 209483
Submission Date: January 30, 2017
Brand Name: (b) (4) Cream
Generic Name: Clobetasol propionate cream, 0.025%
Dosage Form: Cream
Dosage Strength: 0.025%
Reviewer: Chinmay Shukla, Ph.D.
Secondary Reviewer: CAPT. E. Dennis Bashaw, Pharm. D.
OCP Division: Division of Clinical Pharmacology - 3
OND Division: Division of Dermatology and Dental Products
Applicant: Promius Pharma LLC.
Relevant IND(s): 110799
Submission Type: New-submission
Indication: Topical treatment of moderate to severe plaque psoriasis

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1. Executive Summary

Clobetasol propionate (CBP) is a super potent topical corticosteroid and the applicant has submitted this NDA for twice daily topical treatment of moderate to severe plaque psoriasis in adults using CBP Cream, 0.025% (DFD-06 Cream). The dosing will be limited for up to 2 consecutive weeks.

This new formulation of CBP (0.025%) is half the strength of the currently available products containing CBP (0.05%). The applicant's intent of the lower strength of the product was to reduce the incidence of adverse effects seen with the 0.05% products, particularly with regard to hypothalamic-pituitary-adrenal (HPA) axis suppression, while maintaining efficacy.

The clinical pharmacology program consisted of a pilot HPA axis suppression study, a pivotal HPA axis/ maximal use pharmacokinetic (PK) study, and a single-point vasoconstrictor (VCA) study.

1.1 Recommendation

From a Clinical Pharmacology standpoint, this application is acceptable provided the labeling comments are adequately addressed by the applicant.

1.2 Post-Marketing Requirement

Conduct max use PK trial and HPA axis suppression study in subjects 6 to less than 17 years of age with psoriasis.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Pharmacokinetics and HPA axis suppression: The applicant conducted a relative bioavailability (BA) study in subjects with moderate to severe plaque psoriasis to compare the systemic exposure and HPA axis suppression potential of DFD-06 cream (CBP, 0.025%) and Temovate E[®] cream (CBP, 0.05%) under maximal use conditions.

The results indicated that the DFD-06 cream group had lower proportion of subjects with HPA axis suppression, i.e., abnormal ACTH stimulation test results on Day 15, compared to Temovate E[®] cream. Specifically 3 out of 24 subjects (12.5%) showed abnormal ACTH stimulation test results in the DFD-06 cream group compared to 8 out of 22 subjects that showed abnormal adrenocorticotropin hormone (ACTH) stimulation test results in the Temovate E[®] cream group.

The Day 15 post-treatment plasma concentrations (mean \pm SD) of clobetasol propionate was statistically significantly lower ($p=0.014$) in the DFD-06 cream group (56.3 ± 104.7 pg/mL) compared to Temovate cream group (152.5 ± 140.9 pg/mL).

Vasoconstriction (VCA) study: The single point VCA study using both visual assessment (primary endpoint) and chromameter assessment (secondary endpoint) indicated that DFD-06 cream is a potent topical corticosteroid belonging to Class 2.

Dose finding: The applicant did not conduct a traditional dose finding study; rather they conducted a pilot HPA axis suppression study where 2 different prototype formulations (Formulation #5 and #13) were tested against Temovate E[®] cream following twice daily application for 28 days in subjects with moderate to severe psoriasis. This study was conducted in India and PK was not assessed.

For the primary end point assessment, the proportion of patients with abnormal ACTH stimulation test results were 30.8%, 20.7% and 34.6% for the Formulation-5, Formulation-13 and Temovate E[®] cream arms, respectively. The secondary end point assessment at the end of Day 28 treatment, the success rate with the PGA (clear or almost

clear) score was 38.9%, 36.9% and 30.8% for the Formulation-5, Formulation-13 and Temovate E[®] arms, respectively. There was no statistically significant difference for the primary and secondary end point results between the treatment arms. Based on these results, the applicant selected Formulation # 5 as the to-be-marketed formulation. It should be noted that the treatment duration in the pilot study was 28 days while the product will be labeled to be used for not more than 14 days.

Drug interaction assessments: Since DFD-06 cream is a lower strength compared to other marketed clobetasol products; the applicant has not conducted any drug interaction assessments. Furthermore, since the systemic exposure and HPA axis suppression rate of DFD-06 cream was lower than Temovate E[®] cream, the drug interaction assessments are not needed.

TQT waiver request: The applicant has submitted a request for waiver of TQT assessment based on the fact that the mean systemic exposure of DFD-06 cream is lower than Temovate E[®] cream, absence of any cardiovascular adverse events in the two Phase 3 trials, and literature evidence suggesting that neither hERG channel study nor clinical experience with other topical clobetasol products produced any clinically meaningful QT prolongation.

Pediatric assessment: The applicant has requested for a waiver of pediatric assessment for subjects aged 0 to < 6 years as this product would be unsafe in this age group because of safety concerns since Clobetasol propionate is a potent corticosteroid.

For subjects aged 6 to 16 years and 11 months years, the applicant has requested for a deferral because the applicant wanted to obtain the safety and efficacy data in adults prior to initiating pediatric studies and studies in adults are completed and ready for approval at this stage.

Reviewer comments: *Agreement on the pediatric study plan (PSP) was reached on November 3, 2015 (see communication in DARRTS under IND 110799). At the Pediatric Review Committee (PeRC) meeting on August 16, 2017; PeRC advised that we suggest the applicant to keep the enrollment open to any subjects with psoriasis below the age of 6 years. However, enrolling subjects below the age of 6 years will not be mandated given the low number of subjects with psoriasis in this age group that would require therapy.*

2. Question Based Review

2.1 General Attributes of the Drug

2.1.1 What regulatory pathway has the Applicant followed?

Topical CBP in different formulations is approved for the treatment of psoriasis. The applicant plans to follow the 505(b)(1) regulatory pathway and they plan on relying on the systemic and long term safety of Temovate® NDAs for which the applicant has obtained the right of reference for all NDAs shown in Table 1.

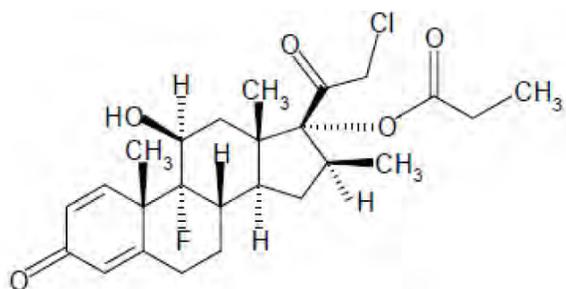
Table 1: Summary of products the applicant has obtained the right of reference

NDA#	Approval date	Brand Name	Indication
019322	12/27/1985	Temovate® Cream, 0.05%	Corticosteroid responsive dermatoses in subjects 12 years of age and older
019323	12/27/1985	Temovate® Ointment, 0.05%	Corticosteroid responsive dermatoses in subjects 12 years of age and older
(b) (4)	02/22/1990	Temovate® Solution, 0.05%	Corticosteroid responsive dermatoses of the scalp in subjects 12 years of age and older
020337	04/29/1994	Temovate® Gel, 0.05%	Corticosteroid responsive dermatoses in subjects 12 years of age and older
020340	06/17/1994	Temovate® E Cream, 0.05%	Corticosteroid responsive dermatoses in subjects 12 years of age and older and plaque psoriasis in subjects 16 years of age and older

2.1.2 What are the highlights of the chemistry the formulation?

Drug substance: Clobetasol propionate is a synthetic, fluorinated corticosteroid. Corticosteroids are a class of compounds which includes steroid hormones secreted by the adrenal cortex, and their synthetic analogs and have anti-inflammatory and/or immunosuppressive effects. The empirical formula for Clobetasol propionate is $C_{25}H_{32}ClFO_5$ and the molecular weight is 467. The structure is shown in Figure 1.

Figure 1: Structure of Clobetasol propionate



Formulation: DFD-06 (Clobetasol propionate Cream 0.025%) is a white to off-white oil-in-water emulsion cream intended for topical application for treatment of moderate plaque psoriasis. The composition of the formulation is shown in Table 2.

Table 2: Qualitative and quantitative composition of to-be-marketed formulation

Ingredients	Reference / Standard	% w/w	Function
Clobetasol propionate	USP	0.025	Active
Cetostearyl alcohol	NF	(b) (4)	(b) (4)
Glyceryl stearate & PEG 100 stearate	IH*		
White wax	NF		
Diethylene glycol monoethyl ether	NF		
Butylated hydroxytoluene	NF		
Isopropyl myristate	NF		
Cyclomethicone	NF		
Methylparaben	NF		
Propylparaben	NF		
Purified water Q.S.	USP		

2.1.3 What are the proposed mechanism of action and the therapeutic indications?

Mechanism of action:

Corticosteroids play a role in cellular signaling, immune function, inflammation, and protein regulation; however, the precise mechanism of action in corticosteroid responsive dermatoses is unknown. The contribution to efficacy by individual components of the vehicle has not been established.

Therapeutic indication: Topical treatment of moderate to severe plaque psoriasis.

2.1.4 What is the proposed route of administration, dosage and dosing frequency?

Proposed route of administration: Topical.

Proposed dosing: Apply a thin layer of the Cream to the affected skin areas twice daily and rub in gently and completely. Use the cream for up to 2 consecutive weeks of treatment.

2.2 General Clinical Pharmacology

2.2.1 What were the clinical trials conducted to support this NDA?

To support this NDA, the applicant has conducted following clinical studies (Table 3) which included three clinical pharmacology studies which were:

- CDS1002: Pilot Phase 2 HPA axis suppression study
- DFD-06-CD-003a: Phase 1 vasoconstrictor potency study
- DFD-06-CD-007: Phase 2 HPA axis suppression/ maximal use PK study

Table 3: Summary of clinical development

Study No.	Study Description	Status
CDS0801	Phase 1 Single Application Study to Assess the Suppression of UV Induced Erythema (N=24)	Completed
CDS1002	Pilot Phase 2 HPA Axis Suppression Study (N=88)	Completed
DFD-06-CD-003a	Phase 1 Vasoconstrictor Potency Study (N=80)	Completed
DFD-06-CD-004	Phase 3 Study of the Efficacy and Safety of DFD-06 Cream in the Treatment of Moderate to Severe Plaque Psoriasis for 14 Days (N=267)	Completed
DFD-06-CD-005	Phase 3 Study of the Efficacy and Safety of DFD-06 Cream in the Treatment of Moderate to Severe Plaque Psoriasis for 14 Days (N=265)	Completed
DFD-06-CD-007	Phase 2 HPA Axis Suppression / Systemic Absorption PK Study in Subjects with Moderate to Severe Psoriasis Compared to Temovate (clobetasol propionate) Cream, 0.05% (N=50)	Completed
DFD-06-CD-008	Phase 1 Phototoxicity Study (N=32)	Completed
DFD-06-CD-009	Phase 1 Photosensitivity Study (N=57)	Completed
DFD-06-CD-010	Phase 1 Repeat Insult Patch Test (Contact Sensitization) Study in 240 Subjects (N=281)	Completed
DFD-06-CD-011	Phase 2 Study to Assess the Potential for Adrenal Suppression and Systemic Drug Absorption Following Multiple Dosing with DFD-06 Cream in Pediatric Subjects with Moderate to Severe Plaque Psoriasis (N=50)	Planned

2.2.2 How was the dose selected?

The applicant did not conduct a classic dose ranging study; however they conducted a pilot HPA axis suppression potential study of DFD-06 Cream compared to Temovate E[®] Cream, 0.05% after 28 days of twice daily treatment (Study CDS1002). This study was

conducted in India and 88 subjects with moderate to severe plaque psoriasis with 25% body surface area (BSA) involved were enrolled. The subjects were randomized into three groups to receive Clobetasol Propionate Cream, 0.025% (Formulation 5, to-be-marketed formulation), Clobetasol Propionate Cream, 0.025% (Formulation 13), or Temovate E[®] cream, 0.05%.

In this study, the treatment success rate for efficacy (clear or almost clear) after 28 days of treatment was 38.7% of subjects in the Formulation 5 group, 36.8% in the Formulation 13 group and 30.8% for the Temovate E[®] group. At the end of treatment, an abnormal ACTH stimulation test, indicating HPA axis suppression, was seen in 30.8% of subjects in the Formulation 5 group, 20.7% in the Formulation 13 group and in 34.6% in the Temovate group.

Overall, 44.8% subjects in the Formulation 5 group, 37.9% subjects in the Formulation 13 group, and 50% subjects in the Temovate E[®] group experienced at least one treatment emergent adverse event. There were no statistical differences between groups. Based on the results of this study, Formulation 5 was selected for further development as the to-be-marketed formulation.

2.2.3 What is the PK?

Maximal use PK trial design in brief: This was a randomized, parallel group, open label, multicenter study to assess the potential for adrenal suppression and systemic drug absorption following multiple dosing with DFD-06 cream versus Temovate E[®] cream (clobetasol propionate 0.05%) in subjects with moderate to severe plaque psoriasis. Approximately 50 subjects with normal ACTH test and moderate to severe psoriasis covering 20% to 50% body surface area (BSA) were included in this study. Subjects applied the drug two times a day for 15 days. The ACTH test at baseline was conducted at least 14 days and no more than 28 days prior to baseline visit and post treatment on Day 15 (after the last dose). Follow-up ACTH test was to be repeated every 28 days after stopping the treatment to confirm recovery. A PK blood sample was taken to obtain a baseline value at the time of the screening ACTH stimulation test. On Day 15, subjects applied the last dose of study product at the clinic up to 60 minutes after a pre-treatment PK blood sample was taken (Day 15 Visit, 0 hour). PK blood samples were then collected at 1, 3, and 6 hours (\pm 5 minutes) after application of the study product.

PK results: On Day 15, the mean systemic exposure of clobetasol propionate following administration of Temovate cream was approximately 2.6 fold higher than DFD-06 cream (Table 4). The systemic exposure of clobetasol propionate in subjects with HPA axis suppression was approximately 3 fold higher compared to the systemic exposure in subjects that did not show HPA axis suppression (Table 5). This indicates that higher systemic exposure leads to the incidence of HPA axis suppression.

Table 4: Systemic exposure of clobetasol propionate (pg/mL) on Day 15

Visit: Time Point	Statistics	DFD-06 Cream	Temovate Cream	p-value
Day 15: Pre-Treatment (0 hour)	N	24	22	NA
	Mean ± SD	50.7 ± 96.0	130.7 ± 146.2	
	95% CI of Mean	(10.1 to 91.2)	(65.9 to 195.5)	
	Median	28	81.1	
	Min, Max	0.00, 477.3	0.00, 571.3	
Average of Post-Treatment*	N	22	22	0.014 ¹
	Mean ± SD	56.3 ± 104.7	152.5 ± 140.9	
	95% CI of Mean	(9.9 to 102.7)	(90.0 to 214.9)	
	Median	29.5	131.5	
	Min, Max	0.00, 503.4	0.00, 517.2	

CI = confidence interval; Max = maximum; Min = minimum; NA = not applicable; SD = standard deviation

A concentration value of <10.0 occurring prior to first quantifiable concentration during a day for a subject was treated as zero and others were set to missing for all statistical analyses.

¹ P-value for treatment comparison from one-way analysis of variance model (ANOVA).

*Average of post-treatment concentrations were calculated using all available post-treatment data except for the plasma concentrations that were >1 hour off-schedule.

Table 5: Plasma concentrations of clobetasol propionate (pg/mL) in subjects with and without HPA axis suppression

Visit: Time Point	Statistics	With HPA Axis Suppression ¹	Without HPA Axis Suppression ²	p-value
Day 15: Pre-Treatment (0 hour)	N	11	35	NA
	Mean ± SD	195.7 ± 150.8	55.4 ± 100.3	
	95% CI of Mean	(94.4 to 297.0)	(20.9 to 89.9)	
	Median	136.5	26.2	
	Min, Max	34.5, 477.3	0.0, 571.3	
Average of Post-Treatment*	N	10	34	0.001 ³
	Mean ± SD	217.1 ± 153.8	71.2 ± 106.0	
	95% CI of Mean	(107.1 to 327.1)	(34.2 to 108.2)	
	Median	185.6	31.7	
	Min, Max	33.4, 503.4	0.0, 517.2	

CI = confidence interval; Max = maximum; Min = minimum; NA = not applicable; SD = standard deviation

A concentration value of <10.0 occurring prior to first quantifiable concentration during a day for a subject was treated as zero and others were set to missing for all statistical analyses.

Subjects with or without HPA axis suppression were identified based on the ACTH data from Day 15.

¹A subject with HPA axis suppression was defined as a cortisol level ≤ 18.00 µg/dL at 30 minutes post stimulation.

²A subject without HPA axis suppression was defined as a cortisol level > 18.00 µg/dL at 30 minutes post stimulation

³ P-value for treatment comparison from one-way analysis of variance model (ANOVA).

*Average of post-treatment concentrations were calculated using all available post-treatment data except for the plasma concentrations that were >1 hour off-schedule.

2.2.4 What are the results of HPA axis suppression test?

In the pivotal maximal use PK and HPA axis suppression study, the results of HPA axis suppression assessment as measured by the number of subjects with abnormal ACTH stimulation is shown in Table 6. The incidence of HPA axis suppression was numerically lower in DFD-06 cream group compared to Temovate cream group.

Table 6: Number of subjects with abnormal ACTH stimulation test results at Day 15

Statistics	DFD-06 Cream	Temovate Cream	p-value
N	24	22	
Number (%) of Subjects with Abnormal Results	3 (12.5%)	8 (36.4%)	0.086

2.2.5 What were the results of the vasoconstriction trial?

The single-point vasoconstrictor (VCA) study suggested that DFD-06 cream is a high potent topical corticosteroid belonging to Class 2.

2.2.6 Did the applicant assess drug metabolism?

The applicant has not conducted any new drug metabolism studies.

2.2.7 What information is submitted to assess or waive TQT trial?

The applicant has submitted a request for waiver of TQT assessment based on the fact that the mean systemic exposure of DFD-06 cream is lower than Temovate E[®] cream, absence of any cardiovascular adverse events in the two Phase 3 trials, and literature evidence suggesting that neither hERG channel study nor clinical experience with other topical clobetasol products produced any clinically meaningful QT prolongation.

Reviewer comments: *In the opinion of this reviewer the TQT waiver request is reasonable; however, the final decision is deferred to the IRT-QT review team.*

2.2.8 What is the summary of safety?

(b) (4) Cream was well tolerated in two large randomized, multicenter, prospective, vehicle-controlled clinical trials in subjects with moderate to severe plaque psoriasis. Subjects applied (b) (4) Cream or vehicle cream twice daily for 14 days. A total of 378 subjects applied (b) (4) Cream and 178 subjects applied vehicle. Adverse reactions that occurred in at least 1% of subjects treated with (b) (4) Cream for up to 14 days are presented in Table 7.

Table 7: Local Adverse Reactions Occurring in $\geq 1\%$ of Subjects Treated with (b) (4) Cream or Vehicle for up to Two Weeks

	(b) (4) Cream b.i.d. (N = 378)	Vehicle Cream b.i.d. (N = 178)
Application site pain	5.3%	9.6%
Application site pruritus	2.6%	12.4%
Application site fissure	0.8%	4.5%
Application site discoloration	1.9%	1.1%

Less common local adverse events occurring in $< 1\%$ of subjects treated with (b) (4) Cream were application site atrophy, telangiectasia and rash.

2.2.9 What is the summary of efficacy?

Efficacy was measured by the Investigator's Global Assessment (IGA). Two double blind randomized vehicle controlled studies evaluated 543 subjects aged 18 years and older with moderate to severe plaque psoriasis (IGA 3 or 4). Subjects were treated twice daily with (b) (4) Cream or vehicle cream for 14 days. Efficacy was assessed as the proportion of subjects who achieve treatment success defined as an IGA score of 0 or 1 with at least a 2 grade reduction from baseline. The efficacy of (b) (4) Cream in treating psoriasis was superior to vehicle at both Day 8 (Table 8) and Day 15 (Table 9).

Table 8: Efficacy Results at Day 8 from Controlled Clinical Trials with (b) (4) Cream in Moderate Psoriasis

	Study 1			Study 2		
	(b) (4) Cream	Vehicle	p-value	(b) (4) Cream	Vehicle	p-value
Total number of subjects	178	89		176	89	
Subjects with treatment success*	15.7%	5.6%	<0.001	14.2%	1.6%	<0.001

*Treatment success defined as IGA of 0 or 1 with at least a 2 grade reduction from baseline

Table 9: Efficacy Results at Day 15 from Controlled Clinical Trials with (b) (4) in Moderate Psoriasis

	Study 1			Study 2		
	(b) (4) Cream	Vehicle	p-value	(b) (4) Cream	Vehicle	p-value
Total number of subjects	189	89		176	89	
Subjects with treatment success*	30.2%	9.0%	<0.001	30.1%	9.7%	<0.001
Change in BSA	-28.9%	-6.1%	<0.001	-25.1%	-7.4%	<0.001

*Treatment success defined as IGA of 0 or 1 with at least a 2 grade reduction from baseline

2.4 Intrinsic Factors

What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

2.4.1 Effect of age and gender

The applicant has not evaluated the effect of age and gender on the PK of the foam formulation.

2.4.2 Pediatric subjects

The applicant has requested for a waiver of pediatric assessment for subjects aged 0 to (b) (4) years as this product would be unsafe in this age group because of safety concerns since betamethasone dipropionate is a potent corticosteroid. For Taclonex ointment and suspension, pediatric assessment was waived for subjects 0 to 11 years.

For subjects aged (b) (4) years, the applicant has requested for a deferral because adult studies are completed and ready for approval at this stage.

Reviewer comments: *A pediatric study plan (PSP) was submitted on June 27, 2013 following the End of Phase 2 meeting. Agreement on the PSP was reached on December 3, 2015 (b) (4)*

2.4.3 Renal and hepatic impairment

The effect of renal and hepatic impairment on PK of clobetasol was not evaluated by the applicant. This study is not needed as the applicant has proposed a lower strength compared to the one that is already marketed.

2.4.4 What pregnancy and lactation use information is there in the application?

The applicant has not conducted any trials in pregnant and lactating women.

2.5 Extrinsic Factors

2.5.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or response and what is the impact of any differences in exposure or response?

The influence of extrinsic factors on dose-exposure and/or response was not evaluated in vivo.

2.5.2 Drug interactions

The applicant has not conducted any new drug interaction studies with this NDA. Since this is a lower strength product and the systemic exposure is lower than Temovate E[®] Cream, drug interaction assessment is not needed.

2.6 General Biopharmaceutics

2.6.1 Based on biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

The concept of BCS classification does not apply to topically applied products.

2.6.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

The to-be-marketed formulation was used in the maximal use PK trial and the Phase 3 trials. Hence relative bioavailability assessment to bridge between clinical and to-be-marketed formulation is not needed.

2.6.3 What data support or do not support a waiver of in vivo BE data?

The to-be-marketed formulation was used in the pivotal maximal use PK trial and the Phase 3 trials. Hence in vivo BE is not needed.

2.6.4 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Effect of food on the BA is not evaluated for topical formulations.

2.7 Analytical Section

2.7.1 How are the active moieties identified, and measured in the clinical trials?

Clobetasol propionate was identified using ultra performance chromatography and tandem mass spectrometry and serum cortisol levels were determined by competitive immunoassay using direct chemiluminescent technology.

2.7.2 Which metabolites have been selected for analysis?

No metabolites were selected for PK assessment.

2.7.3 For all moieties measured, is free, bound, or total measured?

Total concentration was measured.

2.7.4 What is the range of the standard curve? How does it relate to the requirements for clinical studies?

The range of standard curve was 10 to 500 pg/mL

This range was adequate as none of the plasma concentrations of clobetasol propionate exceeded the upper limit of the concentration range.

2.7.5 What are the accuracy and precision of the assay?

Inter-run Results

Accuracy (% bias) = - 3.00 % to - 0.54 %

Precision (% CV) = 3.86 % to 5.66%

Intra-run Results

Accuracy (% bias) = - 4.40 % to 1.48 %

Precision (% CV) = 2.11 % to 6.18%

2.7.6 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler, etc.)?

<i>Parameter</i>	<i>Analyte – Clobetasol propionate</i>
Freeze/Thaw cycle stability	4 cycles at - 20°C and - 80 °C
Bench top stability	23 h 32 min at room temperature and 23 h 23 min at 4°C
Stability of the analyte in whole blood	94 h 08 min at room temperature
Long term stability	164 days at - 20 °C and 122 days at -80 °C

Reviewer comments: *The duration of long term PK sample stability was adequate to cover the duration of PK sample storage for the maximal use PK trial. The long term stability of cortisol was 10 days at 15 °C to 25 °C and this was also adequate.*

2.7.7 What are the results of incurred sample reanalysis (ISR)?

A total of 50 samples (at least 10%) were reanalyzed for the incurred sample reproducibility test to demonstrate that results obtained from study sample analysis are reproducible. A total of 96.00% of the reanalyzed samples met the criteria of assay reproducibility, which was the percentage difference must be within $\pm 20\%$ for at least 67% of the ISR samples.

3. Detailed Labeling Recommendations

The following changes are recommended in applicant's proposed labeling. The **bold and underlined** text indicates insertion recommended by the reviewer and the ~~striketrough~~ text indicates recommended deletion.

5.1 Effects on the Endocrine System

(b) (4) Cream can cause reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency. This may occur during treatment or after withdrawal of treatment. Factors that predispose a patient to HPA axis suppression include the use of high-potency steroids, large treatment surface areas, prolonged use, use of occlusive dressings, altered skin barrier, liver failure, and young age.

Evaluation for HPA axis suppression may be done by using the adrenocorticotrophic hormone (ACTH) stimulation test. In a trial evaluating the effects of (b) (4) Cream on the HPA axis, subjects with plaque psoriasis applied (b) (4) Cream twice daily to at least 20% of involved body surface area for 15 days. Abnormal ACTH stimulation tests suggestive of HPA axis suppression were seen in 3 of 24 (12.5%) (b) (4) on (b) (4) [see *Clinical Pharmacology* (12.2)].

If HPA axis suppression is documented, gradually withdraw the drug, reduce the frequency of application, or substitute with a less potent corticosteroid. If signs and symptoms of steroid withdrawal occur, supplemental systemic corticosteroids may be required.

Systemic effects of topical corticosteroids may also manifest as Cushing's syndrome, hyperglycemia, and glucosuria. These complications are rare and generally occur after prolonged exposure to larger than recommended doses, particularly with high-potency topical corticosteroids.

Minimize the unwanted risks from endocrine effects by mitigating risk factors favoring increased systemic bioavailability and by using the product as recommended [see *Dosage and Administration* (2)]

Pediatric patients may be more susceptible to systemic toxicity due to their larger skin surface to body mass ratios [see *Use in Specific Populations* (8.4)].

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Corticosteroids play a role in cellular signaling, immune function, inflammation, and protein regulation; however, the precise mechanism of action in corticosteroid responsive dermatoses is unknown. The contribution to efficacy by individual components of the vehicle has not been established.

12.2 Pharmacodynamics

Vasoconstrictor Assay

(b) (4) Cream, 0.025% is in the high range of potency as demonstrated in vasoconstrictor studies in healthy subjects when compared with other topical corticosteroids. However, similar blanching scores do not necessarily imply therapeutic equivalence.

Hypothalamic-Pituitary-Adrenal (HPA) Axis Suppression:

HPA axis suppression was evaluated in a clinical trial in adult subjects (N=24) with moderate to severe plaque psoriasis involving a mean body surface area of $26.5 \pm 8.6\%$. Treatment consisted of twice daily application of (b) (4) Cream, 0.025% for 15 days. Adrenal suppression, as indicated by a 30-minute post-stimulation cortisol level ≤ 18 mcg/dL, was observed in 3 out of 24 subjects (12.5%) after 15 days.

(b) (4)

12.3 Pharmacokinetics

Topical corticosteroids can be absorbed from intact healthy skin. The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including the product formulation and the integrity of the epidermal barrier. Occlusion, inflammation, and/or other disease processes in the skin may also increase percutaneous absorption. Once absorbed through the skin, topical corticosteroids are metabolized, primarily in the liver, and are then excreted by the kidneys. Some corticosteroids and their metabolites are also excreted in the bile.

In a ^{(b) (4)} pharmacokinetic study in **24 adult male and female** subjects with **moderate to severe psoriasis**, **were treated twice daily for 15 days with a mean dose of approximately 3.7g of ^{(b) (4)} Cream, 0.025% per application to a mean body surface area of $26.5 \pm 8.6\%$.** ^{(b) (4)} **On Day 15, the mean \pm SD pre-treatment and post-treatment systemic concentrations of clobetasol propionate were 50.7 ± 96.0 pg/mL and 56.3 ± 104.7 pg/mL; respectively.** ^{(b) (4)}



(b) (4)

4. INDIVIDUAL STUDY REVIEW

Trial Number: DFD06-CD-007 Maximal Use PK Trial

Title: A Randomized, Parallel Group, Open Label, Multicenter Study to Assess the Potential for Adrenal Suppression and Systemic Drug Absorption Following Multiple Dosing with DFD-06 Cream versus Temovate® Cream (clobetasol propionate 0.05%) in Subjects with Moderate to Severe Plaque Psoriasis

Objectives:

- To evaluate the potential of DFD-06 Cream to suppress the hypothalamic-pituitary-adrenal (HPA) axis as compared to Temovate (clobetasol propionate) Cream 0.05%, when applied twice daily for 15 days, in subjects with moderate to severe plaque psoriasis under maximal use conditions with the final-to-be-marketed formulation.
- To compare the plasma concentrations of clobetasol propionate after multiple uses of Temovate Cream to DFD-06 Cream under maximal use conditions with the final-to-be-marketed formulation.

Trial design: This was a 15-day, randomized, multicenter, multidose, comparator controlled, open-label study in subjects with moderate to severe plaque psoriasis were randomized (1:1) to treatment with DFD-06 Cream or Temovate Cream.

Subjects applied study product twice daily for 15 days to all affected areas on the body excluding face, scalp, groin, axillae, and other intertriginous areas. Subject visits were scheduled at Screening, Baseline (Day 1), Day 8, Day 15, and Day 43 (if needed to confirm recovery).

Subjects were tested for HPA axis function using the adrenocorticotropin (ACTH) stimulation test (i.e., a cosyntropin intravenous or intramuscular injection) at the Screening Visit (at least 14 days and no more than 28 days prior to Baseline) and at Day 15. If the HPA axis was suppressed at Day 15, another test was to be administered 28 days later (at approximately Day 43) to confirm recovery. The ACTH stimulation test was to be repeated every 28 days until recovery was confirmed (or until the cause of suppression was diagnosed). Blood samples for serum dehydroepiandrosterone sulfate (DHEAS) were taken at the time of the screening ACTH stimulation test, on Day 8, and at the time of the ACTH stimulation test on Day 15 (pre-test sample) as a secondary measure of HPA axis suppression

A pharmacokinetic (PK) blood sample was taken to obtain a baseline value at the time of the screening ACTH stimulation test. On Day 15, subjects applied the last dose of study product at the clinic up to 60 minutes after a pre-treatment PK blood sample was taken (Day 15 Visit, 0 hour). PK blood samples were then collected at 1, 3, and 6 hours (\pm 5 minutes) after application of the study product.

Reviewer comments: *The applicant has assessed serum dehydroepiandrosterone sulfate (DHEAS) test to evaluate HPA axis suppression. Currently this test is not accepted as a standard to assess HPA axis suppression and would not have any regulatory impact.*

Disposition of subjects: A total of 88 subjects were screened for the study, 50 of whom were randomized. Of the 50 subjects randomized, 45 (90%) completed the study and 5 (10%) discontinued early. Three subjects were discontinued from the study due to subject decision/withdrawal of consent and 2 subjects were lost to follow-up. No subject discontinued the study due to an AE (Table 10).

Table 10: Subject Enrollment and Subject Discontinuations by Reason

Parameter	Number (%) of Subjects		
	DFD-06 Cream	Temovate Cream	Overall
Number Randomized	26	24	50
Subjects Included in Safety Analysis	24 (92.3%)	22 (91.7%)	46 (92.0%)
Subjects Excluded from Safety Analysis	2 (7.7%)	2 (8.3%)	4 (8.0%)
Number Who Completed the Study	23 (88.5%)	22 (91.7%)	45 (90.0%)
Total Discontinued	3 (11.5%)	2 (8.3%)	5 (10.0%)
Reason Discontinued			
Subject decision/withdrawal of consent	2 (7.7%)	1 (4.2%)	3 (6.0%)
Significant protocol violation or non-compliant with study protocol	0 (0.0%)	0 (0.0%)	0 (0.0%)
Subject became pregnant	0 (0.0%)	0 (0.0%)	0 (0.0%)
AE related to study product for which the subject desired to discontinue treatment or the investigator determined that it was in the subject's best interest to be discontinued	0 (0.0%)	0 (0.0%)	0 (0.0%)
AE unrelated to study product for which the subject desired to discontinue treatment or the investigator determined that it was in the subject's best interest to be discontinued	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lost to follow-up	1 (3.8%)	1 (4.2%)	2 (4.0%)
Investigator discretion	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)

Reviewer comments: *In the maximal use trial, it is recommended that the applicant target at least 16 completers and the data in the table above shows that 23 subjects completed the DFD-06 cream arm.*

Demographics: Demographic data and proportion of the BSA affected by psoriasis that was recorded at baseline are summarized in Table 11.

Table 11: Demographic Characteristics

Parameter Category	DFD-06 Cream (N = 24)	Temovate Cream (N = 22)	Overall (N = 46)
Gender			
Female	7 (29.2%)	8 (36.4%)	15 (32.6%)
Male	17 (70.8%)	14 (63.6%)	31 (67.4%)
Ethnicity			
Hispanic or Latino	14 (58.3%)	13 (59.1%)	27 (58.7%)
Not Hispanic or Latino	10 (41.7%)	9 (40.9%)	19 (41.3%)
Race			
White	24 (100.0%)	22 (100.0%)	46 (100.0%)
Age Groups			
18 to < 40	10 (41.7%)	2 (9.1%)	12 (26.1%)
40 to < 64	13 (54.2%)	16 (72.7%)	29 (63.0%)
64 to < 75	0 (0.0%)	4 (18.2%)	4 (8.7%)
≥ 75	1 (4.2%)	0 (0.0%)	1 (2.2%)
Age (years)			
N	24	22	46
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
Body Surface Area (BSA %)			
N	24	22	46
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

Max = maximum; Min = minimum; SD = standard deviation

Reviewer comments: For adult subjects with psoriasis, the maximal use PK trial has usually included subjects with at least 20% BSA. The data in the table above indicates that subjects with at least 20% BSA were included in this trial.

Change in disease severity during treatment: All subjects had an Investigator’s Global Assessment (IGA) score of 3 or 4 (moderate or severe psoriasis) at Baseline (Day 1). As shown in Table ABC, the efficacy results were similar between treatment groups. At Day 15, 50% of the subjects in each treatment group had an IGA score of 2 (mild) and 16.7% in the DFD-06 group and 18.1% in the Temovate E[®] Cream group had a score of 0 or 1 (none or minimal). Table 12 summarizes the change in the disease severity.

Table 12: Investigator’s Global Assessment (IGA) of Disease Severity

Visit Grade	DFD-06 Cream (N = 24)	Temovate Cream (N = 22)
Visit 2/ Baseline/ Day 1		
N	24	22
None (0)	0 (0.0%)	0 (0.0%)
Minimal or Almost Clear (1)	0 (0.0%)	0 (0.0%)
Mild (2)	0 (0.0%)	0 (0.0%)
Moderate (3)	19 (79.2%)	15 (68.2%)
Severe/Very Severe (4)	5 (20.8%)	7 (31.8%)
Visit 3/Day 8		
N	24	22
None (0)	0 (0.0%)	0 (0.0%)
Minimal or Almost Clear (1)	1 (4.2%)	1 (4.5%)
Mild (2)	6 (25.0%)	6 (27.3%)
Moderate (3)	16 (66.7%)	13 (59.1%)
Severe/Very Severe (4)	1 (4.2%)	2 (9.1%)
Visit 4/ Day 15		
N	24	22
None (0)	0 (0.0%)	1 (4.5%)
Minimal or Almost Clear (1)	4 (16.7%)	3 (13.6%)
Mild (2)	12 (50.0%)	11 (50.0%)
Moderate (3)	7 (29.2%)	7 (31.8%)
Severe/Very Severe (4)	1 (4.2%)	0 (0.0%)

Reviewer comments: Maximal use PK trial recommends that subjects within the upper range of disease severity be included in the trial. The table above shows that subjects with moderate to severe psoriasis were included in this trial.

Treatment compliance and drug usage: Subjects were instructed to apply study product twice daily for 15 days. The number of applications, the total amount (weight) of study product used, and the amount of the last dose were all similar between the treatment groups (Table 13).

Table 13: Extent of exposure to the study product

Parameter Statistics	DFD-06 Cream	Temovate Cream
Number of Applications Applied		
N	24	22
Mean ± SD	28.3 ± 3.1	31.0 ± 9.3
Median	29.0	29.0
Min, Max	20, 35	22, 71
N(%) Subjects with at least 26 applications	19 (79.2%)	21 (95.5%)
Total Amount of Study Product Used (g)		
N	23	22
Mean ± SD	107.0 ± 42.5	101.7 ± 40.5
Median	103.2	95.1
Min, Max	20.5, 216.5	38.0, 207.3
Amount of Last Dose Used (g)		
N	23	22
Mean ± SD	5.2 ± 3.0	5.3 ± 2.8
Median	4.48	4.6
Min, Max	0.96, 12.0	1.66, 12.9

Max = maximum; Min = minimum; SD = standard deviation

Reviewer comments: The mean daily dose following BID application for DFD-06 Cream was approximately 7.56 g, and for Temovate cream was approximately 6.56 g.

ACTH Stimulation Test: All cortisol samples for the ACTH stimulation test were analyzed within the 10-day stability window. The proportion of subjects who had abnormal ACTH stimulation test results (HPA axis suppression) post-stimulation at Day 15 was numerically lower in the DFD-06 Cream group than in the Temovate Cream group, 12.5% versus 36.4%, and the difference was not considered statistically significance ($p = 0.086$) (Table 14).

Table 14: Number of Subjects with Abnormal ACTH Stimulation Test Result at Day 15

Statistics	DFD-06 Cream	Temovate Cream	p-value
N	24	22	0.086 ¹
Number (%) of subjects with abnormal results	3 (12.5%)	8 (36.4%)	

¹ P-value for comparison between the two treatment groups from Fisher's exact tests.

Serum DHEAS Concentration: On average, DHEAS concentrations were numerically lower compared to Baseline at Day 8 and Day 15. The percent reduction from baseline in serum DHEAS, a secondary measure of HPA axis suppression, was numerically less in the DFD-06 Cream group than the Temovate Cream group at both Day 8 and Day 15; the differences between the treatment groups were not statistically significant (Table 15).

Table 15: Percent Reduction in Serum DHEAS Concentration (µg/dL)

Study Visit	Statistics	DFD-06 Cream	Temovate Cream	p-value
Percent reduction from Screening to Day 8	N	23	22	
	Mean ± SD	6.8 ± 28.3	19.7 ± 39.7	0.216 ¹
	Median	2.5	24.8	
	Min, Max	-50.4, 100.0	-105.3, 100.0	
Percent reduction from Screening to Day 15	N	23	22	
	Mean ± SD	11.0 ± 27.0	21.6 ± 46.4	0.353 ¹
	Median	16.1	28.4	
	Min, Max	-48.7, 69.0	-122.7, 100.0	

Max = maximum; Min = minimum; SD = standard deviation

Percent reduction = 100*(Screening - Day X)/Screening, where X = 8 or 15.

¹ P-value for treatment comparison from one-way analysis of variance model (ANOVA).

The percent reduction in serum concentration of DHEAS from Screening to Day 8 and to Day 15 in subjects with HPA axis suppression was significantly greater than in subjects without HPA axis suppression (TABLE 16).

Table 16: Percent Reduction in Serum DHEAS Concentration (µg/dL) by Subject Status of HPA Axis Suppression

Time Points	Statistics	With HPA Axis Suppression ¹	Without HPA Axis Suppression ²	p-value
Percent reduction from Screening to Day 8	N	11	34	
	Mean ± SD	34.7 ± 29.7	6.1 ± 33.5	0.015 ³
	Median	29.7	9.4	
	Min, Max	1.3, 100.0	-105.3, 100.0	
Percent reduction from Screening to Day 15	N	11	34	
	Mean ± SD	54.8 ± 20.2	3.7 ± 33.4	<0.001 ³
	Median	52.5	13.8	
	Min, Max	29.6, 100.0	-122.7, 65.9	

Max = maximum; Min = minimum; SD = standard deviation

Percent reduction = 100*(Screening - Day X)/Screening, where X = 8 or 15.

¹ A subject with HPA axis suppression was defined as cortisol level ≤ 18.00 µg/dL at 30 minutes post stimulation.

² A subject without HPA axis suppression was defined as cortisol level > 18.00 µg/dL at 30 minutes post stimulation.

³ P-values for group comparisons from one-way analysis of variance model (ANOVA).

Clobetasol propionate concentration: Across all subjects, the mean post-treatment concentration of clobetasol propionate was significantly less in the DFD-06 Cream group than in the Temovate Cream group, 56.3 versus 152.5 pg/mL (p = 0.014) (Table 17).

Table 17: Day 15 Pre-Treatment and Mean Post-Treatment Plasma Concentrations of Clobetasol Propionate (pg/mL)

Visit: Time Point	Statistics	DFD-06 Cream	Temovate Cream	p-value
Day 15: Pre-Treatment (0 hour)	N	24	22	
	Mean ± SD	50.7 ± 96.0	130.7 ± 146.2	NA
	95% CI of Mean	(10.1 to 91.2)	(65.9 to 195.5)	
	Median	28.0	81.1	
	Min, Max	0.0, 477.3	0.0, 571.3	
Average of Post-Treatment*	N	22	22	
	Mean ± SD	56.3 ± 104.7	152.5 ± 140.9	0.014 ¹
	95% CI of Mean	(9.9 to 102.7)	(90.0 to 214.9)	
	Median	29.5	131.5	
	Min, Max	0.0, 503.4	0.00, 517.2	

CI = confidence interval; Max = maximum; Min = minimum; NA = not applicable; SD = standard deviation

A concentration value of < 10.0 occurring prior to first quantifiable concentration during a day for a subject was treated as zero and others were set to missing for all statistical analyses.

¹ P-value for treatment comparison from one-way analysis of variance model (ANOVA).

*Average of post-treatment concentrations were calculated using all available post-treatment data except for the plasma concentrations that were > 1 hour off-schedule.

The mean post-treatment plasma concentrations of clobetasol propionate in subjects with HPA axis suppression were significantly greater than in subjects without HPA axis suppression, 217.1 versus 71.2 pg/mL (p = 0.001) (Table 18).

Table 18: Plasma Concentrations of Clobetasol Propionate (pg/mL) by Subject Status of HPA Axis Suppression

Visit: Time Point	Statistics	With HPA Axis Suppression ¹	Without HPA Axis Suppression ²	p-value
Day 15: Pre-Treatment (0 hour)	N	11	35	
	Mean ± SD	195.7 ± 150.8	55.4 ± 100.3	NA
	95% CI of Mean	(94.4 to 297.0)	(20.9 to 89.9)	
	Median	136.5	26.2	
	Min, Max	34.5, 477.3	0.0, 571.3	
Average of Post-Treatment*	N	10	34	
	Mean ± SD	217.1 ± 153.8	71.2 ± 106.0	0.001 ³
	95% CI of Mean	(107.1 to 327.1)	(34.2 to 108.2)	
	Median	185.6	31.7	
	Min, Max	33.4, 503.4	0.0, 517.2	

CI = confidence interval; Max = maximum; Min = minimum; NA = not applicable; SD = standard deviation

A concentration value of < 10.0 occurring prior to first quantifiable concentration during a day for a subject was treated as zero and others were set to missing for all statistical analyses.

Subjects with or without HPA axis suppression were identified based on the ACTH data from Day 15.

¹ A subject with HPA axis suppression was defined as cortisol level ≤ 18.00 µg/dL at 30 minutes post stimulation.

² A subject without HPA axis suppression was defined as cortisol level > 18.00 µg/dL at 30 minutes post stimulation.

³ P-values for group comparisons from one-way analysis of variance model (ANOVA).

*Average of post-treatment concentrations were calculated using all available post-treatment data except for the plasma concentrations that were > 1 hour off-schedule.

Plasma concentration at each time point in all subjects is shown in Table 19 and in Table 20 plasma concentration at each time point with respect to status of HPA axis suppression is shown.

Table 19: Plasma Concentrations of Clobetasol Propionate (pg/mL) at each time point

Visit: Time Point	Statistics	DFD-06 Cream	Temovate Cream	p-value
Screening	N	24	22	
	Mean ± SD	0.000 ± 0.0000	2.040 ± 9.5663	NA
	95% CI of Mean	(0.000 to 0.000)	(-2.202 to 6.281)	
	Median	0.000	0.000	
	Min, Max	0.00, 0.00	0.00, 44.87	
Day 15: Pre-Treatment (0 hour)	N	24	22	
	Mean ± SD	50.651 ± 96.0016	130.735 ± 146.1732	NA
	95% CI of Mean	(10.113 to 91.189)	(65.926 to 195.545)	
	Median	27.970	81.100	
	Min, Max	0.00, 477.26	0.00, 571.29	
Day 15: 1 Hour	N	23	22	
	Mean ± SD	60.919 ± 142.7070	166.949 ± 183.3209	NA
	95% CI of Mean	(-0.792 to 122.630)	(85.669 to 248.229)	
	Median	31.420	115.735	
	Min, Max	0.00, 704.76	0.00, 737.25	
Day 15: 3 Hours	N	24	21	
	Mean ± SD	50.445 ± 71.1675	156.968 ± 144.6841	NA
	95% CI of Mean	(20.394 to 80.497)	(91.109 to 222.827)	
	Median	28.090	128.360	
	Min, Max	0.00, 335.49	0.00, 566.92	
Day 15: 6 Hours	N	24	21	
	Mean ± SD	58.825 ± 99.1553	146.324 ± 131.2930	NA
	95% CI of Mean	(16.955 to 100.694)	(86.560 to 206.088)	
	Median	30.325	125.860	
	Min, Max	0.00, 469.84	0.00, 491.56	
Average of Post-Treatment*	N	22	22	
	Mean ± SD	56.339 ± 104.6688	152.458 ± 140.8674	
	95% CI of Mean	(9.931 to 102.746)	(90.001 to 214.915)	0.014 ¹
	Median	29.450	131.540	
	Min, Max	0.00, 503.36	0.00, 517.18	

CI = confidence interval; Max = maximum; Min = minimum; SD = standard deviation

A concentration value of < 10.0 occurring prior to first quantifiable concentration during a day for a subject was treated as zero and others were set to missing for all statistical analyses.

¹ P-value for treatment comparison from one-way analysis of variance model (ANOVA).

*Average of post-treatment concentrations were calculated using all available post-treatment data except for the plasma concentrations that were > 1 hour off-schedule.

Table 20: Plasma Concentrations of Clobetasol Propionate (pg/mL) by Subject Status of HPA Axis Suppression

Visit: Time Point	Statistics	With HPA Axis Suppression ¹	Without HPA Axis Suppression ²	p-value
Screening	N	11	35	
	Mean ± SD	0.000 ± 0.0000	1.282 ± 7.5844	NA
	95% CI of Mean	(0.000 to 0.000)	(-1.323 to 3.887)	
	Median	0.000	0.000	
	Min, Max	0.00, 0.00	0.00, 44.87	
Day 15: Pre-Treatment (0 hour)	N	11	35	
	Mean ± SD	195.691 ± 150.7514	55.406 ± 100.3403	NA
	95% CI of Mean	(94.415 to 296.967)	(20.938 to 89.874)	
	Median	136.490	26.230	
	Min, Max	34.48, 477.26	0.00, 571.29	
Day 15: 1 Hour	N	11	34	
	Mean ± SD	210.873 ± 196.2904	81.012 ± 151.2306	NA
	95% CI of Mean	(79.003 to 342.742)	(28.245 to 133.779)	
	Median	155.880	31.730	
	Min, Max	36.38, 704.76	0.00, 737.25	
Day 15: 3 Hours	N	11	34	
	Mean ± SD	200.668 ± 126.0445	67.637 ± 103.9073	NA
	95% CI of Mean	(115.990 to 285.346)	(31.382 to 103.892)	
	Median	195.450	33.185	
	Min, Max	34.84, 422.00	0.00, 566.92	
Day 15: 6 Hours	N	11	34	
	Mean ± SD	205.386 ± 147.4279	65.451 ± 91.5422	NA
	95% CI of Mean	(106.343 to 304.430)	(33.511 to 97.392)	
	Median	178.050	36.260	
	Min, Max	29.09, 469.84	0.00, 491.56	
Average of Post-Treatment ³	N	10	34	
	Mean ± SD	217.123 ± 153.7979	71.244 ± 106.0424	0.001 ⁴
	95% CI of Mean	(107.103 to 327.143)	(34.244 to 108.244)	
	Median	185.565	31.740	
	Min, Max	33.44, 503.36	0.00, 517.18	

CI = confidence interval; Max = maximum; Min = minimum; NA = not applicable; SD = standard deviation

A concentration value of < 10.0 occurring prior to first quantifiable concentration during a day for a subject was treated as zero and others were set to missing for all statistical analyses.

Subjects with or without HPA axis suppression were identified based on the ACTH data from Day 15.

¹ A subject with HPA axis suppression was defined as cortisol level ≤ 18.00 µg/dL at 30 minutes post stimulation.

² A subject without HPA axis suppression was defined as cortisol level > 18.00 µg/dL at 30 minutes post stimulation.

³ P-values for group comparisons from one-way analysis of variance model (ANOVA).

⁴ Average of post-treatment concentrations were calculated using all available post-treatment data except for the plasma concentrations that were > 1 hour off-schedule.

Brief Summary of Adverse Events: One or more treatment emergent adverse events (TEAEs) were reported for 25% of subjects in the DFD-06 Cream group and 50% of subjects in the Temovate Cream group. The most frequently reported TEAEs were HPA axis suppression (12.5% DFD-06, 36.4% Temovate). No deaths were reported and no subjects discontinued treatment with study product or the study due to TEAEs. Results of local cutaneous safety evaluations were similar between the treatment groups. There were no clinically significant findings for vital sign measurements.

Study DFD06-CD-003a: Single point vasoconstrictor study

Title: A Randomized, Evaluator-Blinded, Within-Subject, Single-Center Vasoconstrictor Study to Determine the Potency of DFD06 Cream, 0.025% Clobetasol Propionate Compared to Six Different Currently Marketed Topical Corticosteroid Formulations of Known Potency and a Vehicle Cream Base under Non-Occluded Conditions in Healthy Adult Subjects

Objective: The objective of this study was to use the vasoconstrictor response to determine the potency of DFD06 Cream, 0.025% clobetasol propionate (Promius Pharma, LLC) compared to six currently marketed topical corticosteroid formulations of known potency.

Products used: In addition to the test and vehicle cream base, the six currently marketed topical corticosteroids formulations of known potency were:

- Temovate® cream, 0.05% (clobetasol propionate cream) – Class 1
- Clobex® (clobetasol propionate) 0.05% lotion – Class 1
- Diprolene® (augmented betamethasone dipropionate) lotion, 0.05% - Class 1
- Triamcinolone acetonide cream USP, 0.1% - Class 3
- Fluticasone propionate cream, 0.05% - Class 5
- Hydrocortisone cream USP, 2.5% - Class 7

Reviewer comments: *The bracketing using products of known potency class was adequate.*

Study Design: This study was a single-point, randomized, evaluator-blinded, within-subject, single-center study conducted to evaluate the vasoconstrictor properties of DFD06 Cream, 0.025% clobetasol propionate (Promius Pharma, LLC), six currently marketed topical corticosteroids formulations of known potency (Temovate® cream, 0.05% (clobetasol propionate cream); Clobex® (clobetasol propionate) 0.05% lotion; Diprolene® (augmented betamethasone dipropionate) lotion, 0.05%; fluticasone propionate cream, 0.05%; triamcinolone acetonide cream USP, 0.1%; hydrocortisone cream USP, 2.5%), and a vehicle cream base.

A 10 µl amount of each formulation was applied to a single application site on the flexor surfaces of each subject's forearms (left and right) and kept in place for 16 hours. In addition, two untreated control sites were designated on each forearm. The degree of skin blanching was visually evaluated at each site pre-dose (baseline assessments) and at about 18 hours after the application of the study drug (about 2 hours after washing the test sites to remove study drug) by a trained evaluator using both visual assessment and a calibrated Chromameter. The primary analysis was based on the visual scoring. The post-dose ChromaMeter readings were corrected for both the average pre-dose (baseline) readings and the average baseline-adjusted reading for the untreated sites (on the same arm) at the corresponding post-dose reading time. The relative potency of DFD06 Cream was estimated by comparing it with the reference products of known potency.

Selection of Study Population: The subject population included 80 healthy adult subjects who satisfied all entry criteria and all subjects completed the study. The subjects enrolled had A Fitzpatrick skin type of 3 or less and should have demonstrated blanching response to Triamcinolone Acetonide Cream USP, 0.1% (E. Fougera & Co.) (visual assessment score of at least 1).

Blinding: The visual evaluators and the ChromaMeter operators were blinded as to the treatment at each site. Study personnel who were involved in the preparation/application and removal of the study drugs did not perform the evaluation of responses.

Assessments: The degree of vasoconstriction was assessed using visual scoring as well as using a ChromaMeter (a-scale reading). Assessments were performed under standard fluorescent lighting and at room temperature. The visual evaluator(s) and the ChromaMeter operator(s) did not have knowledge of treatment location at each site.

Visual Assessments: The degree of skin blanching was visually evaluated at each site pre-dose (baseline assessments) and at about 18 hours after the application of the study drug (about 2 hours after washing the test sites to remove study drug) by a trained evaluator according to the following rating scale:

- 0 =No pallor; no change from surrounding area.
- 1= Mild pallor; slight or indistinct outline of application site.
- 2=Moderate pallor; discernible outline of application site.
- 3=Intense pallor; clean, distinct outline of application site.

Any subject with a visual baseline assessment score greater than 0 was not considered eligible for dosing.

ChromaMeter Assessments: In this study, two ChromaMeter operators (L-R and MMT) performed all of the assessments for all subjects using a single ChromaMeter (IC# 4180). Before the study, the intra and inter-site precision of operators were evaluated.

Reviewer comments: *The applicant has submitted validation reports of ChromaMeter. However, these details are not included in this review as visual assessment was the primary endpoint.*

Demographics: Summary of demographics is shown in Table 21.

Table 21: Summary of demographics

SUBJECTS INCLUDED IN STATISTICAL ANALYSIS (N = 80)	
Gender	
Males	38 (47.50%)
Females	42 (52.50%)
Hispanic or Latino Race	
American Indian or Alaskan Native	0 (0.00%)
Asian	0 (0.00%)
Black or African American	0 (0.00%)
Native Hawaiian or Other Pacific Islander	0 (0.00%)
White	3 (3.75%)
Other	4 (5.00%)
Not Hispanic or Latino Race	
American Indian or Alaskan Native	1 (1.25%)
Asian	1 (1.25%)
Black or African American	0 (0.00%)
Native Hawaiian or Other Pacific Islander	0 (0.00%)
White	67 (83.75%)
Other	4 (5.00%)
Age (years)	
Mean ± SD	41.11 ± 13.35
Median	43.50
Range	19 - 65
Age Groups	
< 18	0 (0.00%)
18 – 40	38 (47.50%)
41 – 64	40 (50.00%)
65 – 75	2 (2.50%)
> 75	0 (0.00%)
Weight (lbs)	
Mean ± SD	174.39 ± 33.67
Median	173.50
Range	105 - 283
BMI (kg/m²)	
Mean ± SD	26.92 ± 3.80
Median	26.45
Range	18.9 - 34.7
Tobacco User²	
Yes	0 (0.00%)
No	80 (100.00%)
Fitzpatrick Skin Type	
I	0 (0.00%)
II	44 (55.00%)
III	36 (45.00%)
IV	0 (0.00%)

¹ Determined at screening.

² Defined as current tobacco user (having used tobacco within 30 days before dosing and throughout the entire study).

Results of Vasoconstriction Analysis: Mean results from visual assessments (primary endpoint) and mean results from ChromaMeter assessments (secondary endpoint) are provided in Table 22 and 24. Comparison of p-values for statistical significance after adjusting for multiple testing (Tukey method) of head-to-head study drugs for the visual (primary) and Chromameter-derived data are presented in Tables 23 and 25, respectively.

Table 22: Mean Results from Visual Assessments in Order of Most to Least Potent Formulation (Primary endpoint)

	Formulations	N	Mean and Standard Deviation	REGWQ Grouping*
Reference 2	Temovate [®] Cream, 0.05% (clobetasol propionate cream); PharmaDerm [®] A division of Fougera Pharmaceuticals Inc.; (b) (4)	80	2.1375 ± 0.8678	A
Reference 3	Clobex [®] (clobetasol propionate) 0.05% Lotion; Marketed by: Galderma Laboratories, L.P.; (b) (4)	80	2.0125 ± 0.8418	A B
Reference 4	Diprolene [®] (augmented betamethasone dipropionate) Lotion, 0.05% ; Manuf. for: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. (b) (4)	80	1.8750 ± 0.9463	B
Test 1	DFD06 Cream 0.025%; Promius Pharma, LLC; (b) (4)	80	1.6438 ± 0.9487	C
Reference 6	Triamcinolone Acetonide Cream USP, 0.1% ; E. Fougera & Co., A division of Fougera Pharmaceuticals Inc.; (b) (4)	80	0.9063 ± 0.8460	D
Reference 5	Fluticasone Propionate Cream, 0.05% ; E. Fougera & Co., A division of Fougera Pharmaceuticals Inc.; (b) (4)	80	0.7563 ± 0.7713	D
Reference 7	Hydrocortisone Cream USP, 2.5% ; E. Fougera & Co., A division of Fougera Pharmaceuticals Inc.; (b) (4)	80	0.2000 ± 0.3522	E
Reference 8	Vehicle Cream; Promius Pharma, LLC; (b) (4)	80	0.1438 ± 0.3101	E
Untreated	No Treatment	80	0.1094 ± 0.2099	E

*Products with the same Ryan-Einot-Gabriel-Welsh Multiple Range Test (REGWQ) grouping letter are not statistically significantly different using a global 5% significance level.

Table 23: Comparison of p-values for statistical significance - Visual Assessment (Primary endpoint)

	Reference 2	Reference 3	Reference 4	Reference 5	Reference 6	Reference 7	Reference 8	Test 1	No Treatment
Reference 2	—	0.8932	0.0760	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001
Reference 3	0.8932	—	0.8296	<.0001	<.0001	<.0001	<.0001	0.0012	<.0001
Reference 4	0.0760	0.8296	—	<.0001	<.0001	<.0001	<.0001	0.1835	<.0001
Reference 5	<.0001	<.0001	<.0001	—	0.7500	<.0001	<.0001	<.0001	<.0001
Reference 6	<.0001	<.0001	<.0001	0.7500	—	<.0001	<.0001	<.0001	<.0001
Reference 7	<.0001	<.0001	<.0001	<.0001	<.0001	—	0.9994	<.0001	0.9836
Reference 8	<.0001	<.0001	<.0001	<.0001	<.0001	0.9994	—	<.0001	1.0000
Test 1	<.0001	0.0012	0.1835	<.0001	<.0001	<.0001	<.0001	—	<.0001
No Treatment	<.0001	<.0001	<.0001	<.0001	<.0001	0.9836	1.0000	<.0001	—

Table 24: Mean Results from ChromaMeter Assessments in Order of Most to Least Potent Formulation (secondary endpoint)

Formulations		N	Mean and Standard Deviation	REGWQ Grouping*
Reference 2	Temovate [®] Cream, 0.05% (clobetasol propionate cream); PharmaDerm [®] A division of Fougera Pharmaceuticals Inc.; (b) (4) (b) (4)	80	2.9609 ± 1.1184	A
Reference 3	Clobex [®] (clobetasol propionate) 0.05% Lotion; Marketed by: Galderma Laboratories, L.P.; (b) (4) (b) (4)	80	2.7371 ± 1.0612	A B
Reference 4	Diprolene [®] (augmented betamethasone dipropionate) Lotion, 0.05% ; Manuf. for: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. ; (b) (4) (b) (4)	80	2.4550 ± 0.9930	B
Test 1	DFD06 Cream 0.025%; Promius Pharma, LLC; (b) (4) (b) (4)	80	1.9373 ± 1.0660	C
Reference 6	Triamcinolone Acetonide Cream USP, 0.1% ; E. Fougera & Co., A division of Fougera Pharmaceuticals Inc.; (b) (4) (b) (4)	80	0.9289 ± 1.0202	D
Reference 5	Fluticasone Propionate Cream, 0.05% ; E. Fougera & Co., A division of Fougera Pharmaceuticals Inc.; (b) (4) (b) (4)	80	0.6393 ± 0.8293	D
Reference 7	Hydrocortisone Cream USP, 2.5% ; E. Fougera & Co., A division of Fougera Pharmaceuticals Inc.; (b) (4) (b) (4)	80	0.0618 ± 0.6571	E
Untreated	No Treatment	80	0.0016 ± 0.0024	E
Reference 8	Vehicle Cream; Promius Pharma, LLC; (b) (4) (b) (4)	80	-0.2525 ± 0.5682	E

*Products with the same Ryan-Einot-Gabriel-Welsh Multiple Range Test (REGWQ) grouping letter are not statistically significantly different using a global 5% significance level.

Table 25: Comparison of p-values for statistical significance - ChromaMeter Assessment (Secondary endpoint)

	Reference 2	Reference 3	Reference 4	Reference 5	Reference 6	Reference 7	Reference 8	Test 1	No Treatment
Reference 2	—	0.5964	0.0005	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001
Reference 3	0.5964	—	0.2708	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001
Reference 4	0.0005	0.2708	—	<.0001	<.0001	<.0001	<.0001	0.0003	<.0001
Reference 5	<.0001	<.0001	<.0001	—	0.2377	<.0001	<.0001	<.0001	<.0001
Reference 6	<.0001	<.0001	<.0001	0.2377	—	<.0001	<.0001	<.0001	<.0001
Reference 7	<.0001	<.0001	<.0001	<.0001	<.0001	—	0.1482	<.0001	0.9999
Reference 8	<.0001	<.0001	<.0001	<.0001	<.0001	0.1482	—	<.0001	0.4159
Test 1	<.0001	<.0001	0.0003	<.0001	<.0001	<.0001	<.0001	—	<.0001
No Treatment	<.0001	<.0001	<.0001	<.0001	<.0001	0.9999	0.4159	<.0001	—

Conclusions:

The results of this study show good concordance of potency ranking between the primary visual and secondary ChromaMeter assessments for the reference and test products. The potency of DFD06 Cream, 0.025% clobetasol propionate was found to be between those of the mid and super potent reference products by both visual and ChromaMeter assessments. The study data support classification of DFD06 Cream as a high potent topical corticosteroid belonging to Class 2.

Safety: There were no serious adverse events reported in this study.

Study CDS1002: Pilot HPA axis suppression study

Title: A Multicenter, Randomized, Investigator Blind, Parallel Group, Three Arm Pilot Study To Evaluate The HPA Axis Suppression, Efficacy And Safety Of Clobetasol Propionate Cream 0.025% (Formulation 5) And Clobetasol Propionate Cream 0.025% (Formulation 13) As Compared To Temovate E[®] Emollient 0.05% (clobetasol propionate emollient cream) In Patients with Moderate to Severe Psoriasis for 28 Days.

Primary Objective: To evaluate the effect of twice daily use of Clobetasol Propionate Cream 0.025% (2 different formulations) on HPA axis suppression in patients with moderate to severe psoriasis

Secondary Objective: To evaluate the efficacy and safety of Clobetasol Propionate Cream 0.025% (2 different formulations) as compared to Temovate E[®] emollient cream 0.05% in patients with moderate to severe psoriasis

Investigational Products:

- Formulation 5: Clobetasol Propionate Cream 0.025%
- Formulation 13: Clobetasol Propionate Cream 0.025%
- Comparator product: Temovate E[®] Cream, 0.05%

Methodology: This was a 28-day prospective, randomized, active-controlled, investigator blind, parallel group three arm pilot study. Patients, who were at least 18 years old, with moderate to severe psoriasis, were randomized to treatment with either Clobetasol Propionate 0.025% Formulation 5, Clobetasol Propionate 0.025% Formulation 13, or Temovate E[®] emollient cream 0.05%. These formulations were applied twice daily to the psoriatic lesions so as to cover 25% of body surface area (BSA) at each application.

Seven patient visits were scheduled at Screening, Baseline (Day 0), Days 7, 14, 21, 28, and 42. At the screening visit and on Day 28 or earlier for dropouts, an ACTH stimulation test was administered to each patient to test for adrenal function. Clinical determinations of disease severity using Psoriasis Global Assessment (PGA) were performed by the investigator at scheduled visits. At Day 42, a final safety evaluation was conducted and another ACTH stimulation test if the result at Day 28 or earlier had been abnormal

Primary endpoint: The proportion of patients with abnormal cortisol response level at Day 28.

Disposition of patients: Six centers in 6 cities in India recruited 88 patients (planned 90 patients) for the study. Out of the 88 enrolled patients, 57 patients completed the study and 31 patients were withdrawn from the study. The number of patients enrolled, completed and withdrawn in the three treatment arms is shown in Table 26.

Table 26: Summary of patient disposition

	Test1	Test2	Reference
Number of patients enrolled	29	29	30
Number of patients completed	20	20	17
Number of patients withdrawn	9	9	13
Reason for withdrawal:			
Adverse event	5	9	10
Non-compliance with protocol requirement	4	0	0
Other: lost to follow up	0	0	2
Other: wrong randomization	0	0	1
Test1= Clobetasol propionate 0.025% formulation 5 Test2 =Clobetasol propionate 0.025% formulation 13 Reference = Temovate E [®] 0.05% cream Source Listing: Randomization Enrolled = Number of patients who were randomized in the study Completed = Number of patients who completed the study as planned			

Demographic and other baseline characteristics: Table 27 shows the summary of patient baseline characteristics. The majority of the study population was male (63.6%) and all patients were Asians with a mean age of 43.4 years, mean height of 163.6 cms and mean weight of 62 kgs.

Table 27: Summary of patient demographic characteristics

Variable	Categories	Test1 (N=29)	Test2 (N=29)	Reference (N=30)	All (N=88)
		n(%)	n(%)	n(%)	n(%)
Gender	Female	10(34.5)	11(37.9)	11(36.7)	32(36.4)
	Male	19(65.5)	18(62.1)	19(63.3)	56(63.6)
Race	Asian	29(100.0)	29(100.0)	30(100.0)	88(100.0)
Test1= Clobetasol propionate 0.025% formulation 5 Test2 =Clobetasol propionate 0.025% formulation 13 Reference = Temovate E [®] 0.05% cream Source Listing: Demography					

HPA axis suppression results: Table 28 summarizes the ACTH stimulation test results using imputed. The results indicated that there was no difference between the 3 groups.

Table 28: Summary of HPA axis suppression

	ACTH stimulation test result	Test 1(N=26) n(%)	Test 2(N=29) n(%)	Reference(N=26) n(%)	p-value
VISIT 6 – Day 28	ABNORMAL	8 (30.8)	6 (20.7)	9 (34.6)	0.4932
	NORMAL	18 (69.2)	23 (79.3)	17 (65.4)	
Test1= Clobetasol propionate 0.025% formulation 5 ; Test2= Clobetasol propionate 0.025% formulation 13 ; Reference = Temovate E [®] 0.05% cream n (%) = Number (percentage) of patients with the given characteristics					

Brief Summary of Adverse Events: Thirteen (44.8%) patients in the Formulation 5 arm, 11 (37.9%) patients in the Formulation 13 arm, and 15 (50%) patients in the Temovate E[®] Emollient 0.05% arm experienced a treatment emergent adverse event. As per the applicant there were no statistical differences between groups. Decreased blood cortisol level was the most common adverse event in all the treatment arms. Most of the adverse events reported were mild in severity. There were no serious adverse events reported during the study.

All patients who had an abnormal ACTH value at the end of study were followed up for 15 days. There were withdrawals due to an AE for 5 patients in the Formulation 5 arm, 9 patients in the Formulation 13 arm, and 10 patients in the Temovate E[®] arm. In all the withdrawals due to an AE, decreased blood cortisol was the AE responsible for the withdrawal.

Efficacy Results:

Success with PGA (clear or almost clear) rates were similar across all the treatment arms and a success rate of 38.9%, 36.9% and 30.8% was documented for Formulation 5, Formulation 13 and Temovate E[®] arms, respectively, at the end of 28 days of treatment. Comparisons between Formulation 5, Formulation 13 and Temovate E[®] arms were not statistically significantly different.

Conclusion: The two test formulations, Formulation 5 and Formulation 13, were comparable to the Temovate E[®] cream in terms of HPA axis suppression, efficacy and safety. Formulation #5 was selected for further development.

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/s/

CHINMAY SHUKLA
09/27/2017

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09/27/2017