CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209483Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	209483
Priority or Standard	Standard
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Division / Office	DDDP/ODE 3
Reviewer Name(s)	Hamid Tabatabai, M.D.
Review Completion Date	10/6/2017
Established Name	Clobetasol propionate cream, 0.025%
(Proposed) Trade Name	Impoyz
Therapeutic Class	Corticosteroid
Applicant	Promius Pharma, LLC
Formulation(s)	Cream
Dosing Regimen	Twice daily for 14 Days
Indication(s)	Topical treatment of moderate to severe plaque psoriasis
Intended Population(s)	Adults 18 years and older

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This Medical Reviewer recommends that clobetasol propionate cream, 0.025% be approved for the topical treatment of moderate to severe plaque psoriasis.

1.2 Risk Benefit Assessment

Clobetasol propionate cream, 0.025% is a corticosteroid, which the applicant proposes for the topical treatment of moderate to severe plaque psoriasis. The applicant recommends twice daily dosing for up to two consecutive weeks. The container provides for 60 grams and 122 grams aluminum tubes of clobetasol cream, 0.025%.

Efficacy

The applicant provided substantial evidence of efficacy of clobetasol propionate cream, 0.025% in the treatment of moderate to severe plaque psoriasis from two adequate and well controlled trials, DFD-06-CD-004 and DFD-06-CD-005. The trials were conducted under identical protocols.

In the trial DFD-06-CD-004, 178 subjects were randomized to DFD-06 and 89 subjects were randomized to vehicle treatment. In the trial DFD-06-CD-005, 176 subjects were randomized to DFD-06 and 89 subjects were randomized to vehicle treatment.
The primary efficacy endpoint was the proportion of subjects with treatment success, defined as IGA=0 or 1 and at least 2 grade reduction from baseline at Day 15 visit.

DFD-06 was significantly superior to vehicle in both trials in the target populations, and the treatment effects were similar between the trials. In the trial DFD-06-CD-004, 30.2% of subjects in the DFD-06 treatment arm achieved treatment success on Day 15, compared to 9% of subjects in the vehicle treatment arm. In the trial DFD-06-CD-005, 30.1% of subjects in the DFD-06 treatment arm achieved treatment success on Day 15, compared to 9.7% of subjects in the vehicle treatment arm. The results were statistically significant ($P< 0.001$) for both trials.

For the proposed secondary efficacy endpoint of the proportion of subjects with treatment success at Day 8 (defined as IGA=0 or 1 and at least a 2-grade reduction from baseline at the Day 8 visit), the results were supportive of the primary efficacy endpoint. In the trial DFD-06-CD-004, 15.7% of subjects in the DFD-06 treatment arm achieved treatment success on Day 8, compared to 5.6% of subjects in the vehicle treatment arm ($P=0.006$). In trial DFD-06-CD-005, 14.2% of subjects in the DFD-06 treatment arm achieved treatment success on Day 8, compared to 1.6% of subjects in

the vehicle treatment arm (P=0.001). The results were statistically significant in both trials.

The data from two Phase 3 trials provided evidence of efficacy of DFD-06 cream, in the target population. Efficacy was consistent across sub-groups (by age, gender, race and baseline disease severity) and across study centers.

The applicant established the efficacy of DFD-06 cream compared to vehicle cream in treatment of moderate to severe plaque psoriasis in adult subjects 18 years of age and older.

Safety

The assessment of safety for the DFD-06, clobetasol propionate cream, 0.025% was based on analysis of data from two Phase 3 trials (DFD-06-CD-004 and DFD-06-CD-005) and one Phase 2 trial (DFD-06-CD-007). Safety population included 378 subjects exposed to repeated application of DFD-06 cream over a period of 14 days.

No deaths were reported during the development program of DFD-06.

Three serious adverse events (metastatic lymphoma, stab wound and cellulitis) were reported in the development program for DFD-06. The events of metastatic lymphoma and stab wound were not associated with the study drug administration. The adverse event of cellulitis was reported in a subject treated with vehicle.

The most frequently reported adverse reaction was application site discoloration. This adverse reaction was reported in 7(2%) of subjects treated with DFD-06 and in 2 (1%) of subjects treated with vehicle.

In addition to two Phase 3 trials, safety of DFD-06 was evaluated in two HPA axis suppression trials, DFD-06-CD-007 and CDS-1002.

In a two-week HPA- axis suppression trial DFD-06-CD-007, 3 (12.5%) of subjects in DFD-06 group compared to 8 (36.4%) of subjects in Temovate E (clobetasol propionate cream, 0.05%) group had results consistent with HPA axis suppression.

In a 4-week HPA axis suppression trial CDS-1002, the incidence of HPA axis suppression in DFD-06 treatment group (30.8%) was similar to the incidence of HPA axis suppression in Temovate E (clobetasol propionate, 0.05%) cream treatment group (34.6%).

For the proposed duration of treatment of 2 weeks, DFD-06 appears to have a lower incidence of HPA axis suppression for the indication of treatment of moderate to severe plaque psoriasis under maximal use conditions.

The results of dermal safety studies did not demonstrate a potential for phototoxicity, photoallergenicity or cumulative irritancy / contact sensitization for DFD-06 cream.

The applicant provided sufficient evidence to establish the safety of the drug.

Conclusions

The applicant has adequately demonstrated that clobetasol propionate cream, 0.025%, applied twice a day for up to 2 consecutive weeks, is safe and effective in the treatment of adults with moderate to severe plaque psoriasis.

This reviewer recommends approval of this drug and concludes that the benefits of clobetasol propionate cream, 0.025% outweigh its risks.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

This reviewer does not recommend a Risk Evaluation and Mitigation Strategy (REMS).

1.4 Recommendations for Postmarket Requirements and Commitments

For pediatric patients, ages 6 to (b) (4) years, information is needed on safety pharmacokinetic / HPA axis suppression of clobetasol propionate cream, 0.025% for the treatment of moderate to severe plaque psoriasis. Deferred pediatric studies in pediatric patients ages 6 to (b) (4) years will be conducted as required by PREA.

Under PREA, the following study is recommended as a post-marketing requirement (PMR):

- A safety pharmacokinetic / hypothalamic-pituitary-adrenal (HPA) axis suppression study under maximal use conditions in children and adolescents in the age group of 6 years to 16 year and 11 months old.

In May 2017, the applicant initiated study titled: “An open label, multicenter study to assess the potential for adrenal suppression and systemic drug absorption following multiple dosing with DFD-06 in pediatric subjects with moderate to severe plaque psoriasis” under protocol DFD-06-CD-011.

2 Introduction and Regulatory Background

2.1 Product Information

The applicant proposes marketing of clobetasol propionate cream, 0.025%, for the topical treatment of moderate to severe plaque psoriasis in adults. Clobetasol propionate is a fluorinated, synthetic corticosteroid. Clobetasol, an analog of prednisolone, has a high degree of glucocorticoid activity and a slight degree of mineralocorticoid activity. Clobetasol propionate, like other corticosteroids, have anti-inflammatory, anti-pruritic, and vasoconstrictive properties.

Clobetasol propionate is currently marketed in the U.S. at 0.05% concentration in several dosage forms: cream, ointment, solution, lotion, shampoo, spray, aerosol, foam, and gel. The applicant's product represents a lower concentration of the cream dosage form.

2.2 Tables of Currently Available Treatments for Proposed Indications

The proposed indication is the topical treatment of moderate to severe plaque psoriasis in adults 18 years of age or older. Currently available topical and systemic therapies for the treatment of moderate to severe plaque psoriasis are summarized in Tables 1 and Table 2.

Table 1: Topical Treatments for Moderate to Severe Plaque Psoriasis

Product Class	Example	Warnings / precautions
Corticosteroids	Temovate E cream Topicort spray Olux foam (scalp psoriasis)	Reversible HPA axis suppression, manifestations of Cushing's syndrome, hyperglycemia, glycosuria, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, peri-oral dermatitis, allergic contact dermatitis, secondary skin infections, striae, miliaria
Synthetic vitamin D_3 derivative	[1]calcipotriene cream, 0.005%	Contact dermatitis, reversible hypercalcemia,
Synthetic vitamin D_3 derivative/ corticosteroid combination	[2]calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment	Warning / precautions from both product classes
Retinoid	[3]Tazarotene gel	Teratogen

[1,2] Calcipotriene cream, 0.005% and calcipotriene 0.005% / betamethasone dipropionate 0.064% ointment are indicated for the treatment of plaque psoriasis.
[3] Tazarotene gel is indicated for topical treatment of psoriasis patients with up to 20% of BSA involvement.

Table 2: Approved Systemic Therapies for Moderate to Severe Psoriasis

Product class	Product	Warnings / precautions
PDE4 inhibitor	apremilast	Diarrhea, nausea, vomiting, weight decrease, depression, drug interactions
retinoid	acitretin	teratogen, hepatotoxicity, skeletal and lipid abnormalities,
Folate Antagonist	methotrexate	Teratogen, liver fibrosis/cirrhosis, interstitial pneumonitis, hematologic toxicities, opportunistic infections
IL-2 inhibitor	cyclosporine	Hypertension, nephrotoxicity, malignancy, serious infections
TNF-α blocker	etanercept	Serious infections (including T.B.), malignancy, CNS demyelinating disorders, pancytopenia, hepatitis B reactivation, autoimmunity
	adalimumab	
	infliximab	
IL-12, IL-23 antagonist	ustekinumab	Malignancy, serious infections, posterior leukoencephalopathy syndrome(reversible)
IL-17 antagonist	secukinumab	Serious infections (including T.B.), exacerbation of Crohn's disease, hypersensitivity (suicidal risk for brodalumab)
	ixekezumab	
	brodalumab	
Phototherapy	PUVA	Nausea, erythema, pruritus, avoid sunlight > 24 hrs. for PUVA, increased risk of SCC
	UVB	Increased risk of squamous cell carcinoma(SCC)

2.3 Availability of Proposed Active Ingredient in the United States

Clobetasol propionate is currently marketed in the U.S. at 0.05% concentration in several dosage forms: cream, ointment, solution, lotion, shampoo, spray, aerosol, foam, and gel.

2.4 Important Safety Issues With Consideration to Related Drugs

Topical corticosteroids are labeled for potential systemic and local adverse reactions. Potential systemic adverse reactions include reversible HPA axis suppression, Cushing's syndrome, hyperglycemia, glycosuria and unmasking of latent diabetes mellitus.

Local adverse reactions from topical corticosteroids may include atrophy, striae, telangiectasias, burning, itching, irritation, dryness, folliculitis, acneiform eruptions,

hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, and miliaria.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

This product was developed under IND 110,799 submitted on 3/30/2011. Milestone interactions with the applicant are described below:

iPSP agreement:
The FDA agreed with the applicant's iPSP on 10/7/2015.

SPA – No agreement:

(b) (4)

The agency agreed with the applicant on the following points:

(b) (4)

Pre-NDA meeting:
A pre-NDA meeting was held on 10/12/2016. The content and format of the NDA was discussed during this meeting.

2.6 Other Relevant Background Information

Not applicable.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Inspections were requested for the following three Phase 3 trial sites with high number of subject enrollments:

- Joe Blumenau, Site #101, DFD-06-CD-004, enrolled 20 subjects
- Michael Bukhalo, Site #103, DFD-06-CD-004, enrolled 24 subjects
- Abel Jarell, Site #106, DFD-06-CD-005, enrolled 24 subjects

At present, the final classification of two of the sites above by the office of scientific investigations (OSI) is no action indicated (NAI). The field classification for the third site is also NAI, pending finalization of the draft summary of the report from the field.

3.2 Compliance with Good Clinical Practices

The applicant stated that all of the clinical studies were conducted in accordance with Good Clinical Practices for Clinical Research Studies.

3.3 Financial Disclosures

The applicant certified no financial arrangements with any investigator and that no investigator had disclosed a proprietary interest in this product or a significant equity in the applicant.

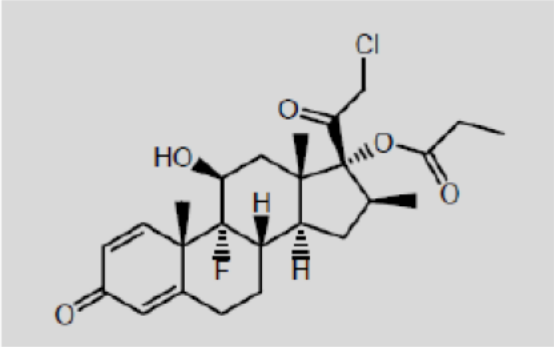
4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Clobetasol propionate cream, 0.025% is a white to off-white cream, an oil-in-water emulsion of clobetasol propionate, a synthetic fluorinated corticosteroid. Clobetasol propionate is a white to cream-colored crystalline powder that is practically insoluble in water.

Drug Substance:
The review of the drug substance of the Quality Assessment Review for this NDA by Dr. Lawrence Perez, states:
“The active pharmaceutical ingredient (API) used in the drug product, clobetasol propionate cream, 0.025%, is clobetasol propionate. Clobetasol propionate is a corticosteroid of the glucocorticoid class used to treat various skin disorders. The

chemical name for clobetasol propionate is 21-chloro-9-fluoro-11β-hydroxy-16β-methyl-3, 20-dioxopregna-1, 4-dien-17-yl propanoate. The chemical structure of clobetasol propionate is:



It has a molecular formula of C25H32ClFO5 and a molecular weight of 467.0 g/mol. The drug substance is being manufactured by (b) (4) as a white to cream, crystalline powder and it is non-hygroscopic. Clobetasol propionate as manufactured by (b) (4) has only one polymorphic form and is chiral with 8 stereogenic centers. Clobetasol propionate from (b) (4) has been shown to be physically and chemically stable at (b) (4) and has a retest period of (b) (4) months.
Clobetasol propionate is a compendial drug substance. For this NDA application, the specification for the drug substance complies with the current USP monograph."

Drug Product:
The review of the drug product of the Quality Assessment Review for this NDA by Dr. Zhengfang Ge, states:
"The drug product, clobetasol propionate cream, is an oil-in-water emulsion containing 0.25 mg clobetasol propionate per gram of the cream".

The drug product, clobetasol propionate cream, 0.025% has the composition listed in Table 3.

Table 3 : Qualitative and Quantitative Composition of DFD-06 (Clobetasol Propionate Cream, 0.025%)

Ingredients	Reference / Standard	% w/w	Function
Clobetasol propionate	USP	0.025	Active
Cetostearyl alcohol	NF	(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		

NF: National Formulary, USP: United States Pharmacopeia
IH: In-house specification set by the excipient manufacturer.
Source: Sponsor's submission, Table 3.2.P.1.2-1, section 3.2.P.1.2

The application Technical Lead reviewer, Yichun Sun, Ph.D. 's quality assessment includes the following executive summary:

"The applicant of this NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug substance and drug product. The facility review team from the Office of Process and Facility (OPF) has issued an "Acceptable" recommendation for the facilities involved in this application."

4.2 Clinical Microbiology

Not applicable. The product is not an antimicrobial.

4.3 Preclinical Pharmacology/Toxicology

Jill C. Merrill, Ph.D. was the pharmacology/toxicology reviewer for this NDA.

Promius has obtained the right of reference from Fougera Pharmaceuticals Inc. for all of the Temovate topical formulations. Therefore, Promius is relying on the data available for Temovate NDAs 19322, 19323, 19966, 20337 and 20340 to support the safety of this drug product.

In addition, Promius has conducted repeat-dose dermal toxicity studies in rats up to 13 weeks (0.001, 0.005 and 0.025% BID; 0.004, 0.02, and 0.1 mg/kg/day) and in minipigs up to 4 weeks (0.005%, 0.025% and 0.05%; 0.1, 0.5 and 1.0 mg/kg/day), an acute dermal study in rabbits, an ocular irritation study using the bovine corneal opacity and permeability (BCOP) assay, a dermal photoirritation study in mice and a dermal sensitization study in guinea pigs. Considering the extent of immune suppression observed during the 13-week repeat-dose dermal toxicity study in rats, the Agency has waived the requirement for a two-year dermal carcinogenicity study in rats.

Per Dr. Merrill's review, "Topical repeat-dose toxicity studies conducted using the clinical clobetasol propionate cream formulation (0.025%) and an enhanced cream formulation (0.05%) produced effects in rats and minipigs that were consistent with the known effects of corticosteroids. The drug substance has been previously tested for systemic toxicity, genetic toxicology and reproductive and developmental toxicology. The sponsor has a right of reference to these studies and they stand in support of the current drug product. Immune suppression observed during 13 weeks repeat-dose dermal toxicity testing in rats precluded conduct of a two-year dermal carcinogenicity study in rats.

Clobetasol propionate cream, 0.025%, for the treatment of plaque psoriasis is approvable from a Pharmacology/Toxicology perspective".

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Topical corticosteroids have anti-inflammatory, anti-pruritic and vasoconstrictive properties. The mechanism of anti-inflammatory activity of the topical corticosteroids, in general, is unclear. Corticosteroids are thought to act by the induction of phospholipase A_2 inhibitory proteins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor, arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A_2.

4.4.2 Pharmacodynamics

Phase 1- Study DFD-06-CD-003a

This was a Phase 1, single center, randomized, evaluator-blinded, within subject vasoconstrictor assay study was conducted to determine the potency of DFD-06, clobetasol propionate cream, 0.025% compared to six different currently marketed topical corticosteroid topical products of known potency and a vehicle cream applied for 16 hours to the flexor surface of each subject's forearm under non-occlusive conditions. This study enrolled 80 healthy adult subjects 18 to 65 years of age, with Fitzpatrick skin type 1-3.

The study results showed that potency of DFD-06 is between those of mid and super-potent reference products, and therefore should be classified as a high potency topical corticosteroid.

4.4.3 Pharmacokinetics

To evaluate the potential for HPA axis suppression, the applicant conducted two HPA axis trials, CDS-1002 and DFD-06-CD-007.

Phase 2 – HPA axis Trial CDS-1002

This was a multicenter, 1:1:1 randomized, investigator blind, parallel group, pilot study to evaluate the HPA axis suppression, efficacy and safety of clobetasol propionate cream, 0.025% in 107 adult subjects with moderate to severe psoriasis (PGA score of ≥ 3 and BSA ≥ 25%), excluding face, scalp, groin, axilla and intertriginous areas).
The study had three arms:

- DFD-06 cream, formulation 5 (to-be-marketed formulation)
- DFD-06 cream, formulation 13
- Temovate E emollient cream, 0.05%

Each subject applied the drug product twice a day for 28 days.

Adrenocorticotropin (ACTH) stimulation test was performed at screening visit and at Day 28 (or on patient's withdrawal from study).

Investigators performed disease severity assessments using Psoriasis Global Assessment (PGA) scale at each weekly visit.

Safety assessment included measurements of plasma cortisol levels, assessment of cutaneous irritation at weekly visits, and recording of adverse events (AEs).

The primary safety variable assessed in this study was the proportion of subjects with abnormal cortisol response level at Day 28 (cortisol ≤ 18 mcg/ 100 mL).

Other safety variables included the proportion of patients with abnormal plasma cortisol at each time point (cortisol ≤ 5 mcg/ 100 mL), cutaneous safety evaluation, AEs, physical exam, vital signs and clinical laboratory results.

Results

Demographic characteristics
The subjects in respective treatment arms (DFD-06 cream formulation 5, DFD-06 cream formulation 13, Temovate E cream) were similar with respect to gender (male: 66%, 62%, 63%), race (Asian 100%, all), mean age (44, 47, 39 years), and disease severity: mean BSA (37% ,38%, 38%) and PGA score at baseline (PGA of 3: 58% ,62%, 54% / PGA of 4: 42% for all).

Subject disposition
A higher proportion of subjects in DFD-06 treatment arms completed the trial compared to Temovate E (69%, 69%, and 57%). Proportions of subjects withdrawn from the study due to an adverse event were similar in each treatment arm (17%, 24%, and 23%).

The proportion of subjects with abnormal ACTH stimulation tests on Day 28 are summarized in Table 4. Formulation 5 was chosen the to-be-marketed formulation.

Table 4: Number (Percentage) of Patients with Abnormal ACTH Stimulation Test Results, Study CDS-1002

Visits	ACTH stimulation test result	F5: clobetasol propionate cream, 0.025% (N=26) n (%)	F13: clobetasol propionate cream, 0.025% (N=29) n (%)	Temovate E cream, 0.05% (N=26) n (%)	p-value
SCREENING VISIT	ABNORMAL	1 (3.8)	1 (3.4)	0 (0.0)	
	NORMAL	25 (96.2)	28 (96.6)	26 (100.0)	
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)	

Imputed (LOCF) Data (Modified - ITT population
n (%) = Number (percentage) of patients with the given characteristics
Source: Sponsor's submission, CSR: CDS-1002, Table 22, page 54

Reviewer's comment

The proportion of subjects with abnormal ACTH Stimulation Tests on Day 28 in the to-be-marketed formulation (F5) treatment arm and Temovate E arm of the trial were similar.

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Phase 2 – HPA axis Trial DFD-06-CD-007

This was a 1:1 randomized, parallel group, open label, multicenter maximum-use study to assess the potential for adrenal suppression and systemic drug absorption of the to-be-marketed formulation of DFD-06 cream compared to Temovate E (clobetasol propionate 0.05%) cream, applied twice daily for fifteen days in 50 adult subjects with moderate to severe plaque psoriasis (IGA of 3 or 4, BSA of 20%-50%, excluding face, scalp, groin, axilla and intertriginous areas).

Adrenocorticotropin (ACTH) stimulation test was performed at screening visit and at Day 15. For subjects with abnormal test results on Day 15, ACTH stimulation test was to be repeated every 28 days, until normalized.

The primary safety variable was the proportion of subjects with abnormal cortisol response (cortisol level ≤ 18 mcg/dL at 30-minutes post-stimulation) for ACTH stimulation test at the end of treatment. Dehydroepiandrosterone sulfate (DHEAS) was a secondary measure of HPA axis suppression.
Safety results related to HPA axis suppression are discussed below.

Other safety assessments included local cutaneous safety evaluation of treated skin, adverse events (AEs), vital signs, and urine pregnancy tests are discussed in section 7 of this review.

Results

Demographic characteristics were similar between treatment arms with respect to gender (male: 71% vs. 64%), race (white 100%, both), mean age (44 vs. 51 years), and disease severity.

Subject disposition: similar number of subjects in each treatment arm completed the trial (89% vs. 92%). No subject in either arm was discontinued due to adverse events.

Extent of exposure included mean number of applications (28 vs. 31), and mean amount of drug (in grams) used (107 vs. 102) were similar.

Safety assessment results for HPA axis suppression on Day 15 showed an abnormal ACTH stimulation test in 12.5% of subjects treated with DFD-06, compared to 36.4% of subjects treated with Temovate E cream. A secondary safety variable, DHEAS reduction showed results supportive of the ACTH stimulation test results, presented in Table 5.

Table 5: Number of Subjects with Abnormal ACTH Stimulation Test Result at Day 15, Trial DFD-06-CD-007

Statistics	DFD-06 Cream, 0.025%	Temovate E Cream (clobetasol propionate, 0.05%)	p-value
N	24	22	0.086[1]
Number (%) of subjects with abnormal results	3 (12.5%)	8 (36.4%)	
Percent reduction in serum DHEAS from screening to Day 15 Mean ± SD	11.0 ± 27.0	21.6 ± 46.4	0.353[2]

[1] P-value for comparison between the two treatment groups from Fisher's exact tests.
[2] P-value for treatment comparison from one-way analysis of variance model (ANOVA).
Max = maximum; Min = minimum; SD = standard deviation
Source: Modified from sponsor's submission, CSR, DFD-06-CD-007, Tables 12.2 and 12.3, page 41

Reviewer's comment
A lower proportion of subjects in DFD-06 treatment arm, compared to Temovate E arm of this trial had HPA axis suppression on Day 15.

The results of HPA axis suppression trials show that when subjects were treated with DFD-06 for up to 2 weeks, the proportion of subjects with HPA suppression was one third of that in Temovate E cream arm. However, when DFD-06 was used for a period longer than 2 weeks, the potential for HPA axis suppression increased and, after 4 weeks of treatment, the proportion of subjects with HPA axis suppression was similar to that in Temovate E cream treatment arm.

This reviewer recommends that the incidence of HPA axis suppression with DFD-06 drug products after 2 weeks and 4 weeks of topical use be included in product labeling.

5 Sources of Clinical Data

The applicant conducted nine clinical trials in the development program of DFD-06. Table 6 outlines eight trials discussed in this review.

5.1 Tables of Studies/Clinical Trials

Table 6: Tabular Listing of all Clinical Studies

Phase 3 - Safety and Efficacy Trials

Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
DFD-06-CD-004	Safety and efficacy	Randomized, double-blind, multicenter, parallel Active, vehicle	Clobetasol proprionate cream, 0.025%, Vehicle Cream Twice daily Topical	267 (178 clobetasol propionate cream, 0.025%, 89 Vehicle Cream)	Moderate to severe psoriasis	15 days
DFD-06-CD-005	Safety and efficacy	Randomized, double-blind, multicenter, parallel Active, vehicle	Clobetasol proprionate cream, 0.025%, Vehicle Cream Twice daily Topical	265 (176 clobetasol propionate cream, 0.025%, 89 Vehicle Cream)	Moderate to severe psoriasis	15 days

Phase 2 - HPA Axis Suppression Trials

Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
CDS-1002	To evaluate the HPA axis suppression, efficacy and safety of clobetasol propionate cream 0.025% formulations F5 and F13 as compared to Temovate E Emollient 0.05% in subjects with moderate to severe psoriasis	Parallel group, three arm pilot study. Six study centers. Two active formulations (F5 and F13) of clobetasol propionate cream 025%; And one comparator: Temovate E 0.05%.	Clobetasol propionate, 0.025% formulations F5 and F13; Temovate E Cream 0.05%, Applied twice daily to the psoriatic lesions so as to cover 25% of body surface area (BSA) at each application.	57	Moderate to severe psoriasis	28 days
DFD-06-CD-007	To evaluate potential for HPA axis suppression and systemic drug absorption following multiple dosing	Randomized, parallel, open label, multicenter Listed drug	Clobetasol propionate cream, 0.025%; Temovate Cream 0.05%; Twice daily Topical	50 (26 clobetasol propionate cream, 0.025%, 24 Temovate cream)	Moderate to severe plaque psoriasis	15 days

Phase 1 - Dermal Safety Studies

Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
DFD-06-CD-008	To evaluate phototoxic potential	Patch test Randomized, double-blind, single-center, within-subject Listed drug, vehicle	Clobetasol propionate cream 0.025% (DFD-06); Vehicle Cream: One application Topical	31	Healthy	24 hours
DFD-06-CD-009	To evaluate photoallergic reaction	Patch test Randomized, double-blind, single center, within subject Negative, vehicle, listed drug	Clobetasol propionate cream 0.025% (DFD-06); Vehicle Cream, saline 0.09% One application Topical	54	Healthy	2 times a week for 3 weeks, plus challenge application
DFD-06-CD-010	To evaluate sensitization and irritation potential	Patch test Randomized, double-blind, single center, within-subject	Clobetasol propionate cream 0.025% (DFD-06); Vehicle Cream, sodium lauryl sulfate 0.2%, saline 0.09% One application Topical	226	Healthy	3 times a week for 3 weeks plus challenge application

Phase 1 - Pharmacodynamic – VCA Trial

Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number and Diagnosis of Subjects	Duration of Treatment
DFD-06-CD-003a	To determine potency of DFD-06 Cream, 0.025% clobetasol propionate compared to six different currently marketed topical corticosteroid formulations of known potency.	Patch test Randomized, evaluator-blinded, within-subject, single-center Active, listed drug and vehicle	DFD-06 Cream, 0.025%; Temovate Cream 0.05%; Clobex Lotion, 0.05%: Diprolene Lotion, 0.05%; Fluticasone Propionate Cream, 0.05%; Triamcinolone Acetonide Cream USP, 0.1%, Hydrocortisone Cream USP, 2.5%; 10 µL of each product applied on the flexor surfaces of ventral forearms. One application Topical	80, Healthy	16 hours

Source: Sponsor's submission, section 5.2, Tabular listing of all clinical trials

5.2 Review Strategy

For assessments of efficacy and safety, this reviewer relied on the results of the two Phase 3 trials, DFD-06-CD-004 and DFD-06-CD-005, presented in section 6 (review of efficacy) and section 7 (review of safety). In addition, safety data from the DFD-06 treatment arm of the Phase 2 trial, DFD-06-CD-007 was pooled with safety data from Phase 3 trials. Trial DFD-06-CD-007 had a similar duration and dosing regimen and a population with similar disease severity to allow pooling of the safety data.

The protocols and the results of the two Phase 2, HPA axis studies were discussed in section 4.4.3.

The protocols and the results of three dermal safety studies, DFD-06-CD-008, DFD-06-CD-9, and DFD-06-CD-010 will be discussed in section 7.4.5.

Reference ID: 4169448

5.3 Discussion of Individual Studies / Clinical Trials

The applicant conducted two Phase 3 trials, DFD-06-CD-004 and DFD-06-CD-005, in support of this NDA. Phase 3 trials were identical with regard to study design, study populations (as defined by inclusion/exclusion criteria with IGA ≥ 3, mean baseline affected body surface area (BSA) of 6.8% and 8.7% respectively), methodology, and endpoints. Protocols for both trials are discussed in this section, and the results are presented in sections 6 and 7 of this review.

Phase 3 Trials: DFD-06-CD-004 and DFD-06-CD-005

Title
A randomized, double-blind, vehicle-controlled, multicenter, parallel group study of the efficacy and safety of DFD-06 cream in the treatment of moderate to severe plaque psoriasis for 14 days

Objective
To compare the efficacy and safety of DFD-06 cream to vehicle cream for topical treatment of moderate to severe plaque psoriasis after 14 days of treatment

Design
Randomized, double-blind, vehicle-controlled, multicenter, parallel group

Study population
Males and females 18 years and older with a clinical diagnosis of moderate to severe plaque psoriasis, with an IGA or 3 or greater, involving at least 3% of BSA, excluding face, scalp, groin, axillae, and intertriginous areas.

Key Inclusion Criteria:
1. Subjects were at least 18 years of age.
2. Subjects presented with a clinical diagnosis of stable (at least 3 months) plaque-type psoriasis.
3. Subject had psoriasis involving 3% or greater BSA, not including the face, scalp, groin, axillae, and other intertriginous areas.
4. Subjects had an IGA Grade of 3 or 4 (moderate to severe) at the Baseline Visit.

Key Exclusion Criteria:
1. Current diagnosis of unstable forms of psoriasis including guttate, erythrodermic, exfoliative, or pustular psoriasis.
2. Other inflammatory skin disease that may have confounded the evaluation of the plaque psoriasis (e.g., atopic dermatitis, contact dermatitis, tinea corporis).

3. Presence of pigmentation, extensive scarring, or pigmented lesions, or sunburn that could have interfered with the rating of efficacy parameters.
4. History of psoriasis unresponsive to biological or topical treatments.
5. History of organ transplant requiring immunosuppression, HIV, or other immunocompromised state.
6. Use within 180 days prior to Baseline Visit of biologic treatment for psoriasis (e.g., infliximab, adalimumab, etanercept, ustekinumab, secukinumab, or alefacept).
7. Had received treatment for any type of cancer within 5 years of the Baseline Visit except skin cancer and cervical cancer (in situ) were allowed if at least 1 year before the Baseline Visit.
8. Use within 60 days prior to the Baseline Visit of: 1) topical or systemic immunosuppressive drugs (e.g., tacrolimus, pimecrolimus); 2) systemic antipsoriatic treatment (e.g., methotrexate, cyclosporine, hydroxyurea); or 3) oral retinoids (e.g., acitretin, isotretinoin).
9. Use within 30 days prior to the Baseline Visit of: 1) systemic steroids; 2) PUVA therapy; 3) systemic anti-inflammatory agents (e.g., mycophenolate mofetil, sulfasalazine, 6-thioguanine); or 4) UVB therapy. Inhaled, intraocular, intranasal steroids were allowed.
10. Use within 14 days prior to the Baseline Visit of: 1) topical antipsoriatic drugs (e.g., salicylic acid, anthralin, coal tar, calcipotriene); 2) topical retinoids (e.g., tazarotene, tretinoin); or 3) topical corticosteroids.

Study visits and procedures

Two hundred sixty-seven (267) subjects were included in DFD-06-CD-004 trial and 265 subjects were included in DFD-06-CD-005 trial. Subjects were randomized in 2:1 ratio to receive treatment with DFD-06 cream or vehicle cream. Subjects applied study product to all affected skin areas except the face, scalp, groin, axilla, and intertriginous areas, twice daily, for 14 days. The schedule of activities is outlined in the Table 7.

Table 7: Schedule of Study Procedures, Trials DFD-06-CD-004 and DFD-06-CD-005

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
	Screen[a,b]	Day 1	Day 4[c]	Day 8[d]	Day 15[e]
Informed Consent	X				
Collect Demographic Data	X				
Inclusion and Exclusion Criteria	X	X			
Medical History/ Prior & Concomitant Medications	X	X			
Vital Signs (BP, Pulse)	X[f]	X	X	X	X
Urine Pregnancy Test[g]		X			X
Determine BSA *Must have had 3% or greater BSA for inclusion*	X[f]	X			X
Assess IGA *Must have had a 3 or 4 (moderate to severe) for inclusion*	X[f]	X	X	X	X
Select Target Lesion and Photograph (selected sites only)		X	X	X	X
Local Safety Evaluation		X	X	X	X
Randomization		X			
Dispense Study Product (as needed)		X	X	X	
Dispense/Review/Collect Study Diary		X	X	X	X
Diagram Affected Areas to be Treated[f]		X	X	X	
Review Subject Instructions		X	X	X	
Initiate Treatment Subjects treated the affected areas under supervision for the first time		X			
Collect Study Product			X	X	X
Evaluate Compliance			X	X	X
Adverse Event Assessment/Collection		X[h]	X	X	X
Concomitant Medications			X	X	X
End of Study					X

[a] No more than 60 days before Visit 2.
[b] Visits 1 and 2 could be combined.
[c] Allowed visit window ± 1 day.
[d] Allowed visit window ± 2 days.
[e] Allowed visit window ± 3 days
[f] Recorded on source only.
[g] For female subjects of childbearing potential.
[h] Related to study procedures only.

Source: Source: sponsor's submission, Section 5.3.5.1, Tables 9.1, pages 27 and 28, Clinical Study Reports DFD-06-CD-004 and DFD-06-CD-005 respectively.

Efficacy Assessment

The ***primary*** efficacy endpoint was the proportion of subjects with treatment success, defined as IGA=0 (clear) or 1 (almost clear) and at least 2 grade reduction from baseline at Day 15 visit.
Efficacy assessment was conducted using IGA scoring for overall disease severity at Visits 1 through 5 as defined in the table 8.

Table 8 : Investigator's Global Assessment (IGA) of Disease Severity, Trials DFD-06-CD-004 and DFD-06-CD-005

Score	Grade	Definition
0	Clear	No signs of psoriasis Post-inflammatory hyperpigmentation may be present
1	Almost clear	No thickening to minimal plaque elevation Normal to slight pink coloration/faint erythema Focal to minimal scaling
2	Mild	Slight elevation/thickening Pink to light red coloration Predominantly fine scaling partially or mostly covering lesions
3	Moderate	Clearly distinguishable/distinct thickening Definite red coloration Coarse scaling covering most plaques
4	Severe	Marked thickening with hard/sharp edges Bright to deep dark red coloration Thick/coarse scaling covering almost all or all lesions

Source: sponsor's submission, Section 5.3.5.1, page 28, Clinical Study Report DFD-06-CD-004

The *secondary* efficacy endpoints were:

- The percentage change in the body surface area (BSA) at Day 15
- The proportion of subjects with treatment success defined as IGA=0 or 1 and at least 2 grade reduction from baseline at Day 8 visit

Safety Assessments:
Safety assessments included: vital signs (blood pressure, pulse) at each visit, local cutaneous safety evaluation of treated skin, Adverse Reactions (AEs), and urine pregnancy test for women of child bearing potential, at baseline and on Day 15.

6 Review of Efficacy

Efficacy Summary

The applicant demonstrated the efficacy of DFD-06 cream in treatment of moderate to severe plaque psoriasis in adult subject 18 years and older in 2 adequate and well-controlled trials. The 2 pivotal Phase 3 trials were conducted under identical protocols.

In trial DFD-06-CD-004, 178 subjects were randomized to DFD-06 and 89 subjects were randomized to vehicle treatment. In trial DFD-06-CD-005, 176 subjects were randomized to DFD-06 and 89 subjects were randomized to vehicle treatment.
The primary efficacy endpoint was the proportion of subjects with treatment success, defined as IGA=0 (clear) or 1 (almost clear) and at least 2 grade reduction from baseline at Day 15 visit.

DFD-06 was significantly superior to vehicle in both trials, and the treatment effects were similar between the trials. In trial DFD-06-CD-004, 29.2% (52/178) of subjects in the DFD-06 treatment arm achieved treatment success on Day 15, compared to 9% (8/89) of subjects in the vehicle treatment arm. In trial DFD-06-CD-005, 30.7% (53/176) of subjects in the DFD-06 treatment arm achieved treatment success on Day 15, compared to 9% (8/89) of subjects in the vehicle treatment arm.
The results were statistically significant (P< 0.001) in both trials.

The applicant analyzed two secondary efficacy endpoints, if the primary efficacy endpoint achieved statistical significance, according to the pre-specified order:

1) The percent change in body surface area (BSA) at Day 15.
2) The proportion of subjects with treatment success at Day 8 (defined as IGA=0 or 1 and at least a 2-grade reduction from baseline at the Day 8 visit).

The secondary efficacy endpoint of the percentage change in BSA at Day 15 is not considered a clinically meaningful measurement of efficacy in psoriasis and is not further discussed in this review.

The results for the secondary efficacy endpoint, the proportion of subjects with treatment success at Day 8, were supportive of the results for the primary efficacy endpoint.

The applicant established the efficacy of DFD-06 cream compared to vehicle cream in treatment of moderate to severe plaque psoriasis in adult subjects 18 years and older.

6.1 Indication

The applicant's proposed indication is for the topical treatment of moderate to severe plaque psoriasis.

6.1.1 Methods

The applicant is relying on two Phase 3 trials of identical design, DFD-06-CD-004 and DFD-06-CD-005, to provide evidence of efficacy to support approval. The primary analysis population for both Phase 3 trials was Intent-to-Treat Population (ITT). ITT population consisted of all subjects who were randomized and dispensed study product. All of 267 randomized subjects from trial DFD 06-CD-004 and, all 265 randomized subjects from trial DFD 06-CD-005, were included in ITT population.

6.1.2 Demographics

Overall, baseline demographic characteristics of the study populations were similar across the two trials and across treatment arms. Baseline characteristics of the study populations are presented in the Table 9.

Table 9 : Baseline Demographics Characteristics (Trials DFD-06-CD-004 and DFD-06-CD-005; ITT population)

Treatment Group	DFD-06-CD-004 Trial		DFD-06-CD-005 Trial	
Demographics	**DFD-06 Cream (N = 178)**	**Vehicle (N = 89)**	**DFD-06 Cream (N = 176)**	**Vehicle (N = 89)**
Gender				
Male	100 (56.2%)	44 (49.4%)	111 (63.1%)	51 (57.3%)
Female	78 (43.8%)	45 (50.6%)	65 (36.9%)	38 (42.7%)
Ethnicity				
Hispanic or Latino	39 (21.9%)	25 (28.1%)	41 (23.3%)	21 (23.6%)
Not Hispanic or Latino	139 (78.1%)	64 (71.9%)	134 (76.1%)	67 (75.3%)
Unwilling to Provide	0 (0.0%)	0 (0.0%)	1 (0.6%)	1 (1.1%)
Race				
American-Indian or Alaska Native	1 (0.6%)	1 (1.1%)	5 (2.8%)	1 (1.1%)
Asian	7 (3.9%)	3 (3.4%)	2 (1.1%)	2 (2.2%)
Black or African-American	18 (10.1%)	9 (10.1%)	15 (8.5%)	2 (2.2%)
Native Hawaiian or Other Pacific Islander	1 (0.6%)	1 (1.1%)	0 (0.0%)	1 (1.1%)
White or Caucasian	149 (83.7%)	74 (83.1%)	146 (83.0%)	79 (88.8%)
Other	2 (1.1%)	1 (1.1%)	8 (4.5%)	4 (4.5%)
Mixed	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Age				
Mean ± SD	49.5±14.78	49.9±14.33	49.5±13.59	50.6±15.93
Min, Max	18.0, 79.0	18.0, 82.0	20.0, 78.0	19.0, 79.0
Age Group				
< 65 Years of Age	151 (84.8%)	75 (84.3%)	152 (86.4%)	70 (78.7%)
65 Years of Age or Older	27 (15.2%)	14 (15.7%)	24 (13.6%)	19 (21.3%)
Investigator's Global Assessment (IGA) Category				
Moderate (3)	154 (86.5%)	77 (86.5%)	142 (80.7%)	72 (80.9%)
Severe (4)	24 (13.5%)	12 (13.5%)	34 (19.3%)	17 (19.1%)
Body Surface Area (%)				
Mean ± SD	6.8 ± 8.11	8.8 ± 11.47	8.7±10.19	9.2±11.34
Min, Max	3.0, 80.0	3.0, 80.0	3.0, 80.0	3.0, 80.0

Source: modified from sponsor's submission, CSR DFD-06-CD-004, Tables 11.2 and 11.3, pages 40-41 and CSR DFD-06-CD-005, Table 11.2 and 11.3, pages 42-43.

Pooled analysis of baseline demographic characteristics for trials DFD-06-CD-004 and DFD-06-CD-005 showed that the majority of subjects were less than 65 years of age (84%), male (57%), and White (84%). Baseline IGA scores were similar across treatment arms in the two trials; however, Trial 005 had a slightly higher proportion of

subjects with a severe (4) baseline IGA score than in Trial 004. In both trials, the mean baseline BSA was slightly higher in the vehicle arm than in the DFD-06 arm.

6.1.3 Subject Disposition

Almost all subjects (99%) of subjects in the DFD-06 treatment arms, compared to (99% and 96%) of subjects in the vehicle arms of each trial completed the trial. The results are presented in Table 10.

Table 10 : Subject Enrollment and Subject Discontinuations by Reason (Trials DFD-06-CD-004, DFD-06-CD-005)

	DFD-06-CD-004 Trial (N=267)		DFD-06-CD-005 Trial (N= 265)	
Parameter	**DFD-06 Cream**	**Vehicle**	**DFD-06 Cream**	**Vehicle**
Subjects Randomized	178	89	176	89
Number Completed Study	176 (98.9%)	88 (98.9%)	175 (99.4%)	85 (95.5%)
Total Discontinued	2 (1.1%)	1 (1.1%)	1 (0.6%)	4 (4.5%)
Reasons for Discontinuation				
A treatment-related AE occurred	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
A non-treatment-related AE occurred	1 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lost to follow-up	1 (0.6%)	1 (1.1%)	0 (0.0%)	1 (1.1%)
Subject decision/withdrawal of consent	0 (0.0%)	0 (0.0%)	1 (0.6%)	2 (2.2%)

Source: modified from sponsor's submission, CSR: DFD-06-CD-004, Tables 10.1, page 38 and CSR: DFD-06-CD-005, Table 10.1, page 40.

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint for the Phase 3 trials was the proportion of subjects with treatment success, defined as IGA=0 or 1 and at least 2 grade reduction from baseline at Day 15 visit. Analysis of the results of primary endpoint for individual trials is presented in Table 11.

Table 11 : Proportion of Subjects with Treatment Success at Day 15 (Trials DFD-06-CD-004 and DFD-06-CD-005; ITT – Population, LOCF)

	DFD-06-CD-004			DFD-06-CD-005		
	DFD-06 cream	Vehicle	P-Value	DFD-06 cream	Vehicle	P-Value
N	178	89	<0.001	176	89	< 0.001
Treatment Success n (%)	30.2%	9%		30.1%	9.7%	

LOCF: Last Observation Carried Forward
Source: modified from sponsor's submission, CSR: DFD-06-CD-004, Tables 11.8, page 46 and CSR: DFD-06-CD-005, Table 11.4, page 44.

The statistical reviewer Rebecca Hager, Ph.D., performed sensitivity analysis where all missing IGA scores at Day 15 were assumed to be a treatment failure and, called missing values treated as failure (MVTF). In addition, the applicant analyzed the primary endpoint for the PP population. The PP population in Trial 005 included one subject who had a treatment-related AE and was therefore considered a treatment failure after Day 4 according to the plan pre-specified by the applicant. The results of these sensitivity analyses for the primary endpoint were consistent with the primary analysis.

Reviewer's comment
The applicant demonstrated that DFD-06 cream was statistically superior to vehicle cream as measured by the primary efficacy endpoint.

6.1.5 Analysis of Secondary Endpoint(s)

The applicant analyzed two secondary endpoints according to the pre-specified order:

1) The percent change in BSA at Day 15. This endpoint is not considered a clinically meaningful measurement of efficacy in psoriasis. Therefore, this endpoint will not be included in labeling will not be discussed in this review.

2) The proportion of subjects with treatment success at Day 8 (defined as IGA=0 or 1 and at least a 2-grade reduction from baseline at the Day 8 visit), if the primary efficacy endpoint at Day 15 achieved statistical significance.

The results for this endpoint are summarized in Table 12.

Table 12 : Proportion of Subjects with Treatment Success at Day 8 (Trials DFD-06-CD-004 and DFD-06-CD-005)

ITT Population[1]	DFD-06-CD-004			DFD-06-CD-005		
	DFD-06 cream	Vehicle	P-Value	DFD-06 cream	Vehicle	P-Value
N	178	89	0.006	176	89	0.001
Treatment Success[2] (%)	15.7%	5.6%		14.2%	1.6%	

Source: Statistical Review and Evaluation of NDA 209483, by Rebecca Hager, Ph.D., Table 7, page 12.

(1) The intent-to-treat (ITT) population was defined as all subjects who were randomized and dispensed study product.
(2) Treatment success defined as an IGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade reduction from baseline. Missing values were handled using multiple imputation and results were averaged over the 5 imputed data sets. The p-value was calculated from a CMH test for general association adjusted for analysis center and baseline IGA score.

Reviewer's comment:

The secondary efficacy endpoint of the percentage change in BSA at Day 15 is not considered a clinically meaningful measurement of efficacy in psoriasis. Therefore, this endpoint will not be included in labeling.

The secondary efficacy endpoint of proportion of subjects with treatment success on Day 8 visit is clinically meaningful and statistically significant. Therefore, the results of this efficacy endpoint may be included in labeling.

6.1.6 Other Endpoints

No additional efficacy endpoints were evaluated by the applicant.

6.1.7 Subpopulations

Subgroup analyses of the primary endpoint responders for ITT population (who achieved treatment success at Day 15) were similar across, gender, race, and ethnicity subgroups. Subjects 65 years and older had a higher likelihood of success (41.2%), compared to subjects 18 to 64 years old (28.1%). The results are presented in the Table 13.

Table 13 : Percentage of Subjects with Treatment Success at Day 15 by Gender, Age, Race, Ethnicity, and Baseline Disease Severity

ITT Population[1]	Trial DFD-06-CD-004			Trial DFD-06-CD-005		
	(ND, NV)[2] (178, 89)	DFD-06	Vehicle	(ND, NV)[2] (176, 89)	DFD-06	Vehicle
Gender						
Male	(100, 44)	30.8%	9.1%	(111, 51)	30.6%	12.2%
Female	(78, 45)	29.5%	8.9%	(65, 38)	29.2%	6.3%
Age						
< 65 Years	(151, 75)	28.9%	10.7%	(152, 70)	27.6%	6.6%
≥ 65 Years	(27, 14)	37.8%	0.0%	(24, 19)	45.8%	21.1%
Race						
White	(149, 74)	31.3%	6.8%	(146, 79)	30.8%	8.4%
Non-White	(29, 15)	24.8%	20.0%	(30 ,10)	26.7%	20.0%
Ethnicity						
Hispanic or Latino	(39, 25)	41.0%	12.0%	(41, 21)	29.3%	12.4%
Non-Hispanic or Latino[3]	(139, 64)	27.2%	7.8%	(135, 68)	30.4%	8.8%
Baseline IGA						
Moderate (3)	(154, 77)	33.6%	10.4%	(142, 72)	31.0%	10.6%
Severe (4)	(24, 12)	8.3%	0.0%	(34, 17)	26.5%	5.9%

Source: Statistical Review and Evaluation of NDA 209483, by Rebecca Hager, Ph.D., Table 16, Page 18.

(1) The intent-to-treat (ITT) population was defined as all subjects who were randomized and dispensed study product. Missing values were handled using multiple imputation and results were averaged over the 5 imputed data sets.
(2) N_D = subgroup sample size in the DFD-06 arm and N_V = subgroup sample size in the vehicle arm.
(3) Includes 1 “Unwilling to Provide” patient in Trial 005.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable. Only one dose strength of DFD-06, 0.025% cream was applied during the trials.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The applicant did not evaluate persistence of efficacy or tolerance effects.

6.1.10 Additional Efficacy Issues/Analyses

There were no additional efficacy issues.

7 Review of Safety

Safety Summary

The assessment of safety for the DFD-06, clobetasol propionate cream, 0.025% was based on analysis of data from two Phase 3 trials (DFD-06-CD-004 and DFD-06-CD-005) and one Phase 2 trial (DFD-06-CD-007). Safety population included 378 subjects in the DFD-06 treatment arms of the three trials. Subjects in the three trials received approximately 28 applications of the drug product over a period of 14 days.
No deaths were reported during the development program for DFD-06 drug product.

Three serious adverse events (SAEs) of metastatic lymphoma, stab wound and cellulitis were reported during the development program for DFD-06. The event of metastatic lymphoma and stab wound were reported in DFD-06 treatment arms. These two SAEs were not treatment related. The SAE of cellulitis was reported in subject treated with vehicle.

Local adverse reactions were consistent with local adverse reactions seen with other topical corticosteroids, including other clobetasol propionate topical products.

The only adverse reaction (AR) that occurred in more than 1% of subjects, and at a higher incidence in DFD-06 treatment arms, was the application site discoloration. Two percent of subjects in DFD-06 treatment arms compared to one percent of subjects in vehicle treatment arms had application site discoloration.

The potential for HPA axis suppression was evaluated in two clinical trials, DFD-06-CD-007 and CDS-1002.

In two-week HPA- axis suppression trial DFD-06-CD-007, on Day 15, HPA suppression was reported in 3 (12.5%) of subjects in DFD-06 treatment arm compared to 8 (36.4%) of subjects in Temovate treatment arm.
In a 4-week HPA axis suppression trial CDS-1002, on Day 28, the incidence of HPA axis suppression in DFD-06 treatment group (30.8%) was similar to that of Temovate E cream treatment group (34.6%).

The strength of clobetasol propionate cream, 0.025% under review in this NDA is one-half the strength of Temovate cream (0.05%), applied with the same frequency and duration of dosing (BID x 14 days). The potential for HPA axis suppression appears to increase with the duration of exposure. After 2 weeks of treatment, the incidence of HPA axis suppression in DFD-06 treatment group is approximately one-third of the incidence of HPA axis suppression in Temovate treatment group however; after 4 weeks of treatment the incidence of HPA axis suppression is similar to that of Temovate E.

For the proposed duration of treatment of 2 weeks, DFD-06 appears to have a lower incidence of HPA axis suppression in subjects with moderate to severe plaque psoriasis.

The results of dermal safety studies did not demonstrate a potential for phototoxicity, photoallergenicity or cumulative irritancy / contact sensitization for DFD-06 cream.

The applicant provided sufficient evidence to establish the safety of the drug.

The applicant did not report any new safety issues in the 120-day safety update for this submission.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety database consists primarily of two Phase 3 trials, DFD-06-CD-004 and, DFD-06-CD-005 and one Phase 2 trial, DFD-06-CD-007. These trials were chosen as the focus of safety review due to the similarity of their study design; enrolled subjects were the targeted patient population for the proposed indication, and the treatment was at doses that reflect anticipated use (twice daily).

7.1.2 Categorization of Adverse Events

Adverse events were classified using the Medical Dictionary for Drug Regulatory Activities (MedDRA) classification system, Version 18.1.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Data from three clinical trials (two Phase 3 trials, DFD-06-CD-004 and DFD-06-CD-005, and one Phase 2 trial, DFD-06-CD-007) were pooled. The safety population included 378 subjects in DFD-06 treatment arms of the three trials. Vehicle arms were pooled from two Phase 3 trials; Temovate treatment arm of the Phase 2 trial was excluded from this safety analysis. The safety data from the other 6 studies in the DFD-06 development program were not pooled due to differences in clinical trial designs.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The extent of exposure and compliance for the three pooled studies were similar. Overall exposure to DFD-06 in terms of frequency, duration of dosing and the target population was adequate for the evaluation of safety, as presented in Table 14.

Table 14 : Summary of Study Drug Exposure

Parameter / Statistic	**DFD-06 (N=375)**
Mean (SD) Number of Applications	28.4 (2.97)
Mean (SD) Days of Exposure	15.0 (1.40)

Source: Table 1.2.1 of ISS, Summary of study drug exposure, safety population

Demographics:

The demographic characteristics were generally similar between DFD-06 and vehicle treatment arms for each subgroup. Most subjects were white, male and less than 65 years of age. Baseline demographic characteristics are presented in Table 15.

Table 15 : Baseline Demographics Characteristics (Safety Population)

Parameter	DFD-06 Cream (N=378) (n%)	Vehicle Control Cream (N=178)
Age at Baseline (Years)		
Mean (SD)	49.1 (14.25)	50.2 (15.11)
Median	50.0	52.0
Min, Max	18, 79	18, 82
Age Group at Baseline		
< 65 Years	326 (86.2%)	145 (81.5%)
≥ 65 Years	52 (13.8%)	33 (18.5%)
Gender		
Male	228 (60.3%)	95 (53.4%)
Female	150 (39.7%)	83 (46.6%)
Race		
White	319 (84.4%)	153 (86.0%)
Black or African American	33 (8.7%)	11 (6.2%)
Asian	9 (2.4%)	5 (2.8%)
American Indian or Alaskan Native	6 (1.6%)	2 (1.1%)
Native Hawaiian or Other Pacific Islander	1 (0.3%)	2 (1.1%)
Other	10 (2.6%)	5 (2.8%)
Ethnicity		
Hispanic or Latino	94 (24.9%)	46 (25.8%)
Non-Hispanic or Non-Latino	283 (74.9%)	131 (73.6%)
Unknown	1 (0.6%)	0
IGA at Baseline		
Clear	0	0
Almost Clear	0	0
Mild	0	0
Moderate	315 (83.3%)	149 (83.7%)
Severe	63 (16.7%)	29 (16.3%)
BSA Affected at Baseline (%)		
Mean (SD)	8.94 (10.272)	8.90 (11.271)
Median	5.00	5.00
Min, Max	3.0, 80.0	3.0, 80.0

Source: applicant's submission, modified from Table 1.1.2, Integrated Summary of Safety

7.2.2 Explorations for Dose Response

The applicant did not conduct any dose-ranging trials. The only dose used for Phase 3 trials was clobetasol propionate cream, 0.025%, applied BID.

7.2.3 Special Animal and/or In Vitro Testing

See Section 4.3.

7.2.4 Routine Clinical Testing

No laboratory or ECG evaluations were performed for Phase 3 clinical trials. Urine pregnancy tests were performed at baseline and at the end of the trials.

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Systemic absorption of topical corticosteroids can result in potential reversible suppression of hypothalamic-pituitary-adrenal (HPA) axis. HPA axis function was evaluated in study CDS-1002 and trial DFD-06-CD-007 by ACTH stimulation test. The results are discussed in Section 4.4.3 of this review.

Local adverse skin reactions associated with topical corticosteroids include skin atrophy, striae, telangiectasias, burning, itching, irritation, dryness, folliculitis, acneiform eruptions, hypopigmentation, hypertrichosis, perioral dermatitis, allergic contact dermatitis, secondary infections and miliaria. Local adverse skin reactions were evaluated as part of the trial safety assessments.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths during the development program for DFD-06.

7.3.2 Nonfatal Serious Adverse Events

Three non-fatal serious adverse events (stab wound; mantel cell lymphoma; cellulitis) were reported during clinical development program for DFD-06. None were deemed related to the study drug by the investigators:

*Trial DFD-06-CD-007, s*ubject 107004, a 45-year-old white male treated with DFD-06 experienced an SAE of a severe stab wound to the lower right abdomen.

*Trial DFD-06-CD-004, s*ubject 118016, a 60-year-old male treated with DFD-06 on Day 1 through Day 10. He was hospitalized on Day 11 for enlarged lymph nodes and was subsequently diagnosed with a metastatic lymphoma (mantle cell lymphoma) and discontinued from the study.

*Trial DFD-06-CD-005, s*ubject 103006, a 39-year-old, male was treated with Vehicle on Day 1 through Day 11 when he was hospitalized for cellulitis of right lower leg.

Reviewer's comment:

This reviewer agrees with investigators' assessments that the SAEs were not related to the study drug.

7.3.3 Dropouts and/or Discontinuations

Of the 378 subjects treated with DFD-06) 374 completed the studies. A total of 4 subjects (1%) in the DFD-06 treatment arm discontinued the trials, compared to 5(3%) in the vehicle arms. No subject treated with DFD-06 discontinued due to treatment related AE. Subject dispositions are summarized in Table 16.

Table 16 : Subject Disposition

Parameter	DFD-06 Cream n (%)	Vehicle Control Cream n (%)
Subjects Included	378	178
Study Status		
Completed Study	374 (98.9%)	173 (97.2%)
Discontinued Study	4 (1.1%)	5 (2.8%)
Reasons for Discontinuation		
Subject decision/withdrawal of consent	2 (0.5%)	2 (1.1%)
A treatment-related AE occurred	0	1 (0.6%)
A non-treatment-related AE occurred	1 (0.3%)	0
Lost to follow-up	1 (0.3%)	2 (1.1%)

Source: Modified from Table 1.1.1, subject disposition, ISS

7.3.4 Significant Adverse Events

No additional significant adverse events were reported. Three subjects who reported severe adverse events were the same subjects with SAEs, as outlined in section 7.3.2.

7.3.5 Submission Specific Primary Safety Concerns

Submission specific primary safety concern is the potential for HPA axis suppression. The potential for HPA axis suppression in the trials CDS-1002 and DFD-06-CD-007 were discussed in section 4.4.3.

Submission specific safety concerns relate to the potential for corticosteroid-induced skin effects. There were no clinically important differences in local safety data between two treatment arms. The results are summarized in Table 17.

Table 17 : Summary of Local Cutaneous Safety Evaluation at Day 15, Excluding Subjects with Symptoms Present at Baseline (Pooled Safety Population)

Preferred Term	DFD-06 n (%) / N	Vehicle n (%) / N
Atrophy	1 (0.3)/349	0/161
Telangiectasia	2 (0.6)/363	0/166
Burning or stinging	7 (2.3)/298	5 (6.7)/131
Itching	5 (3.5)/142	7 (10.8)/65
Striae	0/325	0/166
Hypopigmentation	5 (1.6)/316	2 (1.3)/158
Fissuring	2 (0.6)/324	6 (3.7)/161
Folliculitis	1 (0.3)/340	0/168
Pain	0/23	0/0

Source: modified from Table 15, page 36-38, ISS, MedDRA version 18.1 (percentages are computed based on the total number of non-missing records in each treatment group).

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The only Treatment Emergent Adverse Event (TEAE) that occurred in ≥ 1% of subjects was application site discoloration. This AE was considered treatment related. The results are presented in Table 18.

Table 18 : Summary of Treatment-Emergent Adverse Reactions Occurring in ≥ 1% of Subjects in Any Treatment Group (Pooled Safety Population), With higher incidence in DFD-06 than Vehicle

Preferred Term	DFD-06 (N=378) n (%)	Vehicle (N=178) n (%)
Application site discolouration	6 (1.6)	2 (1.1)

Source: modified from Tables 7, page 23 of Integrated Summary of Safety.
MedDRA version: 18.1

Reviewer's comments:

The higher incidence of application site discoloration in DFD-06 group is consistent with vasoconstriction associated with application of topical corticosteroids.

7.4.2 Laboratory Findings

Routine clinical laboratory evaluations were not performed during the development of DFD-06.

7.4.3 Vital Signs

No clinically significant changes in vital signs from baseline were observed over the study period and between treatment groups in the pooled safety analysis. The results are presented in Table 19.

Reference ID: 4169448

Table 19 : Summary of Vital Signs and Change from Baseline (Pooled Safety Population)

Parameter	DFD-06 (N=378)	Vehicle (N=178)
Baseline Diastolic Blood Pressure (mmHg)		
Mean (±SD)	79.5 (9.51)	78.9 (8.98)
Min, Max	50, 110	54, 98
DBP: Change from Baseline to Day 15		
Mean (±SD)	-0.5 (8.31)	-0.7 (8.54)
Min, Max	-38, 26	-32, 21
Baseline Systolic Blood Pressure (mmHg)		
Mean (±SD)	128.2 (13.41)	128.2 (13.40)
Min, Max	100, 159	88, 181
SBP: Change from Baseline to Day 15		
Mean (±SD)	0.2 (11.71)	0.1 (11.24)
Min, Max	-61, 54	-33, 44
Baseline Pulse (bpm)		
Mean (±SD)	74.9 (10.24)	74.5 (10.28)
Min, Max	48, 105	50, 98
Pulse: Change from Baseline to Day 15		
Mean (±SD)	0.8 (8.07)	1.2 (10.10)
Min, Max	-29, 34	-42, 32

Source: Modified from sponsor's submission, ISS, Table 16, p. 41-42

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were not performed during the DFD-06 clinical development program. The applicant did not conduct Thorough QT (TQT) study and requested a waiver for conducting TQT studies for DFD-06.

The applicant presented the following reasons in support of their request:

- No cardiovascular adverse events were reported by any patient on DFD-06 treatment in DFD-06 trials
- Lower systemic exposure to DFD-06 cream compared to Temovate E, after 2 weeks of treatment under maximal use conditions.
- The applicant cited the long marketing history of clobetasol propionate (since 1974) and absence of any post-marketing reports of cardiovascular safety signals, including arrhythmias possibly related to QT/QTc prolongation
- No corticosteroids are among the 54 drugs with anti-hERG activity
- The applicant performed a literature search which did not identify an increased risk of QT/QTc prolongation associated with the use of clobetasol propionate.

Reviewer's comment:
After two weeks of treatment under maximal use conditions, the systemic exposure to DFD-06 was lower compared to Temovate E (clobetasol propionate 0.05%).

Therefore; it is reasonable to conclude that the conduct of TQT study would not be needed.

7.4.5 Special Safety Studies/Clinical Trials

The applicant conducted 3 Phase 1, provocative dermal safety studies (DFD-06-CD-008, DFD-06-CD-009 and DFD-06-CD-010) in healthy adult subjects with the to-be-marketed formulation to support the safety of clobetasol propionate, 0.025% cream. The trials evaluated the potential of DFD-06 cream for irritation, sensitization, phototoxicity, and photoallergenicity. The results are presented in this section.

Phototoxicity study (DFD-06-CD-008)

This was a single center, randomized, double blind, vehicle controlled within-subject study of 32 healthy, evaluable subjects, 18 years and older with Fitzpatrick skin types 1-3. Minimal Erythema Dose (MED) was determined for each subject on Day 1.

A total of 4 application sites (2 cm x 2 cm) were marked on each subject's back, 2 sites for DFD-06 and 2 sites for vehicle cream. One side of the subject's back (including one DFD-06 and one vehicle site) was designated for irradiation after 24 hours of product application. An additional control site was selected on the irradiation site and received no product application, to serve as untreated, irradiated control.

On Day 1, 0.2 ml of DFD-06 cream or vehicle cream were each applied to infrascapular area of each subject and occluded for 24 hours. Patches were removed on Day 2 (after 24 hours) and one application site of each product and an untreated control site were each irradiated with 16 Joules/cm^2 of UVA followed by 0.5 MED of UVA/UVB. All application site and untreated control site were evaluated on Day 3 (24 hours) and on Day 4 (48 hours) post-irradiation.

Scoring for assessment of drug application sites were done according to Table 20.

Reference ID: 4169448

Table 20 : Scoring for Assessment of Sites, Study DFD-06-CD-008

Score	Response
Erythema	
0	No reaction
1	Mild, but definite erythema
2	Moderate erythema
3	Marked/severe erythema
Edema	
0	No response
1	Mild, but definite edema
2	Definite edema with erosion/vesiculation

Source: Modified from CSR DFD-06-CD-008, Table 3, p. 23

The response score at each site was defined as the sum of erythema and edema scores at application site. A study product was defined as phototoxic if one of the following criteria was satisfied:

- The score of the irradiated active product minus the score of the irradiated vehicle is 2 or more points greater than the score of non-irradiated active product in 3 or more subjects at either 24 or 48 hours (post irradiation).
- The score of the irradiated active product minus the score of the irradiated vehicle is 1 or more points greater than the score of non-irradiated active product in 9 or more subjects at either 24 or 48 hours (post irradiation).

Thirty-one (31) of 32 subjects completed the study. The erythema and edema scores results were as follows:

- On Day 3, 10 (32.3%) of irradiated sites in each of DFD-06, vehicle and untreated arms showed an erythema score of 1, compared to none of the non-irradiated sites. On Day 4, erythema scores were 0 at all application sites.
- Edema scores were 0 for all application sites on Days 3 and 4.

Safety evaluation included all AEs. No SAEs, TEAEs or AEs were reported in the study. None of 31 subjects met phototoxicity criteria at 24 or 48-hour post-irradiation at DFD-06 or vehicle cream application sites. The results of this study demonstrated that there was no phototoxic potential after a single application of DFD-06 cream, 0.025% or the vehicle cream followed by UVA/UVB irradiation.

Photoallergenicity study (DFD-06-CD-009)

This study was a single center, randomized, double blind, vehicle controlled, within-subject comparison of DFD-06, vehicle cream, 0.9% normal saline (negative control), and an untreated irradiated(open) control site for photoallergenicity potential.

Fifty-seven (57) healthy subjects 18 years or older, with Fitzpatrick skin types 1-3 were randomized and analyzed for safety. This study had 3 phases:

- Induction phase:
  DFD-06 cream, vehicle cream, or normal saline were applied, under semi-occlusive conditions, twice weekly for 24 hours to 6 sites (2 sites for each product) on each subject's back for 3 consecutive weeks during the induction phase. Patches were removed 24 hours after application and one application site of each study product was irradiated with 2 MEDs. All patch sites were evaluated 48-72 hours post irradiation during induction phase.

- Rest phase:
  No products were applied during weeks 4-5 of the study.

- Challenge phase:
  At challenge Week 6, DFD-06 cream, vehicle cream, and saline were each applied once to two naïve sites on the infrascapular region of each subject's back under semi-occlusive conditions. All patches were removed 24 hours after application and one site of each test product and an untreated control site was irradiated with 6 Joules/cm^2 of UVA followed by 0.5 MED of UVA/UVB. Patch sites were assessed 24 hours, 48 hours and 72 hours post-irradiation.

Patch test sites were scored using the same scoring criteria as in the study DFD-06-CD-008.

Results

Evaluation of skin assessments during the challenge phase demonstrated:

- No subject had erythema or edema after the application of patches (before irradiation) to any naïve patch site.
- No non-irradiated sites showed any reaction in any subject.
- Three subjects (subjects #2002, #2004, #2037) (5.6%) had mild erythema at all irradiated patch sites for DFD-06 cream, vehicle cream, saline, and untreated control sites at 24 hours post-irradiation that resolved by 48 hours post-irradiation.
- No edema occurred at any patch sites during the challenge phase.

The results of this study demonstrated that there was no evidence of photoallergic potential for DFD-06 cream or vehicle cream.

Safety was evaluated by collection of AEs. Fifty-four (54) of 57 subjects received all treatments and completed the study. One SAE (sciatic nerve injury) was reported in this study. This SAE was considered by the investigator not to be related to the study

drug. All other TEAEs were considered unrelated to study treatment by the investigators.

Cumulative irritancy / Contact sensitization patch test (DFD-06-CD-010)

This study was a 6 week, randomized, double-blind, vehicle-controlled, repeat-insult patch test to assess the irritation and sensitization potential of DFD-06 cream.

Two hundred eighty-one healthy subjects (281), 18 years and older, were randomized to receive 0.2 ml of each of the following: DFD-06, vehicle cream, sterile saline (negative control), or sodium lauryl sulfate (SLS) 0.2% (positive control).

Semi-occlusive patches were applied to the backs of subjects for 48 hours, three times weekly during the first three weeks (the induction phase), followed by a 2-week rest period. A single 48-hour application of each patch was performed at a naïve skin site after rest period (the challenge phase).

Patch test sites were scored for skin reaction before each patch application during the induction phase and at 30 minutes, 1, 2, 3 days after patch removal during the challenge phase.

Two hundred thirty-eight (238) subjects were evaluated for cumulative irritancy and 229 subjects were evaluated for contact sensitization. Patch test sites were evaluated according to the scale in table 21.

Table 21 : Integer Grading Scale of Response, Study DFD-06-CD-010

Grade	Response	Score
0	No evidence of irritation	0
1	Minimal erythema, barely perceptible	1
2	Definite erythema, readily visible; or minimal edema; or minimal papular response	2
3	Erythema and papules	3
4	Definite edema	3
5	Erythema, edema, and papules	3
6	Vesicular eruption	3
7	Strong reaction spreading beyond test site	3

Source: sponsor's submission, Clinical study report DFD-06-CD-010, section 5.3.5.4. Page 25.

The results are summarized in Tables 22 and 23.

Table 22 : Summary of skin Assessments during Induction (Cumulative Irritancy Population), Study DFD-06-CD-010

Percent of subjects within each study arm by response score during induction	DFD-06 Cream (clobetasol propionate) 0.025% (N=238)	Vehicle Cream (N=238)	Saline 0.9% (N=238)	Sodium Lauryl Sulfate 0.2% (N=238)
Baseline Reading (N=238)				
Grade 0	238(100%)	238(100%)	238(100%)	238(100%)
Induction Reading 1(N=235)				
Grade 0	235(100.)0%	234(99.6) %	235(100.0) %	234(99.6) %
Grade 1	0.0%	1(0.4%)	0(0.0%)	1(0.4%)
Induction Reading 2(N=237)				
Grade 0	237(100.)0%	236(99.6) %	237(100.)0%	232(97.9%)
Grade 1	0(0.0%)	1(0.4%)	0(0.0%)	5(2.1%)
Induction Reading 3(N=233)				
Grade 0	231(99.1%)	226(97.0%)	219(94.0%)	211(90.6%)
Grade 1	2(0.9%)	7(3.0%)	14(6.0%)	22(9.4%)
Induction Reading 4(N=237)				
Grade 0	228(96.2%)	218(92.0%)	214(90.3%)	189(79.7%)
Grade 1	9(3.8%)	19(8.0%)	23(9.7%)	48(20.3%)
Induction Reading 5(N=236)				
Grade 0	222(94.1%)	215(91.1%)	194(82.2%)	167(70.8%)
Grade 1	14(5.9%)	21(8.9%)	42(17.8%)	66(28.0%)
Grade 2	0(0.0%)	0(0.0%)	0(0.0%)	3(1.3%)
Induction Reading 6(N=236)				
Grade 0	219(92.8%)	206(87.3%)	185(78.4%)	147(62.3%)
Grade 1	17(7.2%)	29(12.3%)	49(20.8%)	80(33.9%)
Grade 2	0(0.0%)	1(0.4%)	2(0.8%)	8(3.4%)
Induction Reading 7(N=236)				
Grade 0	219(92.8%)	205(86.9%)	175(74.2%)	136(57.6%)
Grade 1	15(6.4%)	29(12.3%)	60(25.4%)	83(35.2%)
Grade 2	2(0.8%)	2(0.8%)	1(0.4%)	16(6.8%)
Grade 3	0(0.0%)	0(0.0%)	0(0.0%)	1(0.4%)
Induction Reading 8(N=234)				
Grade 0	213(91.0%)	196(83.8%)	167(71.4%)	124(53.0%)
Grade 1	19(8.1%)	36(15.4%)	64(27.4%)	91(38.9%)
Grade 2	2(0.9%)	2(0.9%)	3(1.3%)	18(7.7%)
Grade 3	0(0.0%)	0(0.0%)	0(0.0%)	1(0.4%)
Induction Reading 9(N=238)				
Grade 0	215(90.3%)	195(81.9%)	165(69.3%)	119(50.0%)
Grade 1	21(8.8%)	41(17.2%)	70(29.4%)	96(40.3%)
Grade 2	2(0.8%)	2(0.8%)	3(1.3%)	22(9.2%)
Grade 3	0(0.0%)	0(0.0%)	0(0.0%)	1(0.4%)
Make-up Reading(N=20)				
Grade 0	15(75.0%)	14(70.0%)	11(55.0%)	8(40.0%)
Grade 1	5(25.0%)	6(30.0%)	9(45.0%)	9(45.0%)
Grade 2	0(0.0%)	0(0.0%)	0(0.0%)	3(15.0%)

Source: sponsor's submission, section 5.3.5.4., Clinical study report DFD-06-CD-010, Table 14.3.1.1.1, page 64.

In the DFD-06 treatment arm, no subject had a score ≥ 3, consistent with lack of cumulative irritancy potential for DFD-06 during the induction phase of the trial.

Table 23 : Summary of Skin Assessments during Challenge and Re-challenge (Contact Sensitization Population), Study DFD-06-CD-010

Percent of subjects within each study arm by response score during challenge	DFD-06 Cream (clobetasol propionate) 0.025% (N=229)	Vehicle Cream (N=229)	Saline 0.9% (N=229)	Sodium Lauryl Sulfate 0.2% (N=229)
Reading 1 / 30 Minutes Post-Removal				
Grade 0	227(99.1%)	236(98.7%)	224(97.8%)	224(97.8%)
Grade 1	2(0.9%)	3(1.3%)	5(2.2%)	5(2.2%)
Reading 2 / 24 Hours Post-Removal				
Grade 0	227(99.1%)	228(99.6%)	229(100.0%)	227(99.1%)
Grade 1	2(0.9%)	1(0.4%)	0(0.0%)	2(0.9%)
Reading 3 / 48 Hours Post-Removal				
Grade 0	227(99.1%)	229(100.0%)	228(99.6%)	228(99.6%)
Grade 1	2(0.9%)	0(0.0%)	1(0.4%)	1(0.4%)
Reading 4 / 72 Hours Post-Removal				
Grade 0	229(100.0%)	229(100.0%)	229(100.0%)	229(100.0%)
Suspected Sensitization Reaction in the Challenge Phase				
Yes	4 (1.7%)	3 (1.3%)	6 (2.6%)	5 (2.2%)
No	225 (98.3%)	226 (98.7%)	223 (97.4%)	224 (97.8%)
Suspected Sensitization Reaction in the Re-Challenge Phase				
N[a]	4	3	5	3
Yes	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
No	4 (100.0%)	3 (100.0%)	5 (100.0%)	3 (100.0%)

a = Number of subjects who exhibited a suspected sensitization reaction to the test article in the Challenge Phase and completed the Re-Challenge Phase

Source: sponsor's submission, section 5.3.5.4., study report DFD-06-CD-010, Tables 14.3.1.1.2 and 14.3.1.1.3, pages 59-69.

In the DFD-06 treatment arm, no subject had a score ≥ 2 during challenge phase of the trial, and none of the four subjects with a suspected sensitization reaction had a positive re-challenge test, consistent with lack of contact sensitization potential for DFD-06.

Safety was evaluated by collection of AEs. One SAE, deep venous thrombosis, occurred in DFD-06 group. One SAE, cholecystitis, occurred in SLS group. These SAEs were considered unrelated to study treatment.

Overall, 5.7% of all subjects experienced TEAEs. All TEAEs were considered unrelated to the study drug by the investigators.

The results of this study did not demonstrated evidence of cumulative irritancy or contact sensitization potential with DFD-06 cream.

Reviewer's comment:

This reviewer agrees with the assessment of the applicant that the results of dermal safety studies did not demonstrate a potential for phototoxicity, photoallergenicity or cumulative irritancy / contact sensitization for DFD-06 cream.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Only one dose of the study drug was applied during the conduct of this trial.

7.5.2 Time Dependency for Adverse Events

Time dependency of adverse events was not evaluated due to short duration of treatment.

7.5.3 Drug-Demographic Interactions

In the safety population, the majority of subjects were white 319 (84%). Non-white subjects included: African American 33 (9%); Asian 9 (2%), American Indian or Alaskan 6 (2%). The differences in sample size between white and non-white population prevented drawing meaningful conclusions regarding effect of drug treatment by race. Analysis of effects of drug treatment by gender, age and ethnicity did not reveal consistent pattern of higher incidence of AEs in any of subgroups.

The Results are summarized in tables 24, 25 and 26.

Table 24 : Summary of Treatment-Emergent Adverse Events Occurring in ≥ 2% of Patients by Gender (Pooled Safety Population)

Preferred Term	DFD-06 (M: N=228) (F: N=150) n (%)
Application site pain	
Male	11 (4.8)
Female	9 (6.0)
Application site pruritus	
Male	7 (3.1)
Female	3 (2.0)
HPA axis suppression	
Male	2 (0.9)
Female	1 (0.7)
Application site fissure	
Male	1 (0.4)
Female	2 (1.3)
Application site discolouration	
Male	4 (1.8)
Female	3 (2.0)
Dehydroepiandrosterone decreased	
Male	1 (0.4)
Female	1 (0.7)

Source: modified from ISS, Table 8, pages 25-26. MedDRA version 18.1.

Examination of TEAEs in the safety population by gender revealed no gender-related differences in the incidence of TEAEs.

Table 25 : Summary of Treatment-Emergent Adverse Events Occurring in ≥ 1% of Patients by Age Group (Pooled Safety Population)

Preferred Term	DFD-06 (< 65: N=326) (≥ 65: N=52) n (%)
Number of all subjects with at least one TEAE	
Patients ≥ 18 to 64 years	53 (16.3)
Patients ≥ 65 years	4 (7.7)
Application site pain	
Patients ≥ 18 to 64 years	20 (6.1)
Patients ≥ 65 years	0
Application site pruritus	
Patients ≥ 18 to 64 years	9 (2.8)
Patients ≥ 65 years	1 (1.9)
HPA axis suppression	
Patients ≥ 18 to 64 years	3 (0.9)
Patients ≥ 65 years	0
Application site fissure	
Patients ≥ 18 to 64 years	2 (0.6)
Patients ≥ 65 years	1 (1.9)
Application site discolouration	
Patients ≥ 18 to 64 years	6 (1.8)
Patients ≥ 65 years	1 (1.9)
Dehydroepiandrosterone decreased	
Patients ≥ 18 to 64 years	2 (0.6)
Patients ≥ 65 years	0

Source: modified from ISS, Table 9, pages 27-28. MedDRA version 18.1.

Of the 556 subjects in the safety population, 471(85%) were in the age group of 18 to 64 years, and 85(15%) were age 65 years or older. Examination of TEAEs in the safety population by age suggested a slightly higher incidence of “at least one TEAE” and “application site pain” in the 18 to 64-year age group, compared to ≥ 65 years. The small numbers of the TEAEs listed in Table 25 made comparison of the incidence of TEAEs between age groups not clinically meaningful.

Table 26 : Summary of Treatment-Emergent Adverse Events Occurring in ≥ 2% of Patients by Ethnicity (Pooled Safety Population)

Preferred Term	DFD-06 (H/L: N=94) (NH/NL: N=283) n (%)
Number of subjects with at least one TEAE	
Hispanic / Latino	15 (16.0)
Non-Hispanic / Non-Latino	42 (14.8)
Application site pain	
Hispanic / Latino	5 (5.3)
Non-Hispanic / Non-Latino	15 (5.3)
Application site pruritus	
Hispanic / Latino	3 (3.2)
Non-Hispanic / Non-Latino	7 (2.5)
HPA axis suppression	
Hispanic / Latino	2 (2.1)
Non-Hispanic / Non-Latino	1 (0.4)
Application site fissure	
Hispanic / Latino	0
Non-Hispanic / Non-Latino	3 (1.1)
Application site discolouration	
Hispanic / Latino	1 (1.1)
Non-Hispanic / Non-Latino	6 (2.1)
Dehydroepiandrosterone decreased	
Hispanic / Latino	2 (2.1)
Non-Hispanic / Non-Latino	0

Source: modified from ISS, Table 11, pages 30-31. MedDRA version 18.1.

Of the 554 subjects in the safety population, 140(25%) were Hispanic / Latino and 414(75%) were Non-Hispanic/Non-Latino. Examination of TEAEs by ethnicity revealed no ethnicity-related differences in the incidence of TEAEs.

7.5.4 Drug-Disease Interactions

Not applicable. DFD-06 has not been evaluated in subjects with renal or hepatic impairment.

7.5.5 Drug-Drug Interactions

The applicant did not conduct specific drug interaction studies.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

One event of lymphoma identified in trial DFD-06-CD-004. Given the short duration of treatment, it is this reviewer's opinion that the study drug was not a causative agent.

7.6.2 Human Reproduction and Pregnancy Data

Protocols for all clinical trials excluded pregnant or lactating women. No pregnancies were reported during the development program for DFD-06.

The Pregnancy (8.1) and Lactation (8.2) sections of the label will be in the format of Pregnancy and Lactation Labeling Rule (PLLR). Jane Liedtka, M.D. proposed the language for this section of labeling as follow:

HIGHLIGHTS OF PRESCRIBING INFORMATION
----------USE IN SPECIFIC POPULATIONS----------
Pregnancy: May cause fetal harm (8.1)

FULL PRESCRIBING INFORMATION
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
There are no available data on the use of Clobetasol propionate cream 0.025% in pregnant women to inform any drug-associated risk for adverse developmental outcomes. Published data report a significantly increased risk of low birthweight with the use of greater than 300 grams of potent or very potent topical corticosteroid during a pregnancy. Advise pregnant women of the potential risk to a fetus and to use Clobetasol propionate cream 0.025% on the smallest area of skin and for the shortest duration possible (*see Data*). In animal reproduction studies, increased malformations, such as cleft palate and skeletal abnormalities, were observed after subcutaneous administration of clobetasol propionate to pregnant mice and rabbits. No comparisons of animal exposure with human exposure (b) (4) due to minimal systemic exposure (b) (4) after topical administration of Clobetasol propionate cream 0.025% [*see Clinical Pharmacology (12.3)*].
The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S., general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.
Data
Human Data
Multiple observational studies found no significant associations between maternal use of topical corticosteroids of any potency and congenital malformations, preterm delivery, or fetal mortality. However, when the dispensed amount of potent or very potent topical corticosteroid exceeded 300 g during the entire pregnancy, use was associated with an increase in low birth weight

infants [adjusted RR, 7.74 (95% CI, 1.49–40.11)]. In addition, in a small cohort study, 28 sub-Saharan women using potent topical corticosteroids (27/28 used clobetasol propionate 0.05%) for skin lightening during pregnancy noted a higher incidence of low birth weight infants in the exposed group. The majority of exposed subjects treated large areas of the body (a mean quantity of 60 g/month (range, 12—170g) over long periods of time.

APPEARS THIS WAY ON ORIGINAL

Animal Data

In an embryofetal development study in mice, subcutaneous administration of clobetasol propionate resulted in fetotoxicity at the highest dose tested (1 mg/kg) and malformations at the lowest dose tested (0.03 mg/kg). Malformations seen included cleft palate and skeletal abnormalities. In an embryofetal development study in rabbits, subcutaneous administration of clobetasol propionate resulted in malformations at doses of 0.003 and 0.01 mg/kg. Malformations seen included cleft palate, cranioschisis, and other skeletal abnormalities.

APPEARS THIS WAY ON ORIGINAL

8.2 Lactation

Risk Summary

There is no information regarding the presence of clobetasol propionate in breast milk or its effects on the breastfed infant or on milk production. Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of clobetasol could result in sufficient systemic absorption to produce detectable quantities in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Clobetasol propionate cream 0.025% and any potential adverse effects on the breastfed infant from Clobetasol propionate cream 0.025% or from the underlying maternal condition.

Clinical Considerations

To minimize potential exposure to the breastfed infant via breast milk, use Clobetasol propionate cream 0.025% on the smallest area of skin and for the shortest duration possible while breastfeeding. Advise breastfeeding women not to apply Clobetasol propionate cream 0.025% directly to the nipple and areola to avoid direct infant exposure.

17 PATIENT COUNSELING INFORMATION

Pregnancy

Advise a pregnant woman that use of Clobetasol propionate cream 0.025% may cause fetal (b) (4) and to use Clobetasol propionate cream 0.025% on the smallest area of skin and for the shortest duration possible. [*see Use in Specific Populations (8.1)]*.

Lactation

Advise a woman to use Clobetasol propionate cream 0.025% on the smallest area of skin and for the shortest duration possible while breastfeeding. Advise breastfeeding women not to apply Clobetasol propionate cream 0.025% directly to the nipple and areola to avoid direct infant exposure *[see Use in Specific Populations (8.2)]*.

7.6.3 Pediatrics and Assessment of Effects on Growth

Clinical studies were conducted only in adults. The Division agreed to the initial pediatric study plan (iPSP) submitted by the sponsor on 10/7/2015. The pediatric development plan presented in the agreed iPSP included the following:

- Clinical effectiveness:
  Waiver requested for ages 0 to 16.9 years.
  Psoriasis has common pathophysiology and natural history in the adult and pediatric populations. Therefore, it is reasonable to conclude that efficacy of clobetasol propionate cream, 0.025% in the treatment of children with moderate to severe psoriasis may be extrapolated from efficacy in adult population.

- Clinical safety:
  - Partial waiver requested for children from 0 to < 6 years of age for both PK and clinical safety studies.
    The prevalence of psoriasis in pediatric population in this age group is low. Therefore, studies in psoriasis patients less than 6 years of age would be impossible or highly impracticable (because, for example, the number of patients in that age group is so small or the patients in that age group are geographically dispersed)".

  - Deferral requested for PK/HPA axis suppression studies in subjects 6 to < 17 years of age, until after the PK/HPA studies in adults were completed.
    On 4/13/2017, the sponsor submitted a protocol amendment to iPSP for the planned PK/HPA axis studies (DFD-06-CD--011), to include a 2-stage, sequential study of 25 subjects 12 to 16.9 years of age, and 25 subjects 6 to 11.9 years of age, to be initiated in 5/2017.

A Pediatrics Review Committee (PeRC) meeting was held on 8/16/2017. The committee agreed with the applicant's agreed iPSP for partial waiver / deferral requests.

The PeRC agreed with partial waiver in pediatric patients 0 to less than 6 years, agreed to by the Division, as studies are impossible or highly impracticable. The PeRC recommended that the protocol include pediatric subjects that fit the criteria for maximum use data without an age restriction, if they meet enrollment criteria.

The PeRC agreed with deferral plan in pediatrics patients 6 to less than 17 years of age.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable to this review.

7.7 Additional Submissions / Safety Issues

8 Postmarket Experience

DFD-06 has not been marketed in any country.

9 Appendices

9.1 Literature Review/References

Literature review:

The applicant is relying on the safety of Temovate NDA for which it has obtained the right of reference, and is not relying on the published literature to support the clinical efficacy and safety of DFD-06 cream. The applicant performed a literature search using MEDLINE, BIOSIS, Embase, International Pharmaceutical Abstracts and SciSearch for clobetasol propionate and included only the search criteria used, and not the search results in the submission.

References:

1 Valencia IC, Kerdel FA. Chapter 216. Topical Corticosteroids. In: Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Wolff K. eds. *Fitzpatrick's Dermatology in General Medicine, 8e.* New York, NY: McGraw-Hill; 2012. http://accessmedicine.mhmedical.com/content.aspx?bookid=392&Sectionid=41138952. Accessed February 23, 2017.

9.2 Labeling Recommendations

Labeling negotiations were ongoing as this review closed. If the application is approved, final labeling will be attached to the approval letter.

9.3 Advisory Committee Meeting

This application was not discussed at an advisory committee meeting.

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/s/

HAMID N TABATABAI
10/19/2017
Primary Clinical Review of NDA 209483

SNEZANA TRAJKOVIC
10/19/2017