CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208183Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 208183	Submission Date(s): 12/23/2014, 5/29/2015
Brand Name	Ultravate Lotion, 0.05%
Generic Name	Halobetasol propionate lotion, 0.05% w/w
Primary Reviewer	Doanh Tran, 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	Ferndale Laboratories, Inc.
Relevant IND(s)	(b) (4)
Submission Type	Original
Formulation; Strength(s)	Lotion, 0.05% w/w
Indication	Treatment of plaque psoriasis in patients 18 years of age and older

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1 Executive Summary

Halobetasol propionate is a super-potent topical corticosteroid. There are currently two approved formulations of halobetasol propionate, namely Ultravate Cream, 0.05% and Ultravate Ointment, 0.05% and their respective generic cream and ointment formulations. The applicant developed a lotion formulation of halobetasol propionate, 0.05% (hereafter HBP Lotion) for treatment of plaque psoriasis in adults.

The clinical program includes 7 clinical studies, including a vasoconstrictor assay trial, a hypothalamic-pituitary-adrenal (HPA) axis suppression/pharmacokinetic (PK) trial under maximal use conditions, a Phase 2 supportive safety and efficacy trial, and 2 Phase 3 safety and efficacy trials.

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds NDA 208183 acceptable pending agreement on recommended labeling changes.

1.2 Phase IV Requirements and Commitments

The following post marketing requirement is recommended:

A trial evaluating the adrenal suppression potential and pharmacokinetic properties of twice daily halobetasol proprionate lotion, 0.05% under maximal use conditions in subjects 12 years to 16 years 11 months of age with plaque psoriasis.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

PK/HPA axis suppression:
The systemic bioavailability and HPA axis suppression rate were evaluated in a parallel trial comparing HBP lotion, 0.05% vs. Ultravate cream, 0.05% in 43 adult subjects with moderate to severe plaque psoriasis involving ≥20% body surface area (BSA). Approximately 3.5 grams was applied twice daily for 14 days. HPA assessment was done in all subjects and PK assessment was done in subset of 24 subjects (n=12 per treatment arm).

Steady state was achieved by day 8, when serial PK samplings were done. Plasma concentrations of HBP were measurable in all subjects. HBP concentration versus time profiles at steady state were generally relatively flat, but a few subjects did have significant peak/trough variation. The mean (±SD) Cmax concentrations for HBP lotion, 0.05% on Day 8 was 201.1 ± 157.5 pg/mL, with the corresponding median Tmax value of 3 hours (range 0 – 6 hours); mean area under the halobetasol propionate concentration versus time curve over the dosing interval (AUCτ) was 1632 ± 1147 pg*h/mL. Systemic exposure was similar between HBP lotion, 0.05% and Ultravate cream, 0.05%.

For the per protocol population, 25% (5 of 20) of HBP lotion, 0.05% treated subjects and 14.3% (3 of 21) of Ultravate cream, 0.05% treated subjects demonstrated an abnormal HPA axis response at end of treatment. Seven of 8 subjects who were suppressed had normal results at follow up. The one remain subject did not return for follow up assessment.

Potency classification:
Potency classification was evaluated using a single point vasoconstrictor assay (VCA) with visual assessment in 36 subjects. Results showed that HBP lotion, 0.05% (mean VCA score 2.39) was statistically similar to Ultravate cream, 0.05% (Class I, mean VCA score 2.44) and different than triamcinolone acetonide cream, 0.5% (Class III, mean VCA score 1.78). The results indicate that HBP lotion, 0.05% is a super potent corticosteroid product.

Pediatric:
The applicant requested a deferral of pediatric studies for subjects 12 years to 16 years 11 months of age. As per the agreed initial pediatric study plan, the applicant will conduct a PK/HPA axis suppression trial in adolescents aged 12 years to 16 years 11 months with plaque psoriasis. This trial will be included as a PREA post marketing requirement.

Clinical vs. to-be-marketed formulation:
The applicant stated that all 7 clinical trials in the development program used the same formulation as the proposed to be marketed formulation (i.e., formulation R9860).

Method validation:
Plasma HBP and serum cortisol concentrations were evaluated using adequately validated assays.

2 Question-Based Review

2.1 General Attributes

2.1.1 What is halobetasol proprionate (HBP)?

Halobetasol propionate is a super-potent topical corticosteroid. It is indicated for the local topical treatment of various inflammatory skin disorders (e.g., psoriasis). There are currently two approved formulations of halobetasol propionate, namely Ultravate Cream, 0.05% and Ultravate Ointment, 0.05% and their respective generic cream and ointment formulations. The Applicant developed a new lotion formulation to provide additional formulation options for patients.

2.1.2 What are the proposed indication and dosing regimen for HBP lotion, 0.05%?

The proposed indication is for treatment of plaque psoriasis in patients 18 years of age and older. The proposed dosing regimen is to apply a thin layer to the affected areas twice daily for up to 2 weeks with a maximum dose of 50 g per week.

2.1.3 What is plaque psoriasis?

Psoriasis is a chronic autoimmune disease that manifests itself as inflammatory dermatosis and affects 1-3% of the US population. The most common type of psoriasis is plaque psoriasis, which is characterized by well-demarcated, pruritic, thick, scaly skin lesions. Psoriasis pathogenesis involves the abnormal regulation of the cells of the immune system (white blood cells including T lymphocytes, neutrophils, and other leucocytes) prompted by both environmental and genetic factors, which leads to a dysregulation of normal keratinocyte proliferation and an increase in proinflammatory cell signals.

2.2 General Clinical Pharmacology

2.2.1 What were the design features of the clinical pharmacology and clinical trials used to support HBP lotion, 0.05%?

The clinical program includes 7 clinical studies, including a vasoconstrictor assay trial, a hypothalamic-pituitary-adrenal (HPA) axis suppression/pharmacokinetic (PK) trial under maximal use conditions, a Phase 2 supportive safety and efficacy trial, and 2 Phase 3 safety and efficacy trials.

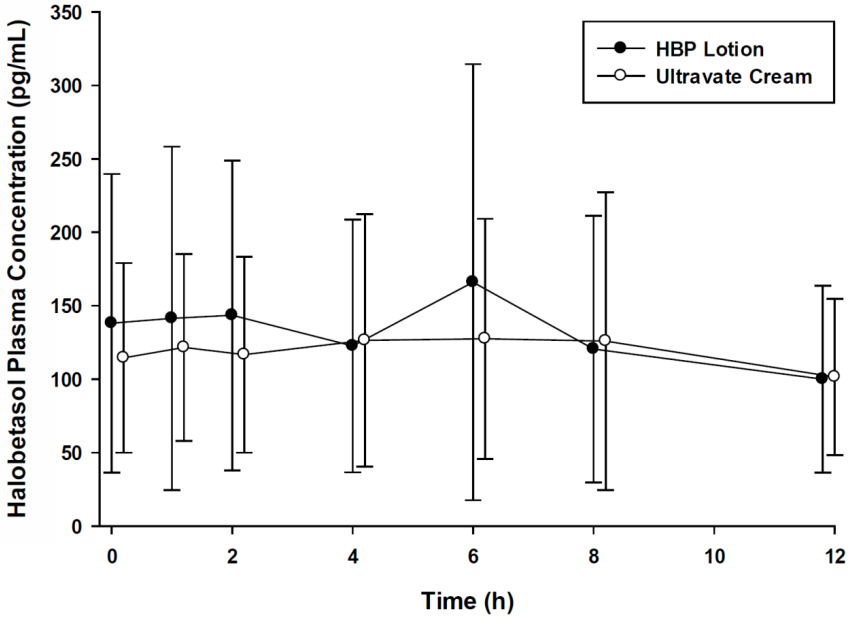
2.2.2 What is the systemic bioavailability of HBP lotion, 0.05% under maximal use conditions and what is the relative bioavailability compared to Ultravate cream, 0.05%?

The Applicant conducted a parallel trial with HBP lotion, 0.05% vs. Ultravate cream, 0.05% in 43 adult subjects with moderate to severe plaque psoriasis involving ≥20% body surface area (BSA) and evaluated HPA axis suppression in all subjects and PK in a subgroup of 24 subjects (n=12 per treatment arm). For the HBP lotion PK subgroup, the

subjects applied a mean (±SD) dose of 3.3 ± 0.89 grams twice daily to an area of 20.3 ± 6.7 %BSA for 14 days. Serial PK sampling was done on Day 8.

Based on Ctrough concentrations before dosing and at end of dosing interval on Day 8 and before dosing on Day 15, the results suggests steady state was achieved by day 8. Plasma concentrations of HBP were measurable in all subjects. Individual HBP concentration versus time profile at steady state was generally relatively flat, but a few subjects did have significant peak/trough variation. The mean (±SD) Cmax concentrations for HBP lotion, 0.05% on Day 8 was 201.1 ± 157.5 pg/mL, with the corresponding median Tmax value of 3 hours (range 0 – 6 hours); mean area under the halobetasol propionate concentration versus time curve over the dosing interval (AUCτ) was 1632 ± 1147 pg*h/mL. Systemic exposure was similar between HBP lotion, 0.05% and Ultravate cream, 0.05% (Figure 1 and Table 1).

Figure 1: Mean Halobetasol Propionate Plasma Concentration-Time Profiles Over a Dosing Interval on Day 8 Following Topical Application of Halobetasol Propionate Twice a Day for 8 Days



(Note: Profiles offset by 0.2 hours to allow visualization of error bars)

Table 1: Comparison of Systemic Exposure Variables for HBP Lotion and Ultravate® Cream

Parameter		Treatment Group	
		HBP Lotion 0.05% (N = 12)	Ultravate® Cream 0.05% (N =12)
C_{max} (pg/mL)	Geometric Mean (CV%) Range: Min to Max	145.9 (106.89%) 33.4 to 497	136.2 (71.44%) 54.9 to 383
T_{max} (h)	Median Range: Min to Max	3 0 to 6	3 0 to 8
AUC_{τ} (pg-h/mL)	Geometric Mean (CV%) Range: Min to Max	1267.7 (89.84%) 326.8 to 3873	1229.8 (67.19%) 490.3 to 2853.5
C_{min} (pg/mL)	Geometric Mean (CV%) Range: Min to Max	80.17 (79.27%) 24 to 197	78.37 (57.29%) 33.2 to 184
T_{min} (h)	Median Range: Min to Max	5 0 to 12	7 0 to 12

2.2.3 What is the effect of HBP lotion, 0.05% on suppressing the hypothalamic pituitary adrenal (HPA) axis?

In the same trial as noted in section 2.2.2, HPA assessment was done in all subjects. Approximately 3.5 grams (range 1.7 – 5.6 grams) HBP lotion, 0.05% or 3.0 grams (range 1.3 – 5.0 grams) Ultravate cream, 0.05% were applied twice daily for 14 days. The results showed 25% (5 of 20) of HBP lotion, 0.05% treated subjects and 14.3% (3 of 21) of Ultravate cream, 0.05% treated subjects demonstrated an abnormal HPA axis response at end of treatment. Seven of 8 subjects who were suppressed had normal results at follow up. The one remain subject did not return for follow up assessment.

2.2.4 What is the potency classification for HBP lotion, 0.05%?

Potency classification was evaluated using a single point vasoconstrictor assay (VCA) with visual assessment in 36 subjects. Five (5) different HBP lotion, 0.05% formulations were compared to 2 reference products, namely Ultravate cream, 0.05% (a Class I product) and triamcinolone acetonide cream, 0.5% (a Class 3 product). All products were applied as a single dose and left on for 16 hours. Visual assessment was done 2 hours after washing the application sites.

Results showed that the to-be-marketed formulation of HBP lotion, 0.05% (formulation R9860) was statistically similar to Ultravate cream, 0.05% (Class I) and different than triamcinolone acetonide cream, 0.5% (Class III) (Table 2). The results indicate that HBP lotion, 0.05% is a super potent corticosteroid product.

Table 2: Summary of vasoconstriction scores

VCA SCORE		STUDY MEDICATION				
SUM	MEAN*	REGWQ Grouping**			NAME	ABBREVIATION
88	2.44		A		Ultravate® (halobetasol propionate) Cream 0.05% (Class I)	Ultravate®
86	2.39	B	A		Halobetasol Propionate Lotion 0.05% (Formulation# R9860)	HBP R9860
86	2.39	B	A		Halobetasol Propionate Lotion 0.05% (Formulation# R9861)	HBP R9861
79	2.19	B	A	C	Halobetasol Propionate Lotion 0.05% (Formulation# R9864)	HBP R9864
73	2.03	B	D	C	Halobetasol Propionate Lotion 0.05% (Formulation# R9862)	HBP R9862
69	1.92		D	C	Halobetasol Propionate Lotion 0.05% (Formulation# R9863)	HBP R9863
64	1.78		D		Triamcinolone Acetonide Cream 0.5% (Class III)	Triamcinolone
6	0.17		E		Lotion Vehicle (Formulation# R9869)	Vehicle R9869

* Means with the same letter (A-E) are not significantly different.
** Grouping based on the Ryan-Einot-Gabriel-Welsch (REGWQ) Multiple Range Test.

2.3 Intrinsic Factors

2.3.1 What is the systemic exposure of HBP lotion, 0.05% in pediatrics?

The applicant requested a deferral of pediatric studies for subjects 12 years to 16 years 11 months of age. As per the agreed initial pediatric study plan, the applicant will conduct a PK/HPA axis suppression trial in adolescents aged 12 years to 16 years 11 months with plaque psoriasis. This trial will be included as a PREA post marketing requirement. A waiver has been granted for studies in pediatrics <12 years of age.

2.4 Extrinsic Factors

The applicant did not provide any information on the effect of extrinsic factors on the PK of HBP lotion, 0.05%. Because the systemic bioavailability of HBP lotion, 0.05% is similar to approved Ultravate Cream, 0.05%, a request for additional studies is not warranted.

2.5 General Biopharmaceutics

2.5.1 What is the formulation composition of HBP lotion, 0.05%?

The formulation composition of HBP lotion, 0.05% is shown below.

Ingredient	Purpose	Composition (% w/w)
Halobetasol Propionate USP	API	0.05
Diisopropyl Adipate		(b) (4)
Octyldodecanol, NF		
Ceteth-20		
Poloxamer 407, NF		
Cetyl Alcohol, NF		
Stearyl Alcohol, NF		
Propylparaben, NF		
Butylparaben, NF		
Propylene Glycol, USP		
Glycerin, USP		
Carbomer Homopolymer, NF		
Sodium Hydroxide, NF (b) (4)		
(b) (4) Water, USP		

2.5.2 Was the to-be-marketed formulation used in the clinical trials?

The applicant stated that all 7 clinical trials in the development program used the same formulation as the proposed to be marketed formulation (i.e., formulation R9860).

2.6 Analytical

2.6.1 What bioanalytical methods were used to assess HBP and cortisol and were they adequately validated?

Plasma HBP:

The analysis of HBP in human plasma was done using an adequately validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay with a range of 20 – 4000 pg/mL. The mean intra-assay and inter-assay precision for the lower limit of quantitation (LLOQ) and 3 levels of quality controls (QC) were between 3.9 and 8.6% and between 7.2 and 11.5%, respectively. The intra-assay and inter-assay accuracy for the same were between 3.0 and 7.1% and between -1.5 and 3.4%, respectively. Incurred samples reanalysis from trial 000-0551-202 showed 73.1% (19 of 26 samples) were within ±20% acceptance criteria.

Sample storage stability was demonstrated at -20 ºC for 532 days and at -80 ºC for 167 days. However, stability at -80 ºC were tested at 532 and 552 days but both failed on the high side by up to 20.6 and 22.0%, respectively, for unknown reason. The QC low samples stored at -80 ºC did meet stability criteria on Day 532. Samples from trial 000-0551-202 were stored at -20 ºC to -80 ºC for up to 333 days (i.e., from start of trial to end

of sample analysis). Overall, as stability was demonstrated at -20 ºC for 532 days and the deviation seen at -80 ºC is not large, this reviewer considers there is adequate storage stability to support the duration of 333 days for samples from trial 000-0551-202.

Serum cortisol:
The analysis of serum cortisol concentration was done at (b) (4) using the validated commercial ADVIA Centau Cortisol assay with a range of 0.2 – 75 µg/dL. Precision and accuracy assessments done at the testing laboratory were within acceptable limits (see Table 3).

Table 3: Summary of accuracy and precision assessments done at (b) (4)

Within Run Precision

Control	Level	N	Assayed Mean	SD	%CV	Verification Limit Within Run	Comment
9833411	1	10	4.38	0.24	5.47	6.55 %CV	Within Acceptable Limits
9833412	2	10	16.08	0.53	3.27	6.20 %CV	Within Acceptable Limits
9833413	3	10	29.28	0.69	2.37	6.20 %CV	Within Acceptable Limits

Accuracy

Control	Level	N	Assayed Mean	Published Control Range	Comment
9833411	1	10	4.38	3.01 - 6.03	Within Acceptable Limits
9833412	2	10	16.08	11.20 - 21.20	Within Acceptable Limits
9833413	3	10	29.28	19.90 - 37.30	Within Acceptable Limits

The applicant provided data to support storage stability for (b) (4) and (b) (4) Hence, there is adequate data to cover samples for trial 000-0551-202, which were stored at (b) (4)

3 Detailed Labeling Recommendations

The following changes are recommended for sections 5 and 12 of the label. For section 5, only edits to the data are noted here. This reviewer defers to the clinical reviewer to convert this section to be consistent with class labeling. Deletions are noted as ~~strikethrough~~ and additions are noted as double underlines.

5.1 Hypothalamic-Pituitary-Adrenal (HPA) Axis Suppression

Systemic effects of topical corticosteroids may include reversible HPA axis suppression, with the potential for glucocorticosteroid insufficiency. This may occur during treatment or upon withdrawal of treatment of the topical corticosteroid.

The potential for hypothalamic-pituitary adrenal (HPA) suppression with ULTRAVATE Lotion was evaluated in a study of (b) (4) 20 adult subjects with moderate to severe plaque psoriasis involving ≥20% of their body surface area. ULTRAVATE Lotion produced HPA axis suppression when used twice daily for two weeks in 5 out of (b) (4) 20 ((b) (4) 25%) adult patients with plaque psoriasis. Recovery of HPA axis function was generally prompt with the discontinuation of treatment [*see Clinical Pharmacology (12.2)*].

Because of the potential for systemic absorption, use of topical corticosteroids, including ULTRAVATE Lotion, may require that patients be evaluated periodically for evidence of HPA axis suppression. Factors that predispose a patient using a topical corticosteroid to HPA axis suppression include the use of more potent steroids, use over large surface areas, (b) (4) prolonged periods, (b) (4) occlusive (b) (4) use on an altered skin barrier, (b) (4) liver failure, and (b) (4) young age. An ACTH stimulation test may be helpful in evaluating patients for HPA axis suppression.

If HPA axis suppression is documented, (b) (4) attempt (b) (4) to gradually withdraw the drug, (b) (4) reduce the frequency of application, or (b) (4) substitute a less potent steroid. Manifestations of adrenal insufficiency may require supplemental systemic corticosteroids. Recovery of HPA axis function is generally prompt and complete upon discontinuation of topical corticosteroids.

Systemic effects of topical corticosteroids may also include Cushing's syndrome, hyperglycemia, and glucosuria. Use of more than one corticosteroid-containing product at the same time may increase the total systemic (b) (4) topical corticosteroids.

Pediatric patients may be more susceptible than adults to systemic toxicity from the use of topical corticosteroids due to their larger surface-to-body mass ratios [*see Use in Specific Populations (8.4)*].

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

(b) (4)

Corticosteroids play a role in cellular signaling, immune function, inflammation, and protein regulation; however, the precise mechanism of action in plaque psoriasis is unknown.

12.2 Pharmacodynamics

A vasoconstrictor assay in healthy subjects with ULTRAVATE Lotion indicated that the formulation is in the super-high range of potency as compared to other topical corticosteroids; however, similar blanching scores do not necessarily imply therapeutic equivalence.

The potential for hypothalamic-pituitary adrenal (HPA) suppression was evaluated in a study of (b) (4) 20 adult subjects with moderate to severe plaque psoriasis. A mean dose of

3.5 grams ULTRAVATE Lotion [redacted] was applied twice daily for two weeks and produced HPA axis suppression in 5 of [redacted] 20 [redacted] 25%) patients. In this study, the criteria for HPA-axis suppression was a serum cortisol level of less than or equal to 18 micrograms per deciliter 30 minutes after stimulation with cosyntropin (adrenocorticotropic hormone). These effects were reversible as recovery of HPA axis function was generally prompt with the discontinuation of treatment [*see Warnings and Precautions (5.1)*].

12.3 Pharmacokinetics

The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including the vehicle, the integrity of the epidermal barrier, and the use of occlusive dressings. Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin may increase percutaneous absorption.

In [redacted] a Phase 2 HPA [redacted] clinical study [*see Clinical Pharmacology (12.2)*], pharmacokinetics was evaluated in a subgroup of 12 adult subjects [redacted] On Day 8, blood was taken just prior to and at 1, 2, 4, 6, 8, and 12 hours following the last application. Plasma concentration of halobetasol propionate was measureable in all subjects. Based on the geometric mean plasma concentrations at 12 hour post-application across time, steady-state was achieved by Day 8. The mean (±standard deviation) C_{max} concentrations for ULTRAVATE Lotion on Day 8 was 201.1 ± 157.5 pg/mL, with the corresponding [redacted] median T_{max} value of [redacted] 3 hours (range 0 – 6 hours); mean area under the halobetasol propionate concentration versus time curve over the dosing interval (AUCτ) was 1632 ± 1147 pg•h/mL. [redacted]

4 Appendix

4.1 Individual Study Reviews

Trial 000-0551-202

Title:
A Comparative Evaluation of the Adrenal Suppression Potential and Pharmacokinetic Properties of Twice Daily Halobetasol Propionate Lotion 0.05% versus Halobetasol Propionate Cream 0.05% in Subjects with Moderate to Severe Plaque Psoriasis Receiving Two Weeks of Treatment.

Study period:
Date of first screened subject: 8/9/2010; date of last completed subject: 5/24/2011.

Objectives:
The primary objective was to determine and compare the adrenal suppression potential and the pharmacokinetic properties of a new halobetasol propionate (HBP) lotion versus Ultravate® Cream applied twice daily in subjects with moderate to severe psoriasis. The secondary objective was to determine and compare the changes in the disease severity during treatment with the two HBP formulations.

Methodology:
This was a comparative, multicenter study of an investigational formulation of halobetasol propionate lotion (HBP Lotion) 0.05% versus Ultravate® Cream 0.05% in subjects with moderate to severe plaque psoriasis. Forty-three subjects, males or females aged 18 and above, with at least moderate to severe plaque psoriasis on at least 20% of their body surface area (excluding the face, scalp, groin, axillae and other intertriginous areas) who fulfilled the inclusion/exclusion criteria were enrolled at five study sites. All subjects had a Cosyntropin Stimulation Test (CST) to assess their HPA axis response at Visit 1 (Screening Visit). At Visit 2 (Baseline), eligible subjects with acceptable laboratory tests (including normal adrenal function) were randomized (1:1) to one of two test articles (HBP Lotion or Ultravate® Cream) for up to 14 days.

Enrollment into the treatment phase of the study at the Baseline Visit was timed such that the screening CST was performed at least four (4) weeks before the projected end of the treatment phase. Half of the subjects applied either the investigational formulation of HBP Lotion 0.05% or Ultravate® Cream 0.05% to all psoriasis plaques identified at Visit 2 twice daily for the assigned treatment period or until the investigator verified the subject's psoriasis had cleared. The study was designed to determine the adrenal suppression potential and pharmacokinetic properties of the investigational test article versus reference drug after the subject applied a maximum of 50 grams per week for up to a two-week treatment period (i.e., approximately 7 grams daily or 3.5 grams per application). All subjects had a CST to reassess their HPA axis response at the end of the scheduled treatment period. In this study, an abnormal HPA axis response to a 0.25 mg

dose of cosyntropin was defined as a 30-minute post-CST serum total cortisol level of ≤ 18 μg/dL at the end of treatment.

At select sites only, eligible subjects had blood drawn on Day 1 before the application of the test article for baseline drug levels in plasma. Twenty-four subjects (12 subjects per treatment group) participated in the PK assessment. On Day 8, these PK subjects had serial blood draws taken just prior to the morning application of test article and at 1, 2, 4, 6, 8, and 12 hours post-application and then, on the following day (Day 9), 24 hours post-application. If any of these subjects were clear of lesions at Day 8, a final CST evaluation and collection of blood and urine was to have been performed at Day 9; however, since no subjects were clear at Day 8, collection of the final laboratory specimens and the CST were performed at Day 15 after the subjects completed twice daily dosing for an additional week following the final PK specimen draw on Day 9.

Number of subjects:
Planned: 40; Analyzed: 43 (intent-to-treat), 41 (per-protocol), 24 (pharmacokinetic).

Treatment:
Subjects applied the assigned test article (HBP Lotion vs. Ultravate® Cream) to the affected areas designated by the investigator, twice daily for two weeks.

Halobetasol propionate lotion (HBP Lotion, formulation R9860) 0.05% was manufactured, packaged and labeled by Ferndale Laboratories Inc., Ferndale, MI and packaged in 2 ounce (60 gram) HDPE bottles.

Ultravate® Cream 0.05% (50 gram aluminum tubes) was manufactured by Ranbaxy Inc. and purchased from commercial sources.

PK assessment:
At selected sites (PK sites), eligible subjects had blood drawn on Day 1 before the application of the test article for baseline drug levels in plasma. On Day 8, subjects at these sites (regardless of lesion clearance) had serial blood draws taken just prior to the morning application of test article, and taken at 1, 2, 4, 6, 8, and 12 hours post-application and then, on the following day (Day 9), 24 hours post-application as part of their CST evaluation (for subjects whose lesions had cleared completely). PK subjects who had not cleared completely at Day 8 withheld application of the test article until after the 24-hour blood draw had been taken on Day 9 and then continued daily application of the test article until Day 15. At the Day 15 visit, PK subjects had a final blood sample collected for plasma HBP levels just prior to the initiation of the CST. All PK plasma samples were stored (at -20°C) at the PK sites until transfer to the bioanalytical laboratory for analysis.

Cosyntropin stimulation testing:
At Visit 1 (Screening Visit, Part B) and at the End of Treatment (i.e., the visit at which psoriasis had cleared or end of the assigned treatment period), CST (and any follow-up CSTs) was performed. If the results of the Visit 1 (Screening) cosyntropin stimulation test indicated the subject had an abnormal HPA axis response (defined as a post-

stimulation serum cortisol level of ≤ 18µg/dL), the subject was to be withdrawn. If a subject's End of Treatment cosyntropin stimulation test showed an abnormal HPA axis response, the test article was considered to have caused adrenal suppression in the subject.

Assay:
Plasma HBP concentrations and serum cortisol concentrations were evaluated using adequately validated assays. See section 2.6 of this review for further details.

Results:

Demographic:
The demographic of the PP population is shown in Table 4. The majority (66%) of subjects were male and most (81%) were White race.

Table 4: Demographic information of PP population

CHARACTERISTIC	N (%) N=41
SEX	
Male	27 (65.9%)
Female	14 (34.1%)
ETHNICITY	
Hispanic or Latino	6 (14.6%)
Not Hispanic or Latino	35 (85.4%)
RACE	
White	33 (80.5%)
Black	4 (9.8%)
Asian	1 (2.4%)
Islander	1 (2.4%)
Hispanic	1 (2.4%)
White & Euro-American	1 (2.4%)
AGE (years)	
Mean	48.4
Median	48.7
Standard Deviation	11.21
Range	22.7 – 71.5

Dosing:
Overall, subjects were compliant with respect to doses applied. The mean percent of expected doses applied at end of treatment was >98% for all populations across both treatment groups. Regarding per-protocol (PP) exclusions, dosing compliance was at least 80% for all subjects except Subject 01-123 (HBP Lotion) who missed 6 out of 29 possible doses (compliance rate of 79.3%); this subject was excluded from the PP population. All PK subjects met the requirement for at least 80% of the expected doses.

The average dose of test article applied for the PP population was 3.5 g (HBP Lotion) and 3.0 g (Ultravate® Cream) with a range of 1.7 g to 5.6 g (HBP Lotion) and 1.3 g to 5.0 g (Ultravate® Cream). The average dose of test article applied for the PK population was 3.3 g (HBP Lotion) and 3.5 g (Ultravate® Cream) with a range of 1.7 g to 4.8 g (HBP Lotion) and 2.4 g to 5.0 g (Ultravate® Cream).

PK:
Key dosing parameters for subjects in the PK subgroup are shown in Table 5. The mean dose and treated area for the HBP PK population were 3.3 g and 20.3 % BSA, respectively. The area and amount applied were similar between the 2 treatment groups.

Table 5: Summary of dosing parameters for PK subgroup

Dosing Parameter		Treatment Group	
		HBP Lotion 0.05% N=12	Ultravate® Cream 0.05% N=12
Total Amount of Test Article Applied (g)	Mean (CV%) Median Range (Min to Max)	87.2 (27.7%) 89.5 46.5 to 129.7	92.8 (16.4%) 93.8 68.3 to115.3
Average Dose per Application (g)	Mean (CV%) Median Range (Min to Max)	3.3 (27.1%) 3.43 1.7 to 4.8	3.5 (21.5%) 3.36 2.4 to 5.0
Average % BSA† Treated	Mean (CV%) Median Range (Min to Max)	20.3 (33.1%) 20 6 to 30	19.3 (30.6%) 20 9 to 27
Average Dose/Treatment Area ‡ (g/m^2)	Mean (CV%) Median Range (Min to Max)	8.5 (71.5%) 6.3 5.0 to 26.2	11.0 (63.2%) 8.7 4.5 to 27.2

* Data from End of Text Tables 1 and 2 (Appendix 16.1.13) and rounded up to one decimal place.
† BSA = Body Surface Area was an average of the % BSA treated at Baseline and at Day 8.
‡ Average dose per application / % BSA treated; N=11.

Halobetasol propionate trough plasma concentrations occurring at the end of the 12-hour dosing interval (i.e., Day 8, 0 and 12 hours and Day 15, 12 hours) in subjects treated with the cream and lotion formulations were determined (Table 6). Based on the geometric means for trough plasma concentrations at 12 hour s post-application across time, steady-state for both formulations appears to be achieved by Day 8 (time of first observation after the start of test article application).

HBP plasma concentrations were measureable in all subjects (Tables 7 and 8). Individual HBP concentration versus time profiles at steady state were generally relatively flat, but a few subjects did have significant peak/trough variation. The mean (±SD) Cmax concentrations for HBP lotion, 0.05% on Day 8 was 201.1 ± 157.5 pg/mL, with the corresponding median Tmax value of 3 hours (range 0 – 6 hours); mean area under the halobetasol propionate concentration versus time curve over the dosing interval (AUCτ) was 1632 ± 1147 pg*h/mL (Table 7). The mean steady state PK profiles for HBP lotion

and Ultravate cream are shown in Figure 2. The individual PK profiles for HBP lotion is shown in Figure 3.

Table 6: Comparison of Halobetasol Propionate Trough Plasma Concentrations at 12 Hours Post-Application for Ultravate® Cream and HBP Lotion

		Treatment Group	
Plasma [HBP]		**HBP Lotion 0.05% N=12**	**Ultravate® Cream 0.05% N-12**
Day 8 (t=0 h)† (pg/mL)	**Geometric Mean (CV%) Range: Min to Max**	110.2 (96.28%) 26.3 to 305	101.2 (53.7%) 49.6 to 261
Day 8 (t = 12 h)‡ (pg/mL)	**Geometric Mean (CV%) Range: Min to Max**	86.65 (75.19%) 25.6 to 217	88.91 (59.06%) 33.6 to 200
Day 15 (t = 12 h)‡ (pg/mL)	**Geometric Mean (CV%) Range: Min to Max**	87.38 (70.11%) 21.5 to 237	106.5 (53.69%)§ 46.3 to 262§

* Data from End of Text Tables 4 and 5 (Appendix 16.1.13).
† t=0 h is 12 hours after the previous dose in the evening on Day 7.
‡ Time after previous dose.
§ N =11.

Table 7: Individual Halobetasol Propionate Pharmacokinetic Parameters on Day 8 Following Topical Application of HBP Lotion Twice a Day for 8 Days.

Subject	C_{max}	T_{max}	AUC_{τ}	C_{min}	T_{min}	C_{max}/D	AUC_{τ}/D	C_{min}/D
	(pg/mL)	(h)	(pg-h/mL)	(pg/mL)	(h)	(pg/mL/D)	(pg-h/mL/D)	(pg/mL/D)
105	75.4	0	704.91	47.2	1.03	26.18	244.8	16.39
107	278	0	2484.86	167	12	80.81	722.3	48.55
111	336	2	2963.5	197	4	87.05	767.7	51.04
112	158	6	1083.1	60.6	0	32.92	225.6	12.63
115	497	6	3873	173	12	144.90	1129.2	50.44
122	33.4	6	326.8	24	4	19.42	190.0	13.95
126	84.8	2	771.9	45.7	4	28.75	261.7	15.49
127	269	2	2451.5	179	12	CNC	CNC	CNC
129	67	6	745.35	58.1	4	18.82	209.4	16.32
131	432	6	2425.5	111	12	104.35	585.9	26.81
142	117	0	1116.85	82.8	6	58.50	558.4	41.40
143	65.1	4	633.75	41.3	12	20.41	198.7	12.95
N	12	12	12	12	12	11	11	11
Mean	201.1	3.33	1631.8	98.89	6.92	56.56	463.1	27.82
CV%	78.30	78.20	70.30	64.10	68.40	75.00	67.60	59.30
Min	33.4	0	326.8	24	0	18.82	190	12.63
Median	137.5	3	1100.0	71.7	5	32.92	261.7	16.39
Max	497	6	3873	197	12	144.9	1129.2	51.04
Geometric Mean	145.9	CND	1267.7	80.17	CND	43.84	379.3	23.68
CV% Geometric Mean	106.89	CND	89.84	79.27	CND	86.62	73.18	64.71

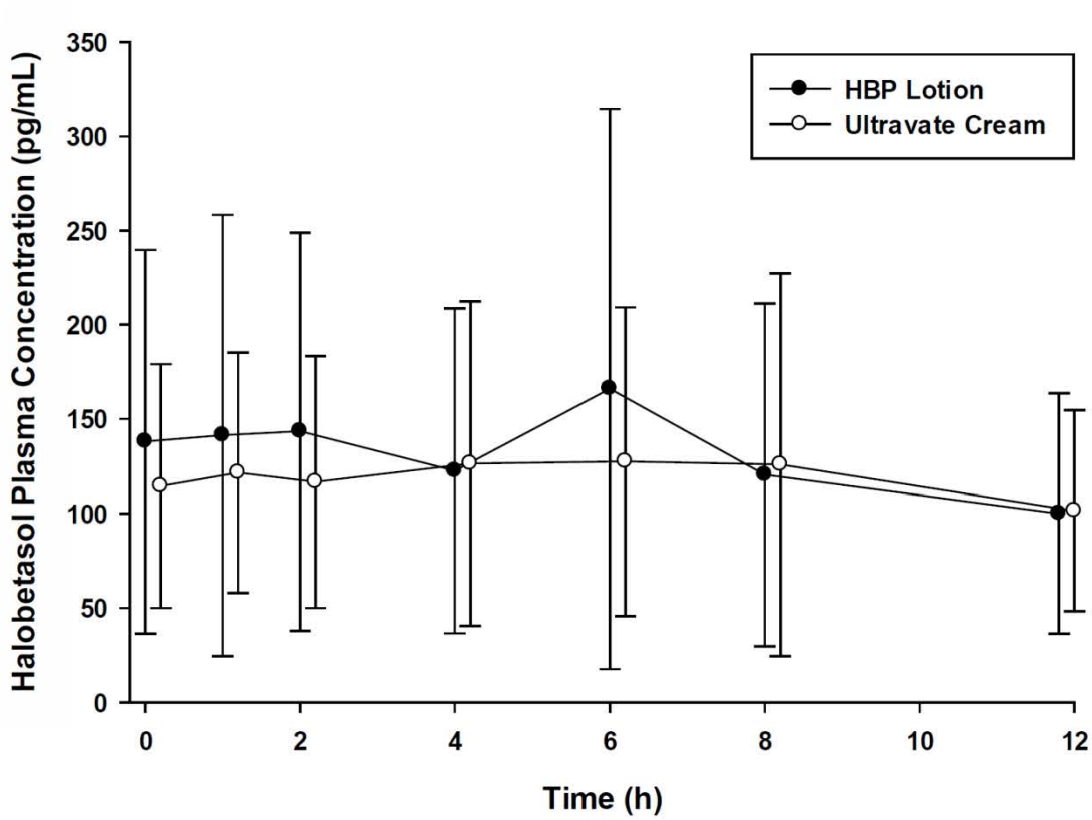
C_{max} = the maximum plasma concentration over the dosing interval; T_{max} = the time associated with C_{max}, AUC_{τ} = the area under the plasma concentration-time profile over the dosing interval; C_{min} = the minimum plasma concentration over the dosing interval; T_{min} = the time associated with C_{min}; C_{max}/D = the dose adjusted C_{max}; AUC_{τ}/D = the dose adjusted AUC_{τ}; C_{min}/D = dose adjusted C_{min}; CNC = could not calculate since dose was unknown; and CND = could not determine due to zeros in the data.

Table 8: Individual Halobetasol Propionate Pharmacokinetic Parameters on Day 8 Following Topical Application of Ultravate® Cream Twice a Day for 8 Days.

Subject	C_{max}	T_{max}	AUC_{τ}	C_{min}	T_{min}	C_{max}/D	AUC_{τ}/D	C_{min}/D
	(pg/mL)	(h)	(pg-h/mL)	(pg/mL)	(h)	(pg/mL/g)	(pg-h/mL/g)	(pg/mL/g)
106	97.7	1	843.7	57.2	12	27.37	236.3	16.02
108	54.9	6	618.45	46.6	4	17.48	197.0	14.84
110	383	8	2953.5	107	12	107.58	829.6	30.06
121	97	0	1002.5	72.1	8	37.31	385.6	27.73
124	240	1	2555	184	2	47.90	510.0	36.73
125	199	2	1699	103	0	CNC	CNC	CNC
128	72.3	0	490.3	33.2	8	21.52	145.9	9.88
130	114	6	1071.2	56.2	8	36.19	340.1	17.84
132	95.7	0	869.75	69.8	6	22.52	204.6	16.42
141	304	4	2548	149	12	74.15	621.5	36.34
144	246	6	2061.5	143	1	104.24	873.5	60.59
145	72.4	8	743.95	49.6	0	21.61	222.1	14.81
N	12	12	12	12	12	11	11	11
Mean	164.7	3.50	1454.7	89.23	6.08	47.08	415.1	25.57
CV%	65.00	90.80	59.60	53.70	76.30	70.60	62.50	58.10
Min	54.9	0	490.3	33.2	0	17.48	145.9	9.88
Median	105.8	3	1036.8	70.95	7	36.19	340.1	17.84
Max	383	8	2953.5	184	12	107.6	873.5	60.59
Geometric Mean	136.2	CND	1229.8	78.37	CND	38.42	348.8	22.33
CV% Geometric Mean	71.44	CND	67.19	57.29	CND	72.56	68.08	57.68

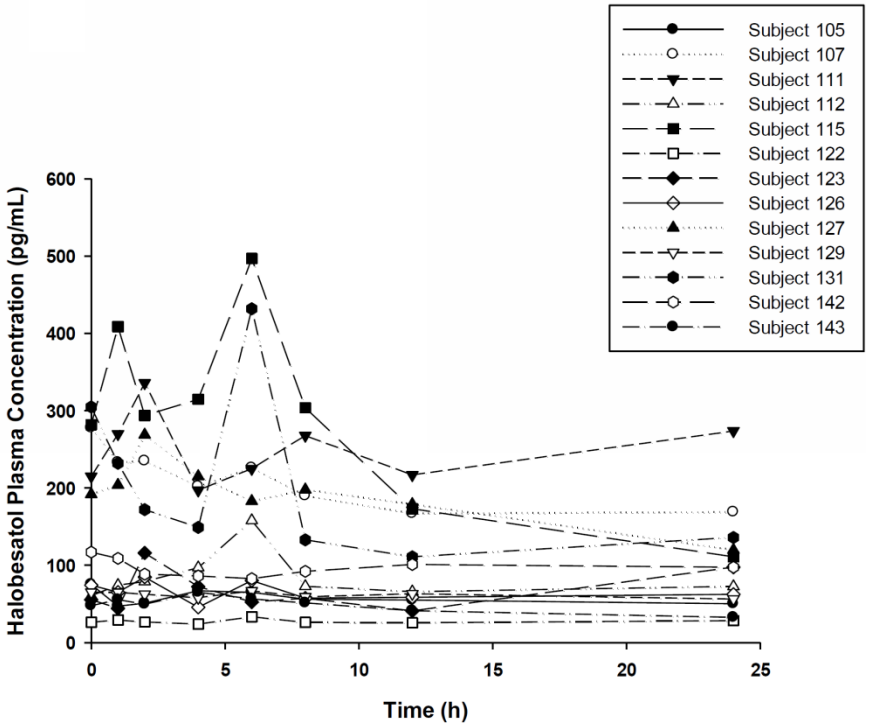
C_{max} = the maximum plasma concentration over the dosing interval; T_{max} = the time associated with C_{max}, AUC_{τ} = the area under the plasma concentration-time profile over the dosing interval; C_{min} = the minimum plasma concentration over the dosing interval; T_{min} = the time associated with Cmin. C_{max}/D = the dose adjusted C_{max}; AUC_{τ}/D = the dose adjusted AUC_{τ}; C_{min}/D = dose adjusted C_{min}; CNC = could not calculate since dose was unknown; and CND = could not determine due to zeros in the data.

Figure 2: Mean Halobetasol Propionate Plasma Concentration-Time Profiles Over a Dosing Interval on Day 8 Following Topical Application of Halobetasol Propionate Twice a Day for 8 Days



(Note: Profiles offset by 0.2 hours to allow visualization of error bars)

Figure 3: Individual Halobetasol Propionate Plasma Concentration-Time Profiles Over 24 Hours on Day 8 Following Topical Application of HBP Lotion Twice a Day for 8 Days.



Relative bioavailability comparison:
Corresponding pharmacokinetic parameters and statistical assessments for Ultravate® Cream 0.05% and HBP Lotion 0.05% are shown in Tables 9 and 10, respectively. The results showed that HBP lotion has similar systemic exposure to Ultravate Cream, 0.05%. However, the confidence intervals do not meet the standard bioequivalence threshold of 80 – 125%.

Table 9: Comparison of Systemic Exposure Variables for HBP Lotion and Ultravate® Cream

		Treatment Group	
Parameter		**HBP Lotion 0.05% (N = 12)**	**Ultravate® Cream 0.05% (N =12)**
C_{max} (pg/mL)	**Geometric Mean (CV%)** **Range: Min to Max**	145.9 (106.89%) 33.4 to 497	136.2 (71.44%) 54.9 to 383
T_{max} (h)	**Median** **Range: Min to Max**	3 0 to 6	3 0 to 8
AUC_{τ} (pg-h/mL)	**Geometric Mean (CV%)** **Range: Min to Max**	1267.7 (89.84%) 326.8 to 3873	1229.8 (67.19%) 490.3 to 2853.5
C_{min} (pg/mL)	**Geometric Mean (CV%)** **Range: Min to Max**	80.17 (79.27%) 24 to 197	78.37 (57.29%) 33.2 to 184
T_{min} (h)	**Median** **Range: Min to Max**	5 0 to 12	7 0 to 12

Table 10: Ratio of Geometric Means and Corresponding 90% Confidence Intervals for Day 8 Halobetasol Propionate Systemic Exposure Parameters

Parameter	Ultravate® Cream Geometric Mean	HBP Lotion Geometric Mean	Ratios HBP Lotion/ Ultravate® Cream (%)	Lower 90% Confidence Interval	Upper 90% Confidence Interval
C_{max} (pg/mL)	136.17	145.88	107.13	62.6	183.34
AUC_{τ} (pg-h/mL)	1229.83	1267.73	103.08	63.35	167.74
C_{min} (pg/mL)	78.37	80.17	102.3	66.19	158.13

HPA axis suppression:
An abnormal HPA axis response (HPA suppression) was defined as a 30-minute post-stimulation serum cortisol level of < 18 µg/dL at the end of treatment. For the PP population, 25.0% (5/20) of HBP Lotion-treated subjects and 14.3% (3/21) of Ultravate® Cream-treated subjects demonstrated an abnormal HPA-Axis response at end of treatment (EOT).

In the eight subjects who had adrenal suppression at EOT, there does not appear to be a correlation between adrenal suppression and the total amount of test article applied. In the five HBP Lotion-treated subjects who suppressed, the amount of test article applied ranged from 2.0 to 4.68 grams/dose was within the range of other subjects who did not show evidence of suppression (Table 11).

Table 11: Dosing information for subjects who had adrenal suppression

Treatment	Subject #	Total Test Article Applied (grams)	Average Dose Applied (grams)	Dose/Treatment Area (g/m^2)	EOT Post-CST Cortisol (µg/mL)
HBP Lotion	01-111	104.3	3.86	7.70	8.5
	02-107	89.5	3.44	6.25	6.1
	02-131	111.7	4.14	6.56	4.6
	02-142	54.1	2.00	4.96	16.0
	05-118	140.5	4.68	15.78	9.0
Ultravate® Cream	01-124	115.3	5.01	27.18	3.3
	02-125	CND†	CND†	CND†	16.2
	05-119	101.0	3.89	15.49	12.1

* Data from Listing 16.2.5.2 and rounded up to two decimal places.
† CND = could not be determined (some test article not returned -lost/missing).

Efficacy and other safety assessments:
Please see Clinical review.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DOANH C TRAN
09/02/2015

EDWARD D BASHAW
09/08/2015

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA/BLA Number	208183	**SDN**	1
Applicant	Ferndale Laboratories, Inc.	**Submission Date**	12/23/2014
Generic Name	Halobetasol propionate	**Brand Name**	To be determined
Drug Class	Topical corticosteroid		
Indication	Treatment of plaque psoriasis in adults		
Dosage Regimen	Apply a thin layer to the affected skin twice daily for up to 2 weeks and rub in gently.		
Dosage Form	Lotion, 0.05% w/w	**Route of Administration**	Topical
OCP Division	Division of Clinical Pharmacology 3	**OND Division**	Division of Dermatology and Dental Products

OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**
Division	Doanh Tran, Ph.D	Capt. E. Dennis Bashaw, Pharm. D.
Pharmacometrics		
Genomics		

Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	3/9/2015	**74-Day Letter Date**	2/13/2015
Review Due Date	9/8/2015	**PDUFA Goal Date**	11/8/2015

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☑ Yes

☐ No

If yes list comment(s)

Please see comments for applicant at end of filing memorandum.

Is there a need for clinical trial(s) inspection?

☐ Yes

☑ No

If yes explain

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type	Count	Comment(s)
In Vitro Studies		
☑ Metabolism Characterization	1	In vitro hepatocyte metabolite profiling (Study MC11M-0013)

☐ Transporter Characterization		
☐ Distribution		
☐ Drug-Drug Interaction		
In Vivo Studies		
Biopharmaceutics		
☐ Absolute Bioavailability		
☑ Relative Bioavailability	1	HPA/PK trial 000-0551-202 compared to Ultravate cream
☐ Bioequivalence		
☐ Food Effect		
☐ Other		
Human Pharmacokinetics		
Healthy Subjects ☐ Single Dose		
Healthy Subjects ☐ Multiple Dose		
Patients ☐ Single Dose		
Patients ☐ Multiple Dose		
☐ Mass Balance Study		
☐ Other (e.g. dose proportionality)		
Intrinsic Factors		
☐ Race		
☐ Sex		
☐ Geriatrics		
☐ Pediatrics		
☐ Hepatic Impairment		
☐ Renal Impairment		
☐ Genetics		
Extrinsic Factors		
☐ Effects on Primary Drug		
☐ Effects of Primary Drug		
Pharmacodynamics		
☑ Healthy Subjects	2	VCA trial 000-551-101 and Occlusivity and moisturization potential trial 000-0551-108
☐ Patients		
Pharmacokinetics/Pharmacodynamics		
☐ Healthy Subjects		
☐ Patients		
☐ QT		
Pharmacometrics		
☐ Population Pharmacokinetics		
☐ Exposure-Efficacy		
☐ Exposure-Safety		

Total Number of Studies	**In Vitro**	1	**In Vivo**	3
Total Number of Studies to be Reviewed		1		2

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐Yes ☐No ☑N/A	All clinical trials used the to-be-marketed formulation.
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☑Yes ☐No ☐N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☐Yes ☐No ☑N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☑Yes ☐No ☐N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☑Yes ☐No ☐N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	☑Yes ☐No ☐N/A	

Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ☐No ☐N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☐Yes ☐No ☑N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☐Yes ☐No ☑N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☐Yes ☐No ☑N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☐No ☑N/A	

Filing Memorandum

Clinical Pharmacology Review

NDA: **208183**
Compound: Halobetasol propionate lotion, 0.05% w/w
Sponsor: Ferndale Laboratories, Inc.

Date: 2/20/2015
Reviewer: **Doanh Tran**

Background: Halobetasol propionate is a super-potent topical corticosteroid. There are currently two approved formulations of halobetasol propionate, namely Ultravate Cream, 0.05% and Ultravate Ointment, 0.05% and their respective generic cream and ointment formulations. The sponsor developed a lotion formulation of halobetasol propionate, 0.05% (hereafter HBP Lotion) for treatment of plaque psoriasis in adults.

The clinical program includes 7 clinical studies, including a vasoconstrictor assay trial, a hypothalamic-pituitary-adrenal (HPA) axis suppression/pharmacokinetic (PK) trial under maximal use conditions, a Phase 2 supportive safety and efficacy trial, and 2 Phase 3 safety and efficacy trials.

Bioavailability: The sponsor conducted a HPA axis suppression/PK trial (Trial 000-0551-202) in adult subjects with plaque psoriasis. The trial enrolled a total of 43 subjects (21 HBP Lotion and 22 Ultravate Cream). A subset of 24 subjects (12 HBP Lotion and 12 Ultravate Cream) were included in the PK portion of the protocol. The study population included subjects with moderate to servere plaque psoriasis involving ≥20% BSA. The drugs were applied twice daily for 2 weeks. The sponsor reported 5 of 21 subjects (23.8%) administered HBP Lotion and 3 of 22 subjects (14.3%) administered Ultravate Cream had abnormal ACTH stimulation test (defined a 30-minute post-stimulation serum cortisol level of ≤18 µg/dL) performed at end of treatment. PK analysis suggests steady state was reached by Day 8. Summary of PK parameters are shown in table below.

		Treatment Group	
Parameter		**HBP Lotion 0.05% (N = 12)**	**Ultravate® Cream 0.05% (N =12)**
C_{max} (pg/mL)	**Geometric Mean (CV%) Range: Min to Max**	145.9 (106.89%) 33.4 to 497	136.2 (71.44%) 54.9 to 383
T_{max} (h)	**Median Range: Min to Max**	3 0 to 6	3 0 to 8
AUC_{τ} (pg-h/mL)	**Geometric Mean (CV%) Range: Min to Max**	1267.7 (89.84%) 326.8 to 3873	1229.8 (67.19%) 490.3 to 2853.5
C_{min} (pg/mL)	**Geometric Mean (CV%) Range: Min to Max**	80.17 (79.27%) 24 to 197	78.37 (57.29%) 33.2 to 184
T_{min} (h)	**Median Range: Min to Max**	5 0 to 12	7 0 to 12

Pediatrics: The sponsor has requested a deferral of pediatric studies for subjects 12 – 17 years of age. As per the agreed initial pediatric study plan, the sponsor will conduct an HPA axis suppression and PK study in adolescents aged 12 – 17 years with plaque psoriasis. The sponsor has requested a waiver of pediatric studies for subjects less than 12 years of age.

Clinical vs. to-be-marketed formulation: The sponsor stated that all 7 clinical trials in the development program used the same formulation as the proposed to be marketed formulation (i.e., formulation R9860).

Method validation:
For the evaluation of halobetasol propionate concentration, the sponsor has submitted the method validation reports and bioanalytical report for trial 000-0551-202 for review. The bioanalytical report states that sample storage stability has been demonstrated for 532 days. However, the available data only supports stability up to 167 days. Trial 000-0551-202 started enrollment on 8/9/2010 and samples were analyzed up to (b) (4) for maximum potential storage duration of 397 days. The sponsor will be requested to provide data to support the 532 storage stability.

For the evaluation of serum cortisol concentration, the sponsor has provided method validation data for review. Information on sample storage is not clear and it appears that some samples were stored for up to 2.5 months before analysis. In addition data to support storage stability is not available. A request will be made for the complete bioanalytical report for serum cortisol for trial 000-0551-202.

Recommendation:

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds that the Human Pharmacokinetics and Bioavailability section for NDA 208183 is fileable.

Comments for sponsor:

1. The bioanalytical report for the analysis of halobetasol propionate in human plasma for trial 000-0551-202 states that sample storage stability has been demonstrated for at least 532 days at -20 ºC. However, the validation report submitted only support stability up to 167 days. Provide data to support storage stability of 532 days or a duration sufficient to support the storage duration of samples from trial 000-0551-202.
2. Provide a bioanalytical report for the analysis of serum cortisol concentration for samples from trial 000-0551-202. Include specific details of sample storage (e.g., temperature and duration) for all samples. It appears that some samples were stored for extended period (up to 2.5 months) prior to analysis at (b) (4). Provide in tabular format and electronic dataset all individual samples' measured cortisol level and duration of sample storage. Provide storage stability data to support the duration and storage temperature of all samples in this trial.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DOANH C TRAN
02/20/2015

EDWARD D BASHAW
03/04/2015