CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208183Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	208183
Priority or Standard	Standard
Submit Date(s)	December 23, 2014
Received Date(s)	January 8, 2015
PDUFA Goal Date	November 8, 2015
Division / Office	DDDP/ODE 3
Reviewer Name(s)	Brenda Carr, M.D.
Review Completion Date	October 22, 2015
Established Name	Halobetasol propionate, 0.05%
(Proposed) Trade Name	Ultravate Lotion
Therapeutic Class	Corticosteroid
Applicant	Ferndale Laboratories Inc.
Formulation(s)	Lotion
Dosing Regimen	twice daily for two weeks
Indication(s)	topical treatment of plaque psoriasis
Intended Population(s)	18 years and older

Table of Contents

Table of Tables

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The Medical Officer recommends approval of this application, contingent on agreement on final labeling.

1.2 Risk Benefit Assessment

Halobetasol propionate lotion, 0.05% (HBP Lotion) is a corticosteroid, which the applicant proposes for topical treatment of plaque psoriasis. The applicant recommends twice daily dosing for up to two weeks, and that the total dosage not exceed 50 grams (gm) per week because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal axis. The container provides for 59 gm of HPB Lotion.

Psoriasis is a chronic disease that is classically characterized by symmetrically-distributed, sharply-demarcated, scaly, erythematous plaques. These plaques commonly involve the extensor surfaces of the extremities, but may present anywhere from the scalp to the soles of the feet. Extent of body surface area affected may vary from being limited to extensive, and the extent of involvement is one consideration in the approach to patient management. Disease of limited extent may be effectively managed with topical treatment, and corticosteroids are among the topical treatment options. There are several approved topical corticosteroids available for treatment of psoriasis, including other halobetasol propionate products, marketed in cream and ointment dosage forms. The applicant's product provides for a new lotion dosage form for halobetasol propionate.

Efficacy

The applicant provided substantial evidence of efficacy of HBP Lotion for treatment of plaque psoriasis from two adequate and well-controlled studies, 304 and 305. The studies were conducted under identical protocols and evaluated HBP Lotion and its vehicle in subjects with moderate to severe plaque psoriasis.

In Study 304, 110 subjects were randomized to HBP Lotion treatment, and 111 subjects were randomized to vehicle treatment. In Study 305, 110 subjects were randomized to HBP Lotion treatment, and 112 subjects were randomized to vehicle treatment. The primary endpoint was "treatment success" at Day 15, defined as a score of 0 (clear) or 1 (almost clear) with at least a two-grade decrease in severity score relative to Baseline and measured on a five-point scale Investigator's Global Assessment (IGA).

HBP Lotion was significantly superior to vehicle in both studies in the target population, and the treatment effect was similar between the studies. In Study 304, 44.5% (49/110) subjects in the HBP Lotion group achieved "treatment success" at Day 15 compared to 6.3% (7/111) subjects in the vehicle group; the results were statistically significant ($p<0.001$). In Study 305, 44.5% (49/110) subjects in the HBP Lotion group achieved "treatment success" at Day 15 compared to 7.1 % (8/112) subjects in the vehicle group; the results were again statistically significant ($p<0.001$).

The pre-specified secondary endpoints were the proportion of subjects with "treatment success" at Day 15 for each of the following clinical signs of psoriasis: scaling, erythema and plaque elevation. The applicant demonstrated that HBP Lotion also was significantly superior to vehicle in achieving "treatment success" for each of these clinical signs, and these results are sufficient to support inclusion in labeling.

The applicant established that HBP Lotion is effective in the treatment of plaque psoriasis.

Safety

The clinical development program was comprised of seven clinical studies, in which 591 subjects were exposed to HBP Lotion. The applicant pooled data from four of these studies to derive the "Safety Population" for the integrated safety analyses. These four studies enrolled 536 subjects with plaque psoriasis: 277 subjects (51.7%) received treatment with HBP Lotion and 259 subjects (48.3%) received treatment with vehicle. Subjects in the Safety Population were exposed to up to approximately 50 gm per week of study product for two weeks.

Three serious adverse events were reported across the seven studies comprising the clinical development program: death due to an apparent drug overdose, hospitalization for a syncopal episode (in a subject with a history of syncope), and hospitalization for an exacerbation of chronic obstructive pulmonary disease. All of these events occurred in subjects exposed to HBP Lotion, and none of these events suggested HBP Lotion effect.

A total of 74 treatment-emergent adverse events (TEAEs) occurred in the Safety Population [50 (67.6%%) in the HBP Lotion group; 24 (32.4%) in the vehicle group]. These 74 TEAEs occurred in 48 subjects [32 subjects (11.6%) in the HBP Lotion group and 16 (6.2%) subjects in the vehicle group]. TEAEs that occurred in ≥ 1% of subjects and that occurred at a higher incidence in the HBP lotion group (incidences are for the HBP Lotion group) were: telangiectasia 3 subjects (1%), application site atrophy 2 (1%), and headache 2 (1%).

Hypothalamic–Pituitary–Adrenal Axis Evaluation

The applicant evaluated the potential for hypothalamic–pituitary–adrenal (HPA) axis suppression with HBP Lotion in a maximal use study. The treatment duration was two weeks. The maximum amount of HBP lotion to be applied per application was 3.5 gm, for a total of approximately 50 gm per week.

Five of 20 (25%) subjects treated with HBP-lotion were adrenal suppressed at the end of the two-week treatment period. Adrenal suppression was observed in three subjects who used more than 100 gm of HBP Lotion during the two-week dosing period (up to 140.5 gm). Adrenal suppression was also observed in two subjects who used less than 100 gm of HBP Lotion over the two-week dosing period (down to 54.1 gm). Four of the five subjects who were adrenal-suppressed at the end of treatment showed a normal adrenal response on post-treatment follow-up testing (the 5th subject did not return for this testing). There was no apparent correlation between adrenal suppression and the total amount of product applied or dose per treatment area.

In summary, adverse events were not worrisome in pattern or character and were generally consistent with those that may be seen with corticosteroid use. The applicant established the safety of HBP Lotion in the treatment of plaque psoriasis.

Conclusions

The applicant has adequately demonstrated that halobetsol propionate lotion, 0.05% is safe and effective for treatment of plaque psoriasis. Approval of this application would add to the treatment armamentarium for plaque psoriasis by providing a new dosage form of a super-potent corticosteroid. This reviewer concludes that the benefits of halobetasol propionate lotion, 0.05% outweigh its risks.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The reviewer recommends routine pharmacovigilance and the product label as methods for postmarket risk evaluation and mitigation. The reviewer does not recommend a Risk Evaluation and Mitigation Strategy (REMS).

1.4 Recommendations for Postmarket Requirements and Commitments

A postmarketing requirement (PMR) is recommended. This PMR should be a deferred pediatric study, conducted as required under the Pediatric Research Equity Act (PREA). The applicant would be required to conduct a safety pharmacokinetic/ hypothalamic-pituitary-adrenal axis suppression study under maximal use conditions in adolescents 12 years to 16 years 11 months of age with plaque psoriasis.

The recommended timeline for the PMR is:

- Final Protocol Submission: 10/07/2014
- Study/Trial Completion: 09/30/2017
- Final Report Submission: 12/30/2017

Also see Section 7.6.3 of this review for additional discussion pertaining to pediatric development.

2 Introduction and Regulatory Background

2.1 Product Information

The applicant proposes marketing of halobetasol propionate lotion, 0.05% for the topical treatment of plaque psoriasis in adults. Halobetasol propionate is a corticosteroid, and halobetasol propionate, 0.05% products are ranked as super-potent (Class I).[1] The applicant's lotion represents a new dosage form for this moiety. See Section 2.3 of this review for the history of the moiety and Section 4.1 for details of the product's composition.

The applicant proposes dosing twice daily, with maximum treatment duration of two weeks, and a maximum exposure of 50 grams (gm) per week.

This review will follow the naming conventions applied by the applicant in the NDA: halobetasol propionate lotion, 0.05% will be referred to as **HBP Lotion**, and the vehicle lotion will be referred to as **VEH Lotion**. Unless otherwise noted, "HBP Lotion" in this review refers to the to-be-marketed formulation, R9860.

2.2 Tables of Currently Available Treatments for Proposed Indications

The proposed indication is the topical treatment of plaque psoriasis in patients eighteen (18) years of age and older. Products available for the topical treatment of plaque psoriasis include those listed in Table 1.

Table 1: Topical treatments for plaque psoriasis

Product Class	Example
Corticosteroid*	Clobetasol ointment
Synthetic vitamin D_3 derivative	Calcipotriene cream

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 August 31, 2015.

Synthetic vitamin D_3 derivatives/corticosteroid combination product	Calcipotriene and betamethasone dipropionate ointment
Retinoid	Tazarotene gel

*Some corticosteroids are indicated for the "treatment (or relief) of inflammatory and pruritic manifestations of moderate to severe corticosteroid-responsive dermatoses," which is inclusive of the psoriasis indication.

2.3 Availability of Proposed Active Ingredient in the United States

The halobetasol propionate moiety was first approved on December 17, 1990 in an ointment dosage form for topical use for "the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses" (Ultravate® ointment; NDA 19968). A cream dosage form was approved for the same indication on December 27, 1990 (Ultravate® cream; NDA 19967). In addition to the innovators, several generic cream and ointment products are currently marketed.

2.4 Important Safety Issues With Consideration to Related Drugs

Prescription topical corticosteroids, including halobetasol propionate products, are labeled for potential systemic and local risks. Potential systemic risks include reversible hypothalamic-pituitary adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria. Potential local safety risks include folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, striae and miliaria.

Labeled adverse reactions from clinical trials conducted with marketed dosage forms of halobetasol propionate products (cream and ointment) include erythema, skin atrophy, and leukoderma.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The product was developed under IND (b) (4). Milestone interactions with the applicant include those described below.

End-of-Phase 2 Meeting

The applicant had an End-of-Phase 2 meeting on July 25, 2012. During the meeting, the Agency agreed to waive clinical photosensitization and photoallergenicity studies because the drug product revealed no absorption in the 200 to 700 nm range (spectra results submitted in Section 1.12.5 of the NDA).

The applicant also requested a waiver for a clinical 21-day cumulative irritation study. The Agency did not object, but did inform the sponsor that they would "need to provide sufficient information in (the) NDA…to support labeling with reference to local adverse events, such as irritation."

Special Protocol Assessment

The applicant submitted Phase 3 protocols for Special Protocol Assessment (SPA) in October 2012. The Agency issued a SPA agreement letter on December 5, 2012. The Agency agreed with the following clinical elements of the Phase 3 protocols (except where otherwise stated):

1. The general design of the Phase 3 studies, except the proposal to determine success at Day 8 or Day 15. The Agency recommended use of one timepoint for establishment of an efficacy claim.
2. The definition of the primary efficacy endpoint (again, except for the proposal to determine success at Day 8 or Day 15).
3. The primary efficacy measure, the Investigator's Global Assessment scale.
4. The proposed dose regimen: application to all psoriatic plaques (excluding the face, scalp, groin, axillae and other intertriginous areas) twice daily.
5. The proposed population of subjects with a clinical diagnosis of stable plaque psoriasis involving a minimum of 2% affected body surface area (BSA) (excluding the face, scalp, groin, axillae and other intertrigineous areas) and an overall disease severity (ODS) on an agreed upon scale of at least 3 (moderate).
6. The proposed schedule for follow-up visits, Baseline/Day 1, Day 8, and Day 15.
7. The proposed definition of the secondary efficacy endpoints as the proportion of subjects with "treatment success" for each of the clinical signs of psoriasis (scaling, erythema and plaque elevation) with treatment success defined as a score of 0 or 1 representing "cleared" or "almost cleared" with at least a two-grade decrease in severity score relative to Baseline (except the two timepoints for assessment; see numbers 1 and 2, above).
8. The proposed safety assessments.

The Agency also recommended that the intent to treat (ITT) population used for the primary efficacy analysis be defined as all subjects randomized and dispensed the study medication, regardless of whether the subjects have post-baseline data.

Pre-NDA Meeting

The applicant had a pre-NDA meeting on October 27, 2014. Based on Agency feedback, the applicant had completed nonclinical toxicology studies with the to-be-marketed formulation, HBP Lotion. The applicant also communicated that they had obtained a right-of-reference to the Ultravate cream NDA 19-967 and the Ultravate ointment NDA 19-968 and planned to include the full study reports for toxicity studies that supported approval of the Ultravate NDAs. The applicant sought agreement that no additional nonclinical studies would be needed, and the Agency agreed. See Section 4.3 for additional details regarding the nonclinical program.

Pertaining to evaluation of the potential for their product to cause QT/QTc interval prolongation, the Agency advised the applicant to provide their scientific rationale in the NDA for why their product does not present a risk for prolongation of cardiac repolarization. See Section 7.4.4 of this review for additional discussion on this topic.

See Section 7.6.3 for discussion of presubmission regulatory activity pertaining to pediatric development.

2.6 Other Relevant Background Information

Other relevant background information includes the following:

- At the pre-NDA meeting, the then-sponsor (b) (4) informed the Agency of their plans to transfer sponsorship of IND (b) (4) to Ferndale Laboratories, Inc. which would assume all responsibilities and commitments and file the NDA.

- The Division of Medication Error Prevention and Analysis (DMEPA) concluded that the proposed proprietary name Ultravate for NDA 208183 is acceptable from a promotional and safety standpoint.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

On submission, the application was sufficiently complete and organized, such that necessary data could be accessed and reviewed without difficulty.

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.

One site from each pivotal study was selected for inspection (i.e., two sites total). The sites were selected based on the number of subjects enrolled and the size of the treatment response rates:

- Sunil S. Dhawan, M.D. enrolled 23 subjects (10.4%) under protocol 000-0551-304 (site 07). Dr. Dhawan reported a successful treatment response in 90.9% of subjects randomized to the HBP Lotion group and no subjects in the vehicle group.
- Eduardo Tschen, M.D. enrolled 21 subjects (9.5%) under protocol protocol 000-0551-305 (site 11). Dr. Tschen reported a successful treatment response in

80.0% of subjects randomized to the HBP Lotion group and 9.1% of subjects in the vehicle group.

The final Clinical Inspection Summary was provided by Roy Blay, Ph.D. of the Good Clinical Practice Assessment Branch in the Division of Good Clinical Practice Compliance in the Office of Scientific Investigations (OSI). Review of the records at both investigational sites revealed "no significant discrepancies or regulatory violations." The OSI final assessment of the data integrity for both sites was that the "study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication." However, the observations for Dr. Tschen's site were preliminary pending receipt and review of the Establishment Inspection Report, and OSI would provide an inspection summary addendum if the conclusions change for Dr. Tschen's site. No addendum was provided, and the preliminary conclusions regarding Dr. Tschen's site were unchanged as this clinical review closed.

Dr. Blay's overall assessment of findings for the clinical sites included that, "(t)he studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication."

3.3 Financial Disclosures

The applicant disclosed financial arrangements with one investigator, (b) (6)

(b) (6) enrolled all subjects (100%) in the single-center study which evaluated the (b) (6) of halobetasol propionate lotion formulations in healthy volunteers (study (b) (6)). Additionally, (b) (6) in the study which evaluated (b) (6) of twice daily halobetasol propionate lotion 0.05% and halobetasol propionate cream 0.05% (study (b) (6)).

The applicant stated that the steps taken to minimize any potential investigator bias were the designs of the individual studies in which (b) (6) participated:

(b) (6)

The final study report for Study (b) (6) lists (b) (6) was previously the

investigator at this site. Appendix 16.1.4 of the study report ("*List and Description of Investigators and Other Important Participants in the Study, Including Brief CVs or Equivalent Summaries of Training and Experience Relevant to the Performance of the Clinical Study*") states [redacted] (b) (6); the reason(s) for the resignation were not provided.

The applicant appears to have adequately disclosed financial arrangements with clinical investigators. The applicant took reasonable steps to minimize any potential investigator bias.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The following discussion is based on information from the product quality review.

HBP Lotion is a white to off-white smooth non-sterile lotion. HBP lotion is supplied in white oval tapered high density polyethylene bottles with polypropylene, [redacted] (b) (4) disc top caps. Each bottle contains 60 ml (2 oz) of lotion.

Table 2: Product Composition (Source: NDA, Module 2.5, Table 2.5.2-1)

Ingredient	Purpose	Composition (% w/w)	Quantity (kg)
Diisopropyl Adipate	[redacted] (b) (4)		
Octyldodecanol, NF			
Ceteth 20 [redacted] (b) (4)			
Poloxamer 407, NF			
Cetyl Alcohol, NF			
Stearyl Alcohol, NF			
Propylparaben, NF			
Butylparaben, NF			
Glycerin, USP			
Carbomer Homopolymer, NF			
Propylene Glycol, USP			
Sodium Hydroxide, NF [redacted] (b) (4)			
Halobetasol Propionate	Active	0.05	0.05
[redacted] (b) (4) Water, USP	[redacted] (b) (4)		
Total			100.00

* [redacted] (b) (4)

Stability of the Drug Product

Hitesh Shroff, Ph.D. was the drug product reviewer.

The applicant performed the stability studies according to ICH Q1A (R2) guidelines. Appearance, assay, preservatives amount, impurities, pH, viscosity, weight loss/gain, and particle size were assessed. Microbial testing was performed at 12 months and 6 months in the long-term and accelerated stability studies, respectively. The applicant claimed that a slight increase in the total unknown impurities was due to extractables and proposed to monitor the identified extractables apart from unknown impurities.

The applicant proposed a 24-month expiration dating period for the product when stored at 25°C. However, degradant levels in the registration batches were beyond their acceptance limits at 12 months (long-term stability testing) and at 6 months (accelerated stability testing). This represented a significant change, and the expiration dating period of the product (b) (4) .

In discussions regarding this issue, the applicant stated that the impurities also contained extractable/ leachable impurities from the container closure. The Agency requested that the applicant confirm that the impurities were extractables/leachables from the container closure and correlate retention times with unknown impurities. The applicant submitted data demonstrating that (b) (4) are the extractables/leachables present during the stability testing, and their levels are below the ICH qualification threshold. Note: (b) (4) is a genotoxic leachable impurity. A reader is also referred to Section 4.3 of this clinical review for nonclinical discussion of impurities/degradants.

The applicant submitted recalculated stability data up to 18 months at 25ºC. The recalculated stability data documented that the total impurities and individual extractables/leachables were within the acceptance levels up to 18 months (long-term) and 6 months (accelerated) stability testing.

Dr. Shroff concluded that, "The long-term stability and accelerated stability testing on three registration batches…demonstrated that there is no significant change in the drug product quality during the time tested. Based on the stability testing results the 24-month expiration dating period was granted when stored at room temperature in the proposed container closure system."

Additional Information from the Product Quality Review

Sukhamaya (Sam) Bain, Ph.D. was the drug substance reviewer. Dr. Bain identified no deficiencies related to the drug substance.

Xueli Zhu, Ph.D. was the process reviewer. Dr. Zhu concluded that the overall manufacturing process was adequate.

Neal J. Sweeney, Ph.D. was the microbiology reviewer. The product is non-sterile. Dr. Sweeney identified no quality microbiology deficiencies.

Denise M. DiGiulio, R.Ph. was the facilities reviewer. The drug substance, halobetasol propionate is manufactured by (b) (4). Ferndale Laboratories Inc. is located in Ferndale, MI. Ferndale Laboratories Inc. and performs the manufacturing, filling, packaging and analytical testing of the drug product for release and stability for HBP Lotion. (b) (4) (b) (4) and conducts excipient analytical testing and microbiological testing of the finished drug product. (b) (4) and conducts droplet size testing of drug product. Ms. DiGiulio found that (b) (4) (b) (4) commercial manufacturing capability…"

Vidula Kolhatkar, Ph.D. was the biopharmaceutics reviewer. Dr. Kolhatkar found that the applicant's IVRT method development and validation reports were not complete according to Agency standard, and the applicant should address these issues. When the development and validation are complete, the applicant should test the production batches with that method and propose to the Agency an IVRT release specification (based on data from at least 6 production batches). The applicant should report *in vitro* release data that support the selection of their IVRT method parameters to the Agency by the first Annual Report (at the latest).

Yichun Sun, Ph.D. was the application technical lead for this application. Dr. Sun and all product quality reviewers recommended approval of the application from the quality perspective.

4.2 Clinical Microbiology

The product is not an antimicrobial.

4.3 Preclinical Pharmacology/Toxicology

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

Having obtained the right-of-reference to the Ultravate cream NDA (19-967) and the Ultravate ointment NDA (19-968), the applicant submitted the full study reports for the following nonclinical studies that supported approval of the Ultravate NDAs (per agreement with the Agency at the pre-NDA meeting, October 27, 2014): 3-month

repeat dose oral toxicity in rats and dogs; genetic toxicity (Ames, *in vitro* cytogenetics, *in vivo* micronucleus, nuclear anomaly, chromosomal aberration, sister chromatid exchange); fertility and early embryonic development in rats; and embryofetal development in rats and rabbits. These studies addressed systemic toxicity.

The applicant completed the following nonclinical toxicology studies with HBP Lotion to address local toxicity: dermal and ocular irritation studies in rabbits, a 28-day repeat-dose dermal minipig study, and a 13-week repeat-dose dermal toxicity study in rats.

Per Dr. Merrill's review, the toxicity profile for HBP Lotion in the repeat-dose dermal study in minipigs was consistent with established corticosteroid effects and included adrenal atrophy, bone marrow hypocellularity and minimal to severe generalized lymphoid depletion in lymph nodes, GALT, spleen, thymus gland. "Based on these data, HBP lotion…0.05%...did not produce any new or unique toxicity that has not been previously observed with corticosteroid drugs."

"HBP Lotion, 0.05% was not a dermal irritant in rabbits after a 4-hour application…HBP Lotion, 0.05% was slightly irritating to the rabbit eye…"

In a letter dated August 13, 2014, the Agency waived the conduct of a dermal carcinogenicity study. According to the letter, the Agency granted the waiver "based on the severe immunosuppression noted in the 13 week dermal toxicity study in rats." From Dr. Merrill's review, "(m)ortality attributed to opportunistic infections resulting from test article-induced immunosuppression occurred… Therefore, the carcinogenicity study was waived since rats would not be able to tolerate long term topical treatment with HBP lotion, 0.05%."

Comments on Impurities/Degradants of Concern

The applicant listed 3 halobetasol propionate degradation products and other impurities. Each of these was reported at (b) (4) %. The ICH Q3B(R2) guideline states that if the daily dose of drug substance is <10 mg, the identification threshold is 0.5% or 20 µg total daily intake (TDI), whichever is lower. Based on data provided in the original submission of the application, Dr. Merrill determined that the impurities are present in the drug product at levels lower than the identification threshold: "The label limits use of the drug product to 50 g/week, or ~ 7g/day. Since the drug product is 0.05% HBP, the amount of drug substance used per day is 3.5 mg (7 g x 0.05%)."

During the review process, the applicant submitted recalculated stability tables for total impurities, including the genotoxic leachable, (b) (4) (also see discussion of stability of the drug product in Section 4.1 of this clinical review). The maximum level of (b) (4) after 18 months of storage was (b) (4). In a review addendum (memorandum to file dated 10/14/2015), Dr. Merrill put forward the following discussion:

"Based on the maximum dose recommended for this drug product (50 g/week) and using drug product stored for up to 18 months, the maximum dermal dose of leachable [redacted] (b) (4)
[redacted] (b) (4)

Calculations

[redacted] (b) (4)

The appropriate ICH guideline, Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (ICH M7, June 23, 2014), has developed a Threshold of Toxicological Concern (TTC) concept to define acceptable intakes for any unstudied chemical that is considered to pose a negligible risk of carcinogenicity. Using the TTC concept in the assessment of acceptable limits of mutagenic impurities in drug products, a value of 1.5 µg/day corresponds to a theoretical 10^{-5} excess lifetime risk of cancer. Balanced by the drug's benefit to the patient, this level of excess lifetime cancer risk associated with drug use is considered justifiable. Although the potential daily dose of [redacted] (b) (4) in the proposed halobetasol propionate drug product [redacted] (b) (4) is [redacted] (b) (4) than this threshold level, Pharmacology/Toxicology does not have concerns about this level of potential mutagenic impurity because the 1.5 µg/day threshold level was developed based on oral exposure to the drug product. The sponsor's halobetasol propionate drug product is a lotion (i.e., intended for dermal application). The systemic exposure to [redacted] (b) (4) will be much less than the calculated dermal dose due to the low level of dermal absorption of halobetasol propionate after topical administration."

Thus, the systemic exposure to the level of [redacted] (b) (4) that may be present in HBP Lotion after 18 months is acceptable. Additionally, because dermal absorption is low, systemic exposure to [redacted] (b) (4) from 60 gm of halobetasol propionate lotion per week, i.e. the entire contents of a bottle, would remain within acceptable limits.

Dr. Merrill recommended that the application is "approvable."

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Dr. Merrill's recommended description of the mechanism of action for the label is: "Corticosteroids play a role in cellular signaling, immune function, inflammation, and protein regulation; however, the precise mechanism of action in plaque psoriasis is unknown."

4.4.2 Pharmacodynamics

Doanh Tran, Ph.D. was the clinical pharmacology reviewer for this application.

Potency Ranking

Study 000-0551-101 established the potency ranking of the applicant's product as a Class I, super-potent corticosteroid and is discussed in brief below.

Study # 000-0551-101*: "A Randomized, Evaluator Blinded, Within Subject, Single-Center Evaluation of the Vasoconstrictive Properties of Halobetasol Propionate Lotion Formulations in Healthy Volunteers"*

This was a single-center, evaluator-blinded, randomized within subject, vehicle and reference controlled, visual assessment. The study objective was to determine and compare the relative vasoconstrictive potency of five HBP Lotion formulations compared with the VEH Lotion and two reference products (test articles further described below). The study enrolled 36 healthy male and female subjects, aged 18-65 years who had a history of positive skin blanching response to topical corticosteroids. All subjects received all test articles. Test articles were randomized to one of eight test sites on the ventral aspects of the forearms. Test articles were:

- five HBP Lotion, 0.05% formulations: R9860, R9861, R9862, R9863, R9864 (R9860 is the formulation proposed for marketing)
- VEH Lotion
- Ultravate Cream (Class I potency corticosteroid)
- Triamcinolone acetonide cream, 0.5% (Class III potency corticosteroid)

One application of ~10 milligrams of each test article was applied to the randomized test site, and study product was left in place for 16 hours, covered by non-occlusive tape.

The endpoint was the amount of skin blanching assessed visually at 18 hours after test article applications.

The HBP Lotion to-be-marketed formulation (R9860) had a VCA grade similar to Ultravate Cream. Ultravate Cream had a statistically higher ($p<0.05$) VCA grade versus triamcinolone acetonide cream (mean grade of 2.44 vs. 1.78). Not surprisingly, the VEH Lotion had the lowest VCA grade with a mean grade of 0.17. The results confirmed that the HBP Lotion to-be-marketed formulation is a Class I super-potent corticosteroid, and Dr. Tran agreed with the applicant's findings.

4.4.3 Pharmacokinetics

The applicant evaluated hypothalamic-pituitary-adrenal (HPA) axis suppression and the pharmacokinetics (PK) of HBP Lotion in the study described herein.

Study # 000-0551-202: "*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"

***Objective*:** The primary objective was to determine and compare the adrenal suppression potential and the PK properties of 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 the study.

Study Design: Multi-center, evaluator-blinded, randomized, parallel group study.

Treatment Groups: Subjects were randomized (1:1) to one of two treatment groups:

- HBP Lotion, N=21
- Ultravate Cream, N=22

Diagnosis and Main Criteria for Inclusion: Male and female subjects, aged ≥18 years with plaque psoriasis [moderate to severe, involving ≥20% BSA].

Method of Treatment: Subjects applied test article to all psoriasis plaques within the designated Treatment Area twice daily for 14 days. The maximum amount of lotion to be applied per application was approximately 3.5 gm (7.0 gm per day), for a total of approximately 50 gm per week.

Study Procedures: Routine labs were performed and a Cosyntropin Stimulation Test (CST) was part of the screening process. Enrollment into the treatment phase of the study (Baseline) was timed so that the screening CST occurred approximately 4 weeks before the projected end of the two-week treatment phase.

A normal response to CST was defined as a 30-minute post-stimulation serum cortisol > 18µg/dL. Subjects with a normal CST response were randomized to treatment with either HBP Lotion or Ultravate Cream (if they continued to meet all enrollment criteria). Subjects with an abnormal screening CST test would have been considered screen failures. The study was evaluator-blinded because of the differences in appearance of the study products (lotion and cream). Eligible subjects at select sites had blood drawn at baseline for drug levels, for the PK aspect of the study. Approximately 12 subjects per treatment group were to participate in PK testing.

For subjects whose lesions had cleared by Day 8, treatment was discontinued. Non-PK subjects who had cleared by Day 8 had CST and other end of treatment procedures completed. Subjects with a cortisol level < 18µg/dL (i.e. evidence of adrenal suppression) were to have post-treatment follow-up. Non-PK subjects who still had psoriasis lesions at Day 8 continued treatment. All PK subjects had serial blood draws for drug levels over 24 hours on Day 8. PK subjects who still had lesions had PK testing repeated on Day 9 and resumed treatment on Day 9.

All subjects (non-PK and PK) who continued treatment after Day 8 were to return at Day 15, the end-of-treatment (EOT) visit. Study procedures at this visit included the CST and routine labs. PK subjects had a final blood draw (prior to the CST). Subjects who were adrenal suppressed at the end of treatment were to have a CST every four weeks until the return of a normal adrenal response.

Efficacy assessments of psoriasis at each visit included the Overall Disease Severity (ODS) at EOT. The ODS evaluations were dichotomized to a) "success" on a severity scale of a subject's psoriasis in the Treatment Area, and which considered scaling, erythema and plaque thickness on a five-point scale ranging from 0 = clear to 4 = severe/very severe; where success was a score of 1 or 0 at the End of Treatment and b) "improvement" defined as > 2 decrease in grade from baseline. The ODS will be discussed in more detail in Section 5.3 of this review.

Safety measures recorded at Baseline, Day 8, and Day 15/EOT, included: local skin reactions (telangiectasia, skin atrophy, burning/stinging, and folliculitis; all scored as absent or present), adverse events, routine labs (hematology, serum chemistries, and urinalysis).

Parameters measured in the PK analyses included*:* peak concentration in plasma (C_{max}), time to peak concentration (T_{max}), minimum concentration in plasma (C_{min}), time to minimum concentration (T_{min}), and area under halobetasol propionate plasma concentration-time curve over 12-hour dosing at steady state ($AUC\tau$). Trough halobetasol propionate plasma concentrations were measured at Day 8: pre-dose and Days 9 and 15: post-dose.

Subject Disposition:
A total of 43 subjects were enrolled into the study: 21 subjects (48.4%) randomized to the HBP Lotion group; 22 subjects (51.2%) randomized to the Ultravate Cream group. A total of 41 subjects (95.3%) completed the study (20 HBP Lotion treated subjects and 21 in the Ultravate Cream group). Discontinuations were because of the adverse event of itching due to psoriasis for one subject, and the other subject had been randomized too early after Screening.

Safety Endpoint- HPA axis evaluation:
Pertaining to the ITT population (subjects enrolled in the study who were dispensed and applied test article at least once and had at least one follow-up visit after the Baseline visit), the mean number of days treated was similar between treatment groups: 15.2 for HBP Lotion and 14.7 for Ultravate® Cream. The average percent BSA treated (m^2) was similar between treatment groups: 17.7% (HBP Lotion) and 17.2% (Ultravate® Cream). Per Listing 14.2.4a of the study report, the mean total amount of test article applied for the ITT population was 95.1 g for HBP Lotion (range 46.1 to 168.4) and 78.2 g for Ultravate® Cream (33.9 to 115.3).

The applicant's results for subjects who were adrenal suppressed at the end of treatment are presented in the following table.

Table 3 Dosing Information for Subjects who had Adrenal Suppression (Source: Table 11.4.2-1 the clinical study report)

Treatment	Subject #	Total Test Article Applied (grams)	Average Dose	Dose/Treatment (g/m^2)	EOT Post-CST Cortisol
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

† CND = could not be determined (some test article not returned -lost/missing).

Two subjects were excluded from the PP population: Subject 01-109 in the Ultravate® Cream group was randomized too early and was discontinued at Visit 3/Day 8. Subject 01-123 in the HBP Lotion group had <80% dosing compliance (missed 6 doses; took 23/29 expected doses; compliance rate of 79.3%).

This reviewer agrees with Dr. Tran's recommendation that determination of rates of HPA axis suppression be based on the PP population, which stipulated that subjects have at least an 80% dosing compliance. Therefore, 5 of 20 (25%) of HBP lotion treated subjects and 3 of 21 (14.3%) of Ultravate cream treated subjects demonstrated evidence of adrenal suppression at EOT. Seven of these 8 subjects demonstrated recovery of adrenal function (i.e. normal adrenal response) at follow up. The eighth subject (02-107 in the HBP Lotion group) did not return for follow up testing.

There was no apparent correlation between adrenal suppression and the total amount of product applied or dose/treatment area (gm/m^2). Suppression was observed in subjects who exceeded use of more than 100 gm in the 2 week dosing period, but also in subjects who used less than 100 gm over 2 weeks. Subject 02-142 used 54.1 gm of HBP Lotion over the 2-week dosing period, barely exceeding the recommended use amount for one week. Thus, there was no apparent correlation between adrenal suppression and the total amount of product applied or dose/treatment area.

Dr. Tran summarized the PK data as below:

"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) C_{max} concentrations for HBP lotion, 0.05% on Day 8 was 201.1 ± 157.5 pg/mL, with the corresponding median T_{max} value of 3 hours (range 0 – 6 hours); mean area under the halobetasol propionate concentration versus time curve over the dosing interval (AUC_T) was 1632 ± 1147 pg*h/mL. Systemic exposure was similar between HBP lotion, 0.05% and Ultravate cream, 0.05%."

Overall Disease Severity:

Efficacy outcomes (ODS scores) at EOT are presented in the following tables:

Table 4: "Success"*- Overall Disease Severity (ITT Population) at EOT (Source: Table 14.3.1a of the clinical study report)

	HBP Lotion N(%)	Ultravate Cream N(%)
Success	1 (4.8%)	5 (22.7%)
	95% CI for (p1 - p2): (-42.36, 6.43)	

*** score of 1 or 0**

Table 5: "Improved"*- Overall Disease Severity (ITT Population) at EOT (Source: Table 14.3.1a of the clinical study report)

	HBP Lotion N(%)	Ultravate Cream N(%)
Improved	2 (9.5%)	7 (31.8%)
	95% CI for (p1 - p2): (-50.11, 5.52)	

*** > 2 decrease in grade from baseline**

The applicant appeared to attribute the relatively and comparatively low rate of "success" and "improved" in the HBP lotion group in part to the limitation of 3.5 gm of study treatment per application and the distribution of %BSA between treatment groups. This limitation meant that subjects with larger BSA involvement would have some areas untreated. At Day 1, the overall distribution of subjects with respect to %BSA with active plaque psoriasis was higher for the HBP Lotion group: HBP Lotion (33.0%; range 20.0 – 75.0%) and Ultravate® Cream (29.5%; range 20.0 - 70.0%). The applicant provided a detailed discussion and reasonable assessment of how enrollment and outcomes at one site seemed to favor positive efficacy outcomes for Ultravate (subjects were thought to have treated a larger portion of affected skin during the treatment period). Efficacy outcomes will not be further discussed in this review, as the applicant is not relying on this study to provide evidence of efficacy, nor does the reviewer consider those outcomes to impact the HPA axis and PK outcomes for HBP lotion.

Adverse Events:

No serious adverse events were reported in the study. A total of 17 subjects (39.5%) reported 30 adverse events: nine subjects in the HBP Lotion group reported 17 events,

and eight subjects in the Ultravate cream group reported 13 events. These counts include the cases of adrenal suppression ("abnormal ACTH stimulation test"), which the applicant considered as adverse events. Aside from adrenal suppression, the most common adverse event was application site pain (three reports). As the evaluation for HPA axis suppression was a study objective, this reviewer would find it reasonable to not consider "abnormal ACTH stimulation test" in the adverse event count in the context of this study.

Labs (hematology, chemistry and urinalysis) were similar for both groups at both testing time points (screening and end of treatment).

Conclusions: The applicant adequately evaluated the potential for HPA axis suppression associated with use of their product. The applicant adequately characterized the PK of HBP Lotion.

From Dr. Tran's review, "The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds NDA 208183 acceptable pending agreement on recommended labeling changes." Dr. Tran also recommended a postmarketing requirement for a pediatric study (See Section 1.4 of this review).

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The applicant's clinical development program for HBP Lotion consisted of seven studies:

- Study # 000-0551-101 (101): a single point vasoconstrictor assay (VCA) study [N=36].
- Study # 000-0551-108 (108): a transepidermal water loss (TEWL) study [N=16].
- Study # 000-0551-103 (103): a repeat insult patch test (RIPT) study [N=262].
- Study # 000-0551-202 (202): a hypothalamic-pituitary-adrenal (HPA) axis suppression / pharmacokinetic (PK) study under maximal use conditions [N=43].
- Study # 000-0551-207 (207): a supportive, vehicle-controlled, safety and efficacy study [N=72].
- Study # 000-055-304 (304): a pivotal, vehicle-controlled, safety and efficacy study (Pivotal 1) [N=221].
- Study # 000-0551-305 (305): a second pivotal, vehicle-controlled, safety and efficacy study (Pivotal 2) with the same study design as Study # 000-0551-304 [N=222].

All seven studies evaluated the to-be-marketed formulation, R9860.

Table 6: All Clinical Studies
(Source: Table 1.2-1 of the Integrated Summary of Safety Clinical Studies: Evaluation of HBP Lotion Safety

Protocol (Study Phase)	Study Objective(s)	Study Design	Subject Population [Plan/ITT/PP]	Number of Study Sites	Treatment Groups [Randomized]	Dosing Regimen & Duration of Treatment	Endpoints	Study Period
000-0551-101 (Phase 1)	To determine and compare the relative vasoconstrictive potency of novel HBP Lotion formulations with VEH Lotion, Ultravate Cream, and triamcinolone acetonide cream in healthy subjects	Single-center, evaluator-blinded, randomized, vehicle and reference controlled, within subject study	Male and female subjects aged 18-65 years who were healthy and had a history of positive skin-blanching response to topical corticosteroids [36/36/36]	1	Each subject received all test articles • HBP Lotion Formulations: o R9860 o R9861 o R9862 o R9863 o R9864 • VEH Lotion • Ultravate Cream, Class I • Triamcinolone acetonide cream 0.5%, Class III	Applied test articles to ~1 cm^2 sites on the ventral forearms for 16 hours	Amount of skin-blanching (scale 0-3) AEs	24 Nov 2008 to 26 Nov 2008
000-0551-108 (Phase 1)	To determine and compare the occlusivity and moisturization potential of HBP Lotion and Ultravate Cream when applied to skin whose barrier integrity has been challenged by shaving in healthy subjects	Single-center, evaluator-blinded, randomized, active controlled, within subject study	Male and female subjects aged 18-55 years who were healthy [24/16/15]	1	Each subject received both test articles • HBP Lotion • Ultravate Cream	Applied test articles to razor "chafed" skin of the volar forearms for 6 hours	Trans-epidermal water loss (TEWL) & conductance values AEs	23 July 2012 to 26 July 2012

Protocol (Study Phase)	Study Objective(s)	Study Design	Subject Population [Plan/ITT/PP]	Number of Study Sites	Treatment Groups [Randomized]	Dosing Regimen & Duration of Treatment	Endpoints	Study Period
000-0551-103 (Phase 1)	To evaluate the potential of the test articles to induce allergic contact dermatitis using the Jordan-King modification of the standard Draize Test in healthy subjects	Single-center, double-blind, randomized, vehicle and reference controlled, within subject study	Male and female subjects aged 18-65 years who were healthy [250 planned; 262 enrolled; 204 completed]	1	Each subject received all test articles • HBP Lotion • VEH Lotion • 0.9% aqueous sodium chloride (low irritant control) • 0.05% aqueous sodium lauryl sulfate (positive irritant control)	Applied test articles (0.2 mL; 9 applications total) under occlusion for 48-72 hour over 3 weeks, followed by 2 week rest period, 48 hour challenge, & re-challenge (if applicable)	Skin reaction evaluation (scale 0-3 + letter grades) AEs	20 Jan 2014 to 16 May 2014
000-0551-202 (Phase 2)	To determine and compare the adrenal suppression potential and the PK properties of HBP Lotion and Ultravate Cream in subjects with moderate to severe psoriasis	Multi-center, evaluator-blinded, randomized, active controlled, parallel group study	Male and female subjects aged ≥18 years with moderate to severe psoriasis involving ≥20% BSA [40/43/41] & [24(PK)]	5	1:1 • HBP Lotion [21] • Ultravate Cream [22]	Applied twice daily for 2 weeks	HPA axis response, PK parameters: trough and plasma HBP concentration [C_{max}, T_{max}, C_{min}, T_{min}, AUC_τ] AEs, LSRs, lab tests	09 Aug 2010 to 24 May 2011

Protocol (Study Phase)	Study Objective(s)	Study Design	Subject Population [Plan/ITT/PP]	Number of Study Sites	Treatment Groups [Randomized]	Dosing Regimen & Duration of Treatment	Endpoints	Study Period
000-0551-207 (Phase 2)	To determine and compare the efficacy and safety of HBP Lotion and VEH Lotion in subjects with moderate to severe plaque psoriasis	Multi-center, double-blind, randomized, vehicle controlled, parallel group study	Male and female subjects aged ≥18 years with moderate to severe plaque psoriasis involving 2-10% BSA [72/71/69]	3	1:1 • HBP Lotion [36] • VEH Lotion [36]	Applied twice daily for 2 weeks	Proportion of subjects with ODS "treatment success" at Day 15 AEs & LSRs	14 Nov 2011 to 17 Feb 2012
000-0551-304 (Phase 3)	To determine and compare the efficacy and safety of HBP Lotion and VEH Lotion in subjects with moderate to severe plaque psoriasis	Multi-center, double-blind, randomized, vehicle controlled, parallel group study	Male and female subjects aged ≥18 years with moderate to severe plaque psoriasis involving 2-12% BSA [220/221/213]	10	1:1 • HBP Lotion [110] • VEH Lotion [111]	Applied twice daily for 2 weeks	Proportion of subjects with IGA "treatment success" at Day 15 AEs & LSRs	14 May 2013 to 12 Dec 2013
000-0551-305 (Phase 3)	To determine and compare the efficacy and safety of HBP Lotion and VEH Lotion in subjects with moderate to severe plaque psoriasis	Multi-center, double-blind, randomized, vehicle controlled, parallel group study	Male and female subjects aged ≥18 years with moderate to severe plaque psoriasis involving 2-12% BSA [220/222/200]	11	1:1 • HBP Lotion [110] • Vehicle Lotion [112]	Applied twice daily for 2 weeks	Proportion of subjects with IGA "treatment success" at Day 15 AEs & LSRs	26 Jun 2013 to 27 Feb 2014

5.2 Review Strategy

Study 108 was entitled, "Study to Assess the Occlusivity and Moisturization Potential of Test Products Using the Skin Trauma after Razor Shaving (STARS) Bioassay." The objective of this evaluator-blinded study was to determine and compare the occlusivity and moisturization potential of halobetasol propionate lotion, 0.05% and Ultravate cream, 0.05% when applied to skin whose barrier integrity had been challenged by dry shaving.

At the preNDA meeting, (b) (4) communicated the following:

> *As the objective of the (transepidermal water loss) study (000-0551-108) was to evaluate the occlusivity and moisturization potential of the HBP Lotion formulation, datasets were neither generated for this study nor does* (b) (4) *plan to prepare datasets for this study in the NDA. We do not believe the inclusion of datasets for this study would provide pivotal information for FDA's review of safety and efficacy of HBP Lotion, 0.05%. Does the Agency agree?*

The Agency found the applicant's position to be "reasonable at this time." The regulatory utility of this study is unclear, and it will not be further discussed in this review.

The applicant is relying on three trials as providing evidence of efficacy:

- Two pivotal **Phase 3** studies 304 (N=221) and 305 (N= 222). The two pivotal Phase 3 studies were conducted using identical protocols and are discussed in Section 6.
- The **Phase 2** study 207 provided supportive evidence of efficacy and is discussed in Section 5.3.

5.3 Discussion of Individual Studies/Clinical Trials

The applicant described the Phase 2 study (207) as being *identical* to the Phase 3 protocols (304 and 305) in the following ways: dosing regimens, study methodology, and efficacy endpoints. The applicant described the Phase 2 as being *similar* to the Phase 3 protocols in baseline disease characteristics, and global severity disease scales for measuring efficacy endpoints ("slightly different descriptive terms were used to define the score categories").

The Phase 2 study 207 is discussed here.

Study # 000-0551-207: *"A Double-Blind, Randomized, Multicenter, Vehicle-Controlled, Parallel Group Study to Determine the Efficacy and Safety of Halobetasol Propionate Lotion 0.05% in Subjects with Plaque Psoriasis Receiving Two Weeks of Treatment"*

Test articles*:* HBP Lotion and VEH Lotion. Test articles were packaged in 60 gm (2 oz) bottles.

Study Objective*:* To determine and compare the efficacy and safety of HBP Lotion 0.05% and VEH Lotion applied twice daily for two weeks in subjects with moderate to severe plaque psoriasis.

Study Design: Double-blind, multicenter, vehicle-controlled, parallel group comparison study. The maximum amount of test article to be applied per week should not exceed 50 grams.

Treatment Groups: Eligible subjects were randomized (1:1) to treatment with either HBP Lotion or VEH Lotion. Assigned treatments were applied by the subjects twice daily (up to ~ 3.5 grams per application). The duration of treatment was 14 days.

Study Population: Male and female subjects, aged 18 years or older with moderate to severe plaque psoriasis, defined as 2% to 10% BSA (excluding the face, scalp, groin, axillae and other intertriginous areas) and an Overall Disease Severity (ODS) score for the Treatment Area of at least 3 at the Baseline. The determination of 1% BSA was approximately equal to the surface of the subject's hand with fingers together.

The ODS score was an evaluation of the overall severity of a subject's psoriasis within the Treatment Area and considered three individual signs of psoriasis: scaling, erythema and plaque elevation. The ODS score was assessed on a 5-point scale where 0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, and 4 = severe/very severe.

Table 7: Overall Disease Severity (ODS) (Source: study protocol)

Clear (0)	
Scaling	No evidence of scaling.
Erythema	No erythema (hyperpigmentation may be present).
Plaque elevation	No evidence of plaque elevation above normal skin level.
Almost Clear (1)	
Scaling	Limited amount of very fine scales partially covers some of the plaques.
Erythema	Faint red coloration.
Plaque elevation	ery slight elevation above normal skin level, easier felt than seen.
Mild (2)	
Scaling	Mainly fine scales; some plaques are partially covered.
Erythema	Light red coloration.
Plaque elevation	Slight but definite elevation above normal skin level, typically ith edges that are indistinct or sloped, on some of the plaques.
Moderate (3)	
Scaling	Somewhat coarser scales predominate; most plaques are partially covered.
Erythema	Moderate red coloration.
Plaque elevation	Moderate elevation with rounded or sloped edges on most of the plaques.
Severe/Very Severe (4)	
Scaling	Coarse, thick tenacious scales predominate; virtually all or all plaques are covered; rough surface.
Erythema	Dusky to deep red coloration.
Plaque elevation	Marked to very marked elevation, with hard to very hard sharp edges on virtually all or all of the plaques.

Efficacy Endpoints: At each study visit, investigators evaluated all active psoriasis plaques in the Treatment Area and recorded the one whole integer score that described the average ODS score. The ODS scores and the clinical signs of psoriasis (scaling, erythema, and plaque elevation) were dichotomized to "treatment success" or "treatment failure" where "treatment success" was defined as a score of 0 or 1. These scores were also dichotomized to "improved" or "not improved" where "improved" was defined as at least a two (2) grade decrease in severity score relative to Baseline. Dichotomization of scores for clinical signs and symptoms of psoriasis excluded

subjects with Baseline scores of 0 or 1 unless the corresponding sign score at Day 8 or Day 15 was >1.

The primary efficacy endpoint was the proportion of subjects with ODS "treatment success" at the end of treatment (EOT), where EOT was the last visit (Day 8 if early termination or Day 15) with LOCF imputation for early terminations.

Disposition: The study enrolled 72 subjects, with 36 subjects being randomized to each treatment group. Seventy-one subjects (98.6%) completed the study (one subject in the vehicle group was lost to follow-up.

Baseline Clinical Evaluations: At baseline, all subjects were categorized as having moderate or "severe/very severe" disease:

Table 8: Baseline Evaluations
(Source: Table 14.1.9a of the clinical study report)

	HBP Lotion	**VEH Lotion**
Moderate	30 (83.3%)	30 (85.7%)
Severe/Very Severe	6 (16.7%)	5 (14.3%)

***Extent of Exposure*:** Mean number of days dosed in the HBP Lotion group (ITT) was 14.8 days (range 14 to 17). In the VEH Lotion group, the mean was 15 days (range 14 to 19 days). The mean amount of study product used was 34 to 36 gm each week across both treatment groups in the ITT population. Mean total amount of study product used during the study was 70.7 grams for HBP Lotion and 69.2 grams for VEH Lotion

Efficacy: The primary efficacy endpoint was the proportion of subjects with ODS "treatment success" at EOT where "Treatment success" was defined as a score of 0 or 1, and EOT was the last visit (Day 15).

In the HBP group, "Success" was achieved by 30.6% of subjects (11/36) in the HBP Lotion group and "Improved" status was achieved by 44.4% of subjects (16/36) in this dosing group. Observed results in HBP Lotion treated subjects revealed that 2 (5.6%) of subjects achieved the "clear" state, and 9 (25%) reached the "almost cleart" state. No subjects in the VEH Lotion group achieved either endpoint. See Table 9 below.

Table 9: "Success"*- Overall Disease Severity (ITT Population) at EOT
(Source Table 14.3.1a of the clinical study report)

	HBP Lotion N(%)	**VEH Lotion N(%)**
Success	11 (30.6%)	0 (0.0%)
	p-value 0.0004	

* score of 1 or 0

Table 10: "Improved"*- Overall Disease Severity (ITT Population) at EOT (Source: Table 14.3.1a of the clinical study report)

	HBP Lotion N(%)	VEH Lotion N(%)
Improved	16 (44.4%)	0 (0.0%)
	p-value <.0001	

* > 2 decrease in grade from baseline

Safety: A total of 18 adverse events were reported in the study: 13 in the HBP group and 5 in the VEH group. These events were reported in 16 subjects: 11 the HBP Lotion group and 5 in the VEH group. Telangiectasia and skin atrophy were observed in one subject each in the HBP group at Day 15. Burning/stinging was reported at Day 15 in three HBP subjects (3/36; 8.3%) and two vehicle group subjects (2/35; 5.7%).

Conclusions: This study evaluated the same population as in the pivotal trials and by very similar assessment measures. This study provides supportive evidence of the efficacy of HBP Lotion for treatment of plaque psoriasis. The safety profile was similar to that of the larger scale pivotal studies.

6 Review of Efficacy

Efficacy Summary

The applicant adequately demonstrated that HBP Lotion is effective in the treatment of plaque psoriasis. The applicant provided substantial evidence of efficacy from two adequate and well-controlled studies. The studies, conducted under identical protocols, evaluated HBP Lotion and its vehicle in subjects with moderate to severe plaque psoriasis. In Study 304, 110 subjects were randomized to HBP Lotion treatment, and 111 subjects were randomized to vehicle treatment. In Study 305, 110 subjects were also randomized to HBP Lotion treatment, and 112 subjects were randomized to vehicle treatment. The primary endpoint was "treatment success" at Day 15, defined as a score of 0 (clear) or 1 (almost clear) with at least a two grade decrease in severity score relative to Baseline and measured on a 5-point scale Investigator's Global Assessment (IGA).

HBP Lotion was significantly superior to vehicle in both studies in the target population, and the treatment effect was similar between the studies. In Study 304, 44.5% (49/110) subjects in the HBP Lotion group achieved "treatment success" at Day 15 compared to 6.3% (7/111) subjects in the VEH Lotion group; the results were statistically significant ($p<0.001$). In Study 305, 44.5% (49/110) subjects in the HBP Lotion group achieved "treatment success" at Day 15 compared to 7.1 % (8/112) subjects in the VEH Lotion group; the results were again statistically significant ($p<0.001$).

The pre-specified secondary endpoints were the proportion of subjects with "treatment success" at Day 15 for each of the following clinical signs of psoriasis: scaling,

erythema and plaque elevation. The applicant demonstrated that HBP Lotion also was significantly superior to VEH Lotion in achieving "treatment success" for each of these clinical signs and these results are sufficient to support inclusion in labeling.

Thus, the applicant provided sufficient evidence to establish the efficacy of HBP Lotion.

6.1 Indication

The indication is the topical treatment of plaque psoriasis.

6.1.1 Methods

The applicant conducted two adequate and well-controlled pivotal Phase 3 studies to support the marketing application. The studies were conducted under identical protocols.

Protocol for the Phase 3 studies 304 and 305

Title: *A Multicenter, Randomized, Double-Blind, Parallel Group Comparison of Halobetasol Propionate Lotion 0.05% versus Vehicle Lotion in Subjects with Plaque Psoriasis*

Study Objective: The primary objective was to determine and compare the efficacy and safety of HBP Lotion and the VEH Lotion applied twice daily for two weeks in subjects with plaque psoriasis.

Study Design: Multicenter, randomized, double-blind, vehicle-controlled, parallel group comparison study of HBP Lotion 0.05%. The maximum amount of test article to be applied per week was not to exceed 50 grams.

Treatment Groups: Eligible subjects were randomized (1:1) to treatment with either HBP Lotion or VEH Lotion.

Instructions for Use and Application: Subjects were to apply HBP Lotion or VEH Lotion to all psoriatic plaques (excluding the face, scalp, groin, axillae and other intertriginous areas) twice daily for 2 weeks (14 consecutive days). The total area of psoriatic plaques to be treated (exclusions as previously listed) must have been a minimum of 2% and no more than 12% BSA to meet study inclusion requirements. If the subject's disease was too extensive to be effectively managed using this dose limitation, the subject was not to have been enrolled in the study. As lesions changed (new lesions developed, others cleared, etc.) all psoriatic plaques were to have been treated with the test article (with site exclusions). If the subject's disease became unmanageable within the constraints of the weekly dose limitation, the subject was to have been discontinued from the study.

Total Number of Subjects: Approximately 220 subjects were to be enrolled: approximately 110 to HBP Lotion treatment and 110 VEH Lotion treatment.

Main Inclusion Criteria:

- Subject has a clinical diagnosis of stable plaque psoriasis involving a minimum of 2% and no more than 12% affected body surface area (BSA)4 (excluding the face, scalp, groin, axillae and other intertriginous areas). *1% BSA is approximately equal to the surface area of the subject's palm and fingers, with the fingers extended yet grouped together, creating a flat oval-like surface area. For BSA determination residual discoloration (pigmentation and/or erythema) should not be included.*
- Subject has an Investigator's Global Assessment (IGA) score of at least three (3 = moderate) at the Baseline Visit.
- If subject is a woman of childbearing potential (WOCBP)5, she must have a negative urine pregnancy test (UPT) and agree to use an effective form of birth control for the duration of the study (e.g., abstinence, stabilized on hormonal contraceptives [oral, injectable, transdermal or intravaginal] or intrauterine device (IUD) for at least three months prior to test article application, condom and spermicidal or diaphragm and spermicidal). Other acceptable forms of birth control include: a) Abstinence for subjects who are not sexually active or b) if the subject is in a monogamous relationship with a partner who is sterile (e.g., vasectomy). Subjects who become sexually active or begin to have relations with a partner who is not sterile during the trial must agree to use an effective form of birth control for the duration of the study.

Main Exclusion Criteria:

- Subject had spontaneously improving or rapidly deteriorating plaque psoriasis.
- Subject had guttate, pustular, erythrodermic or other non-plaque forms of psoriasis.
- Subject used any phototherapy (including laser), photo-chemotherapy or other forms of photo based therapy for the treatment of their psoriasis within 30 days prior to the Baseline Visit.
- Subject used any systemic methotrexate, retinoids, systemic corticosteroids [including intralesional, intra-articular, and intramuscular corticosteroids], cyclosporine or analogous products within 90 days prior to the Baseline Visit.
- Subject used any systemic biologic therapy (i.e., FDA-approved or experimental therapy) within five (5) half-lives of the biologic prior to the Baseline Visit. Published or documented half-life of the product provided by the commercial supplier or Sponsor should be used to establish this value.
- Subject had prolonged exposure to natural or artificial sources of ultraviolet radiation within 30 days prior to the Baseline Visit or is intending to have such exposure during the study that is thought by the investigator likely to modify the subject's disease.
- Subject used topical body (excluding the scalp) psoriasis therapy (including coal tar, anthralin, steroids, retinoids, vitamin D analogs) within 14 days prior to the Baseline Visit.
- Subject used emollients/moisturizers on areas to be treated within four hours prior to clinical evaluation at the Baseline Visit.
- Subject was currently using lithium or Plaquenil (hydroxychloroquine).

- Subject was currently using a beta-blocking medication (e.g., propanolol) or angiotensin converting enzyme (ACE) inhibitor at a dose that has not been stabilized, in the opinion of the investigator.
- Subject was pregnant, lactating, or is planning to become pregnant during the study.
- Subject used an investigational drug or investigational device treatment within 30 days prior to the Baseline Visit.
- Subject had been previously enrolled in this study and treated with a test article.

Efficacy Assessments:

Subjects were evaluated at Baseline, Day 8, and Day 15. Efficacy assessments included the following:

Investigator's Global Assessment (IGA)
The IGA score was a static evaluation of the overall or "average" degree of severity taking into account all of the subject's psoriatic lesions (excluding those on the face, scalp, groin, axillae and other intertriginous areas) by the investigator or designee. This evaluation considered three characteristics of psoriasis (scaling, erythema, and plaque elevation) with the IGA score at each visit representing the average of scaling, erythema or plaque elevation present among all of the lesions eligible for treatment. The IGA was assessed on a 5-point scale where 0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, and 4 = severe/very severe.

Table 11 Investigator's Global Assessment (IGA) (Source: protocols for 304 and 305)

Clear (0)	
Scaling	No evidence of scaling.
Erythema	No erythema (hyperpigmentation may be present).
Plaque elevation	No evidence of plaque elevation above normal skin level.
Almost Clear (1)	
Scaling	No more than a limited amount of very fine scales partially covers some of the plaques.
Erythema	No more than faint red coloration.
Plaque elevation	No more than a very slight elevation above normal skin level, easier felt than seen.
Mild (2)	
Scaling	No more than mainly fine scales; some plaques are partially covered.
Erythema	No more than light red coloration.
Plaque elevation	No more than a slight but definite elevation above normal skin evel, typically with edges that are indistinct or sloped, on some of the plaques.
Moderate (3)	
Scaling	No more than somewhat coarser scales predominate; most plaques are partially covered.

Erythema	No more than moderate red coloration.
Plaque elevation	No more than a moderate elevation with rounded or sloped edges on most of the plaques.
Severe/Very Severe (4)	
Scaling	Coarse, thick tenacious scales predominate; virtually all or all plaques are covered; rough surface.
Erythema	Dusky to deep red coloration.
Plaque elevation	Marked to very marked elevation, with hard to very hard sharp edges on virtually all or all of the plaques.

Clinical Signs of Psoriasis
Scaling, erythema and plaque elevation were each scored on a 5-point scale where 0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, and 4 = severe/very severe. These evaluations were an assessment of the overall or "average" degree of each of the three characteristics present within all of the subject's psoriatic lesions (excluding the face, scalp, groin, axillae and other intertriginous areas) by the investigator or designee.

Body Surface Area (BSA)
The percent (%) BSA with active psoriasis (excluding the face, scalp, groin, axillae and other intertriginous areas) was determined at the Baseline Visit, Week 1 (Day 8), and Week 2 (Day 15) and documented. At Baseline, the %BSA must not have exceeded 12%.

Pruritus
Pruritus was assessed on a scale with possible scores range from 5 (no pruritus) to 25 (most severe pruritus).

Safety:
Safety assessments included the following:

Local Skin Reactions (LSRs)
At each visit, subjects were evaluated for LSRs associated with the topical application of corticosteroids within the treatment areas, including telangiectasia, skin atrophy, burning/stinging and folliculitis.

Adverse Events
Adverse events were recorded, and subjects were questioned about the status of ongoing adverse events.

Efficacy Endpoint(s):
IGA scores and the clinical signs and symptoms of psoriasis were dichotomized to "treatment success" or "treatment failure" where "treatment success" was defined as a score of 0 or 1 representing "cleared" or "almost cleared" with at least a two (2) grade decrease in severity score relative to Baseline.

The primary efficacy endpoint was the proportion of subjects with IGA "*treatment success" at Day 15*.

The secondary efficacy endpoints included the proportion of subjects rated a "treatment success" for each of the clinical signs of psoriasis (scaling, erythema and plaque elevation) at Day 15.

Other efficacy endpoints included:

- The proportion of subjects with IGA "treatment success" at Day 8.
- The proportion of subjects rated a "treatment success" for each of the clinical signs of psoriasis (scaling, erythema and plaque elevation) at Day 8.
- Change from Baseline in pruritus score at Day 15.
- Changes in % BSA with active psoriasis at Days 8 and 15.

6.1.2 Demographics

The overall demographics were generally similar between the two pivotal studies. Mean age was 51.8 years in study 304 and 50.8 years in study 305. Most subjects in both studies were White, for study 305 (91.9%) compared to study 304 (79.2%). All subjects had from 2% to 12% BSA involvement of plaque psoriasis. While mean percent affected BSA at Baseline was similar in both treatment groups in both studies, the vehicle group had a slightly higher mean percent affected BSA in both studies (but not a clinically meaningful difference, in the reviewer's opinion). Most subjects in both studies had moderate disease according to the IGA scale, with approximately 8-10% of subjects having severe disease. The details of the demographics of the study populations are found in Tables 12 and 14. See Tables 13 and 15 for baseline disease characteristics.

Study 304

Table 12: Demographics- study 304 (ITT Population)

(Source: Table 11.2.1-1 of the study report for 304

Variable	HBP Lotion N=110	VEH Lotion N=111
SEX		
Female	47 (42.7%)	46 (41.4%)
Male	63 (57.3%)	65 (58.6%)
ETHNICITY		
Hispanic or Latino	5 (4.5%)	15 (13.5%)
Not Hispanic or Latino	105 (95.5%)	96 (86.5%)

RACE		
American Indian or Alaska Native	1 (0.9%)	3 (2.7%)
Asian	5 (4.5%)	7 (6.3%)
Black or African American	11 (10.0%)	10 (9.0%)
Native Hawaiian or Other Pacific	1 (0.9%)	1 (0.9%)
Islander	88 (80.0%)	87 (78.4%)
White	4 (3.6%)	3 (2.7%)
AGE (years)		
Mean	52.9	50.8
Median	52	50
Standard Deviation	12.28	14.15
Range	21 – 86	21 – 76

Table 13: Baseline Clinical Evaluations- study 304 (ITT Population)
(Source: Table 14.1.5.1 of the clinical study report for study 304)

Baseline Assessment	**HBP Lotion (N=110)**	**Vehicle Lotion (N= 111)**
IGA, n (%)		
3- moderate	102 (92.7)	101 (91.0)
4- severe/very severe	8 (7.3)	10 (9.0)
BSA		
Mean	5.0	5.4
Median	4	4
Std	2.97	3.12
(minimum, maximum)	(2,12)	(2,12)
Psoriasis Signs		
Scaling, n (%)		
2- mild	7 (6.4)	10 (9.0)
3- moderate	90 (81.8)	86 (77.5)
4- severe/very severe	13 (11.8)	15 (13.5)
Erythema, n (%)		
2- mild	6 (5.5)	11 (9.9)
3- moderate	92 (83.6)	90 (81.1)
4- severe/very severe	12 (10.9)	10 (9.0)
Plaque Elevation, n (%)		
2- mild	6 (5.5)	5 (4.5)
3- moderate	96 (87.3)	93 (83.8)
4- severe/very severe	8 (7.3)	13 (11.7)

***Study 305*:**

Table 14: Demographics-study 305 (ITT Population)
(Source: Table 11.2.1-1 of the clinical study report for study 305)

Variable	HBP Lotion N=110	VEH Lotion N=112
SEX		
Female	50 (45.5%)	60 (53.6%)
Male	60 (54.5%)	52 (46.4%)
ETHNICITY		
Hispanic or Latino	19 (17.3%)	21 (18.8%)
Not Hispanic or Latino	91 (82.7%)	91 (81.3%)
RACE		
American Indian or Alaska Native	0 (0.0%)	1 (0.9%)
Asian	4 (3.6%)	0 (0.0%)
Black or African American	4 (3.6%)	9 (8.0%)
Native Hawaiian or Other Pacific	0 (0.0%)	0 (0.0%)
Islander	102 (92.7%)	102 (91.1%)
White	0 (0.0%)	0 (0.0%)
AGE (years)		
Mean	50.8	50.8
Median	51	54
Standard Deviation	14.49	15.15
Range	18 – 81	19 – 89

Table 15: Baseline Clinical Evaluations-study 305 (ITT Population)
(Source: Table 14.1.5.1 of the clinical study report for 305)

Baseline Assessment	HBP Lotion (N=110)	Vehicle Lotion (N= 112)
IGA, n (%)		
3- moderate	101 (91.8)	98 (87.5)
4- severe/very severe	9 (8.2)	14 (12. 5)
BSA		
Mean	5.4	5.8
Median	4	5
Std	3.08	3.19
(minimum, maximum)	(2,12)	(2,12)
Psoriasis Signs		
Scaling, n (%)		
2- mild	4 (3.6)	4 (3.6)
3- moderate	97 (88.2)	92 (82.1)
4- severe/very severe	9 (8.2)	16 (14.3)
Erythema, n (%)		
2- mild	2 (1.8)	0
3- moderate	99 (90.0)	94 (83.9)
4- severe/very severe	9 (8.2)	18 (16.1)
Plaque Elevation, n (%)		
2- mild	1 (0.9)	1 (0.9)
3- moderate	97 (88.2)	99 (88.4)
4- severe/very severe	12 (10.9)	12 (10.7)

6.1.3 Subject Disposition

Overall rates of discontinuation were higher in the vehicle group compared to the HBP lotion group in both studies. “Lost to follow-up” was the most commonly-reported reason for study discontinuation in both pivotal studies, and the rates were low and did not correlate with treatment group. “Withdrawal by subject” was reported only in the vehicle group in both studies.

Table 16: Subject Disposition-study 304
(Source: Table 14.1.2.1 of the clinical study report for 304)

Completion Status	HBP Lotion (N=110)	VEH Lotion (N=111
Completed, n (%)	109 (99.1%)	108 (97.3%)
Discontinuation, n (5)	1 (0.9%)	3 (2.7%)
Lost to Follow-up	1 (0.9%)	0
Non-Compliance with Study Drug	0	1 (0.9%)
Withdrawal by Subject	0	2 (1.8%)

Table 17 Subject Disposition-study 305
(Source: Table 14.1.2.1 of the clinical study report for 305)

Completion Status	HBP Lotion (N=110)	VEH Lotion (N=112
Completed, n (%)	108 (98.2%)	106 (94.6%)
Discontinuation, n (5)	2 (1.8%)	6 (5.4%)
Lost to Follow-up	2 (1.8%)	2 (1.8%)
Withdrawal by Subject	0	4 (3.6%)

6.1.4 Analysis of Primary Endpoint(s)

The ITT population included all enrolled subjects who were randomized and dispensed the test article. As the first dose of the test article was applied at the study site, all enrolled subjects were included in the ITT (and Safety) populations.

As mentioned, the primary efficacy endpoint was the proportion of subjects with IGA “treatment success” at Day 15. “Treatment success” was defined as a score of 0 (clear) or 1 (almost clear) with at least a two grade decrease in severity score relative to Baseline.

304: IGA "Treatment Success" at Day 15
In the applicant's analysis of the ITT population, 44.5% (49/110) subjects in the HBP Lotion group achieved "treatment success" at Day 15 compared to 6.3% (7/111) subjects in the VEH Lotion group. The results were statistically significant (p<0.001).

305: IGA "Treatment Success" at Days 8 and 15
In the applicant's analysis of the ITT population, 44.5% (49/110) subjects in the HBP Lotion group achieved "treatment success" at Day 15 compared to 7.1 % (8/112) subjects in the VEH Lotion group. The results were statistically significant (p<0.001).

Kathleen Fritsch, Ph.D. was the statistical reviewer for this application. Dr. Fritsch described that the applicant "did not provide sufficient details in the protocol or statistical analysis plan (SAP) about how to implement multiple imputation, the applicant's stated primary method for handling missing data. From p. 11 of Dr. Fritsch's review: "The protocol specified two sensitivity analyses for handling missing data—treating all subjects with missing data as failures and treating all subjects with missing data as successes. Because of the low rates of missing data in these studies, the results of these sensitivity analyses are similar. Even doing a conservative imputation where all subjects with missing data on the halobetasol arm are imputed as failures and all subjects with missing data on the vehicle arm are imputed as successes leads to a large observed treatment effect and a statistically significant outcome (p<0.001). The primary efficacy endpoint under various imputation methods are presented in Table (18)."

Table 18: – Treatment Success at Day 15 under Various Missing Data Imputations
(Source: Table 6 of Dr. Fritsch's review)

	Study 304		Study 305	
	Halobetasol N=110	Vehicle N=111	Halobetasol N=110	Vehicle N=112
Logistic Regression Imputation (*Applicant's Primary Analysis*)	49 (44.5%)	7 (6.3%) p<0.001	49 (44.5%)	8 (7.1%) p<0.001
Missing as failure *(Applicant's Sensitivity Analysis)*	49 (44.5%)	7 (6.3%) p<0.001	48 (43.6%)	7 (6.3%) p<0.001
Missing as success *(Applicant's Sensitivity Analysis)*	50 (45.5%)	10 (9.0%) p<0.001	50 (45.5%)	13 (11.6%) p<0.001
Active as failure/Vehicle as success *(Reviewer's Sensitivity Analysis)*	49 (44.5%)	10 (9.0%) p<0.001	48 (43.6%)	13 (11.6%) p<0.001
Multiple Imputation *(Reviewer's Sensitivity Analysis)*[a]	49.6 (45.1%)	7.6 (6.8%) p<0.001	49.8 (45.3%)	7.6 (6.8%) p<0.001

[a] 5 imputations, imputation model: logistic regression with terms for treatment, baseline IGA, and baseline plaque elevation, CMH test stratified on analysis site, log transform of relative risk.
Source: pg 79 of study-000-0551-304-study-report-body and 81 of study-000-0551-305-study-report-body and reviewer analysis.

The results for "treatment success" remain statistically significant under each imputation methods applied.

6.1.5 Analysis of Secondary Endpoints(s)

The secondary efficacy endpoints were the proportion of subjects with "treatment success" at Day 15 for each of the clinical signs of psoriasis: scaling, erythema and plaque elevation. The applicant seeks a labeling claim for these endpoints.

Dr. Fritsch indicated that the applicant did not specify a method of handling missing data for the secondary endpoints and reported results only for observed cases. From p. 12 of Dr. Fritsch's review: "Missing as failure was the applicant's first sensitivity analysis proposed for the primary endpoint. Dr. Fritsch recommends using "'missing as failure' imputation to accommodate an ITT analysis." Outcomes for all secondary endpoints were statistically significant in Dr. Fritsch's analyses.

Table 19: Secondary Efficacy Endpoints at Day 15 in Studies 304 and 305 (Source: Table 8 of Dr. Fritsch's review)

	Study 304		Study 305	
Observed Cases (Applicant's Analysis)	Halobetasol N=109	Vehicle N=110	Halobetasol N=108	Vehicle N=106
Clear or Almost Clear for Scaling	61 (56.0%)	12 (11.1%)	65 (60.2%)	11 (10.4%)
Clear or Almost Clear for Erythema	40 (36.7%)	8 (7.4%)	48 (44.4%)	12 (11.3%)
Clear or Almost Clear for Plaque Elevation	50 (45.9%)	9 (8.3%)	48 (44.4%)	9 (8.5%)
Missing As Failure (Reviewer's Analysis)	Halobetasol N=110	Vehicle N=111	Halobetasol N=110	Vehicle N=112
Clear or Almost Clear for Scaling	61 (55.5%)	12 (10.8%)	65 (59.1%)	11 (9.8%)
Clear or Almost Clear for Erythema	40 (36.4%)	8 (7.2%)	48 (43.6%)	12 (10.7%)
Clear or Almost Clear for Plaque Elevation	50 (45.5%)	9 (8.1%)	48 (43.6%)	9 (8.0%)

Note: all nominal p-values are <0.001 and significant under Hochberg's method for either the observed case analysis or missing as failure.
Source: pg 105 of study-000-0551-304-study-report-body and 109 of study-000-0551-305-study-report- body and reviewer analysis.

6.1.6 Other Endpoints

Other efficacy endpoints included:

- The proportion of subjects with IGA "treatment success" at Day 8.
- The proportion of subjects with "treatment success" for each of the clinical signs of psoriasis (scaling, erythema and plaque elevation) at Day 8.
- Change from Baseline in pruritus score at Day 15.

- Changes from Baseline in percent BSA with active psoriasis at Days 8 and 15.

The applicant did not seek to include outcomes for any of these endpoints in the label. Limited discussion will be devoted to "other efficacy endpoints" in this review.

What follows is the applicant's assessment of IGA "treatment success" at Day 8 (the primary endpoint was "treatment success" at Day 15):

- For study 304: "The HBP Lotion group had a significantly greater proportion of subjects classified as IGA "treatment success" (18/109, 16.5%) than the VEH Lotion group (2/110, 1.8%) at Day 8 (p<0.001)" (p. 24 of the Integrated Summary of Efficacy).
- For study 305: "The HBP Lotion group had statistically significantly greater proportion of subjects with IGA "treatment success" (13/107, 12.1%) than the VEH Lotion group (3/107, 2.8%) at Day 8 (p=0.004)" (p. 32 of the Integrated Summary of Efficacy).

The applicant reported an improvement in pruritus by mean decrease in pruritus scores from Baseline to Day 15: mean pruritus score changed from 13.4 at Baseline to 8.0 at Day 15 (mean change = -5.4) in the HBP Lotion group and from 13.7 at Baseline to 11.2 at Day 15 (mean change = -2.5) in the VEH Lotion group. It is unclear whether these mean changes translate into clinically meaningful differences in level of pruritus.

6.1.7 Subpopulations

The applicant evaluated the proportion of subjects with IGA "treatment success" at Day 15 based on age (<65 years / ≥65 years), gender (male/female), and race (White/non-White) for the ITT population. In both pivotal studies, treatment effect appeared to be somewhat higher for subjects ≥65 years when compared to overall study results. Treatment effect in other subgroups was similar to overall study results.

Table 20 – IGA Treatment Success Rates by Subgroup (Logistic Regression Imputation) (Source: Table 12 of Dr. Fritsch's review)

	Study 304		Study 305	
	Halobetasol N=110	Vehicle N=111	Halobetasol N=110	Vehicle N=112
Age (years)				
< 65	38/94 (40.4%)	6.90 (6.7%)	33/87 (37.9%)	6/93 (6.5%)
≥ 65	11/16 (68.8%)	1/21 (4.8%)	16/23 (69.6%)	2/19 (10.5%)
Gender				
Male	28/63 (44.4%)	2/65 (3.1%)	30/60 (50.0%)	5/52 (9.6%)
Female	21/47 (44.7%)	5/46 (10.9%)	19/50 (38.0%)	3/60 (5.0%)
Race				
White	38/88 (43.2%)	5/87 (5.7%)	46/102 (45.1%)	7/102 (6.9%)
Not white	11/22 (50.0%)	4/24 (16.7%)	3/8 (37.5%)	1/10 (10.0%)

Source: reviewer analysis

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The applicant did not conduct any dose-finding studies. They based dosing of their product on the dosing regimens for approved ointment and cream formulations of halobetasol propionate 0.05%.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

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

6.1.10 Additional Efficacy Issues/Analyses

There were no other efficacy issues.

7 Review of Safety

Safety Summary

The applicant pooled data from four studies for the integrated safety analyses (the "Safety Population"). These studies enrolled 536 subjects with plaque psoriasis: 277 subjects (51.7%) received treatment with HBP Lotion and 259 subjects (48.3%) received treatment with VEH Lotion. Subjects in the Safety Population were exposed to up to approximately 50 grams/week of study product for two weeks, the maximum amount stipulated in all of the study protocols. Adverse events were not worrisome in pattern or character. Local adverse reactions were consistent with those which may be seen with a topical corticosteroid and similar to those reported with marketed halobetasol products. Adrenal suppression was observed in the HPA axis study and did not appear to correlate with body surface area treated (gm/m^2) or amount of product used. All adrenal-suppressed subjects who received post-treatment follow-up testing showed a normal adrenal response at follow-up testing.

Three serious adverse events were reported across the entire clinical development program, which was comprised of 7 clinical studies (591 subjects exposed to HBP Lotion). Two of these events (including one death) occurred in the contact sensitization study, and the third occurred in one of the Phase 3 studies in a subject randomized to the HBP Lotion group. None of these events suggested an HBP Lotion effect.

A total of 74 treatment-emergent adverse events (TEAEs) occurred in the Safety Population (50 in the HBP Lotion group; 24 in the VEH Lotion group) in 48 subjects [32 subjects (11.6%) in the HBP Lotion group and 16 (6.2%) subjects VEH Lotion group].

TEAEs that occurred in ≥ 1% of subjects and that occurred at a higher incidence in the HBP lotion group (incidences are for the HBP Lotion group): telangiectasia 3 (1%), application site atrophy 2 (1%), and headache 2(1%).

The contact sensitization study revealed no signal for contact sensitization for neither HBP Lotion nor VEH Lotion.

Routine clinical laboratory evaluations (hematology, chemistry, and urinalysis) were conducted in one of the studies (PK/HPA axis study) and revealed no differences in laboratory parameters between treatment groups.

HBP Lotion was generally well-tolerated. The applicant provided sufficient evidence to establish the safety of HBP Lotion.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The applicant pooled data from four studies for the integrated safety analyses:

- Phase 2 studies: Studies 202 (PK/HPA axis evaluation) and 207 (supportive)
- Phase 3 studies: 304 and 305 (pivotal studies)

The four studies enrolled 536 subjects: 277 subjects (51.7%) were randomized to treatment with HBP Lotion and 259 subjects (48.3%) were randomized to treatment with VEH Lotion.

Subjects in these four studies constituted the Safety Population. Subjects were exposed to up to approximately 50 grams/week of study product for two weeks. All of the protocols stipulated a maximum use of 50 grams of study product per week. All subjects applied the test article at least once.

Table 21: Subject Enrollment and Evaluability-Safety Population (Source: Table 3.2.1-1 of the Integrated Summary of Safety)

	HBP Lotion n (%)	VEH Lotion n (%)	All n (%)
Safety Population	**N=277**	**N=259**	**N=536**
Study 000-0551-202	21 (7.6%)	0 (0.0%)	21 (3.9%)
Study 000-0551-207	36 (13.0%)	36 (13.9%)	72 (13.4%)
Study 000-0551-304	110 (39.7%)	111 (42.9%)	221 (41.2%)
Study 000-0551-305	110 (39.7%)	112 (43.2%)	222 (41.4%)
Completed Study	273 (98.6%)	249 (96.1%)	522 (97.4%)
Discontinued	4 (1.4%)	10 (3.9%)	14 (2.6%)
Adverse Event	1 (0.4%)	0 (0.0%)	1 (0.2%)

Lost to Follow-Up	3 (1.1%)	3 (1.2%)	6 (1.1%)
Non-Compliance with Study Drug	0 (0.0%)	1 (0.4%)	1 (0.2%)
Withdrawal by Subject	0 (0.0%)	6 (2.3%)	6 (1.1%)

7.1.2 Categorization of Adverse Events

The applicant coded adverse events using the Medical Dictionary for Regulatory Activities (MedDRA). Verbatim terms were mapped into a MedDRA system organ class (SOC) and preferred term (PT). If a subject had more than one adverse event within a preferred term, the subject was counted once in that preferred term. This strategy was also applied if a subject had more than one adverse event within a system organ class.

Treatment emergent adverse events (TEAE's) were summarized for each treatment group by SOC and preferred term. TEAE's are defined as those adverse events occurring after the first dose of study treatment.

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

See Section 7.1.1.

7.2 Adequacy of Safety Assessments

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

The extent of exposure (duration of use and amount of product used) was similar between the HBP Lotion and VEH Lotion groups. Most subjects in both treatment groups applied study product between 8 and 15 days. The mean total amount of HBP lotion used was 72.0 grams (4.9 grams per day), and the mean amount of VEH lotion used was 68.0 grams (5 grams per day).

Table 22 Extent of Exposure (Safety Population)
(Source: Table 3.1-1 of the Integrated Summary of Safety)

	HBP Lotion n (%) N=277	VEH Lotion n (%) N=259
Duration		
≤8 Days	4 (1.4%)	11 (4.2%)
≤15 Days	234 (84.5%)	211 (81.5%)
>15 Days	39 (14.1%)	37 (14.3%)

Duration (days)		
Mean	14.6	14.1
Median	15	15
Standard Deviation	1.96	2.96
Range	(1, 20)	(1, 19)
Total Amount Used (g)		
N	273	255
Mean	72.0	68.0
Median	67	60
Standard Deviation	40.82	41.05
Range	(4, 172)	(1, 170)
Average Daily Amount Used (g)		
N	272	251
Mean	4.9	5.0
Median	4	4
Standard Deviation	2.75	5.72
Range	(0, 13)	(0, 83)

Demographics

The demographics were generally similar between the two treatment groups. The mean age was 51.1 years. Most subjects were White (85.8%; 460/536). There were more males than females in both treatment groups. See Table 23 for the demographic details of the Safety Population.

Table 23: Demographics Summary (Safety Population)
(Source: Table 3.2.1-2 of the Integrated Summary of Safety

	HBP Lotion n (%) N=277	**VEH Lotion n (%) N=259**	**Total n (%) N=536**
SEX AT BIRTH			
Female	113 (40.8%)	117 (45.2%)	230 (42.9%)
Male	164 (59.2%)	142 (54.8%)	306 (57.1%)
ETHNICITY			
Hispanic or Latino	37 (13.4%)	39 (15.1%)	76 (14.2%)
Not Hispanic or Latino	240 (86.6%)	220 (84.9%)	460 (85.8%)
RACE			
American Indian or Alaska Native	2 (0.7%)	4 (1.5%)	6 (1.1%)
Asian	9 (3.2%)	8 (3.1%)	17 (3.2%)
Black or African American	19 (6.9%)	20 (7.7%)	39 (7.3%)
Native Hawaiian or Other Pacific	3 (1.1%)	1 (0.4%)	4 (0.7%)
White	238 (85.9%)	222 (85.7%)	460 (85.8%)

Other	6 (2.2%)	4 (1.5%)	10 (1.9%)
AGE (years)			
Mean	51.4	50.9	51.1
Median	51	52	52
Standard Deviation	12.98	14.40	13.67
Range	(18, 86)	(19, 90)	(18, 90)
18 to <65 years	234 (84.5%)	213 (82.2%)	447 (83.4%)
≥65 years	43 (15.5%)	46 (17.8%)	89 (16.6%)

7.2.2 Explorations for Dose Response

See Section 7.2.1.

7.2.3 Special Animal and/or In Vitro Testing

See Section 4.3.

7.2.4 Routine Clinical Testing

The applicant performed laboratory evaluations in the Phase 2 Study 202. In addition to the evaluation for HPA axis suppression, hematology, chemistry, and urinalysis tests were performed in this study at Screening and EOT. Ultravate cream was the comparator in this study. See Section 4.4.3 for the discussion of HPA axis testing.

There were no clinically significant shifts in hematology, chemistry, or urinalysis test parameters in either treatment group, and no differences in laboratory parameters between treatment groups.

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable.

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

The adverse event profile is well-established for topical corticosteroids.

7.3 Major Safety Results

7.3.1 Deaths

One death occurred in the clinical development program. The subject was enrolled in the contact sensitization study (Study 103). Subject 103-01-199 was a 46 y/o White male with a history of bipolar disorder, hepatitis, hypertension, and substance abuse. Date of first patch application was on 02/28/2014. The subject apparently suffered a fatal heroin overdose on (b) (6)

7.3.2 Nonfatal Serious Adverse Events

Two nonfatal serious adverse events were reported in the clinical development program.

Subject 103-01-232
This subject was a 53 y/o Black male who was enrolled in the contact sensitization study (Study 103). His medical history included: hypertension, syncope, Crohn's disease, benign prostatic hyperplasia, neuropathy, depression, and substance abuse (cocaine). Date of first patch application was 03/07/2014. He experienced a syncopal episode on (b) (6) (reportedly several such episodes within the preceding year). He was hospitalized for the event and was discontinued from the study on (b) (6)

Subject 305-06-012
This subject was a 69 y/o White male who was randomized to the HBP Lotion group in the Phase 3 study 305 on 07/25/2013. His medical history included: chronic obstructive pulmonary disease (COPD), congestive heart failure, coronary artery disease, hyperlipidemia, myocardial infarction, hypertension, atrial fibrillation, type 2 diabetes mellitus, depression. He experienced an acute exacerbation of COPD on (b) (6). He was hospitalized for the event, which was reported as resolved on (b) (6).

7.3.3 Dropouts and/or Discontinuations

Of 536 subjects in the Safety Population, 522 (97.4%) completed the studies. A total of 14 subjects discontinued the studies early: withdrawal by subject (6), lost to follow-up (6), noncompliance with study drug (1), and adverse event (1).

Table 24: Subject Enrollment and Evaluability (Safety Population)
(Source: Table 3.2.1-1 of the Integrated Summary of Safety)

	HBP Lotion n (%)	VEH Lotion n (%)	All n (%)
Safety Population	**N=277**	**N=259**	**N=536**
Completed Study	273 (98.6%)	249 (96.1%)	522 (97.4%)
Discontinued	4 (1.4%)	10 (3.9%)	14 (2.6%)
Adverse Event	1 (0.4%)	0 (0.0%)	1 (0.2%)
Lost to Follow-Up	3 (1.1%)	3 (1.2%)	6 (1.1%)
Non-Compliance with Study Drug	0 (0.0%)	1 (0.4%)	1 (0.2%)
Withdrawal by Subject	0 (0.0%)	6 (2.3%)	6 (1.1%)

Across the seven clinical studies in the clinical development program, three subjects discontinued from the study due to an adverse event:

- Subject 202-02-107 in the HBP Lotion group discontinued due to severe itching due to psoriasis (Study 202; PK/HPA axis study).
- Subject 103-01-034 discontinued from the study due to an intravertebral disc protrusion (Study 103; contact sensitization).
- Subject 103-01-230] discontinued due to a manic attack (Study 103; contact sensitization).

7.3.4 Significant Adverse Events

Three subjects experienced severe TEAE's, two of whom have been previously discussed (events: COPD and pruritus; see Sections 7.3.2 and 7.3.3, respectively). The third subject (207-01-136) experienced application site pain, but required no change in dosing of study treatment, VEH Lotion.

7.3.5 Submission Specific Primary Safety Concerns

Systemically, submission specific primary safety concerns relate to the potential for HPA axis suppression. See Section 4.4.3 for discussion of HPA axis testing (Study 202).

Locally, submission specific primary safety concerns relate to the potential for local reactions consistent with corticosteroid-induced effect. At Baseline, Day 8, and Day 15, subjects were evaluated for the following "local skin reactions" (LSRs): telangiectasia, skin atrophy, folliculitis, and burning/stinging. The applicant analyzed and reported LSRs for each of the three time points. However, since the reports do not reflect the extent of LSRs, at the same sites, on the same subjects at each time point, this reviewer finds little meaningfulness in these assessments at the referenced time points. In the reviewer's opinion, the LSRs reflect random reports of these events without context. Therefore, for labeling purposes, the reviewer will consider only the LSRs at Day 15. However, some local adverse reactions (e.g., telangiectasia) were captured as

TEAEs and also as LSRs. If the reported rates differed under the two analyses, the reviewer conservatively recommended the higher rate for the label.

Table 25: Local Skin Reactions present at Day 15 (Safety Population)
(Source: Table 7.3.2.1 of the Integrated Summary of Safety)

	HBP Lotion n (%)	VEH Lotion n (%)
Safety Population N=536	**N=277**	**N=259**
Telangiectasias	3 (1.1%)	0
Skin Atrophy	4 (1.5%)	5 (2.0%)
Folliculitis	0	1 (0.4%)
Burning/Stinging	10	22

At Day 15, only telangiectasias were reported at an incidence > 1% and at a greater rate than vehicle. Because this is the only LSR to meet these criteria, this reviewer recommends that LSRs not be presented separately in the label (b) (4) This reviewer recommends a single table of adverse reactions in the label. Also see the discussion in Section 7.4.1 below.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

A total of 74 treatment-emergent adverse events (TEAEs) occurred (50 in HBP Lotion group; 24 VEH Lotion group) in 48 subjects [32 subjects (11.6%) in the HBP Lotion group and 16 (6.2%) subjects VEH Lotion group]. TEAEs that occurred in ≥ 1% of subjects and that occurred at a higher incidence in the HBP lotion group (subjects treated for up to two weeks) are presented in Table 26. Note this table also includes "telangiectasias" as per the LSRs analyses. This table represents the reviewer's recommendation for the presentation of adverse reactions in the label.

Table 26: Adverse Reactions in ≥ 1% of Subjects Treated for up to Two Weeks and > than Vehicle
(Source: Tables 7.3.1.1 and 7.3.2.1 of the Integrated Summary of Safety)

	HBP Lotion (N=277)	Vehicle Lotion (N=259)
Adverse Reaction	***n (%)***	***n (%)***
Telangiectasia	3 (1%)	0
Application site atrophy	2 (1%)	1 (< 1%)
Headache	2 (1%)	1 (< 1%)

7.4.2 Laboratory Findings

Routine clinical laboratory evaluations (hematology, chemistry, and urinalysis) were performed only in the PK/HPA axis study (Study 202). No clinically significant shift in laboratory parameters was observed with either HBP Lotion or Ultravate Cream treatment.

7.4.3 Vital Signs

Vital signs were measured at baseline in the four studies that comprise the Safety Population dataset. Interval and end-of-treatment evaluation of vital signs were not performed.

7.4.4 Electrocardiograms (ECGs)

The applicant submitted sufficient information to support a conclusion that HBP Lotion does not present a risk for prolongation of cardiac repolarization.

The applicant demonstrated similar systemic exposure to halobetasol propionate at steady state resulting from treatment with HBP Lotion and Ultravate Cream under maximal use conditions in Study 202 (PK/HPA axis). Measures of systemic exposure were within 7%.

The applicant cited the long marketing history (approximately 25 years) of Ultravate cream and ointment in the United States and the absence of any reports of cardiovascular safety signals, including arrhythmias possibly related to QT/QTc prolongation from review of the FDA Adverse Event Reporting System (FAERS) from 1Q2004 to 1Q2014. They also cited a 28-day repeat dose dermal minipig study revealed no effects on ECG parameters.

The applicant performed a literature search in PubMed MEDLINE using the keywords: glucocorticosteroids, halobetasol propionate, QT/QTc prolongation, cardiac repolarization, sudden cardiac death, cardiac arrest, ventricular arrhythmias, ventricular tachycardias, or torsade de pointes and identified no pertinent publications.

Lastly, the applicant reviewed package inserts for marketed topical corticosteroids and identified no warnings or precautions or adverse events indicative of changes in cardiac repolarization.

7.4.5 Special Safety Studies/Clinical Trials

See Section 4.4.3 for discussion of HPA axis testing.

The applicant conducted a dermal safety study to evaluate contact sensitization.

Title: Sensitization Study of Halobetasol Propionate Lotion 0.05% in Healthy Adult Subjects

Study #: 000-0551-103

Study Objective*:* To evaluate the potential of the test articles to induce allergic contact dermatitis (i.e., sensitization) using the Jordan-King modification of the standard Draize Test

Study Design: This was a double-blind, vehicle-controlled within-subject randomized study. Each subject received all test materials (i.e., test articles and control materials). The study had a 3-week induction phase, an approximate 14-17 day rest phase (no test articles were applied) and an approximate 1-week challenge phase. An approximate 1-week re-challenge was conducted if necessary.

Induction Period
Subjects followed an induction phase schedule consisting of visits on Mondays, Wednesdays and Fridays for three consecutive weeks. The 2 test articles (halobetasol propionate lotion 0.05% and vehicle) and 2 control materials [one low irritant control, 0.9% aqueous sodium chloride (NaCl), and one positive irritant control, 0.05% aqueous sodium lauryl sulfate (SLS)] were applied under occlusive conditions to each subject by study personnel. Nine applications (3 patch applications per week) of the all products were applied to their respective sites on the left side of the para-spinal region of the upper back for approximately 48 (±2 hrs.) hours exposure per application on Mondays and Wednesdays. Patches applied on Friday were worn for approximately 72 (±2 hrs.) hours. Staff removed the patches and scored for irritation 20 minutes (±5 mins.) after patch removal. Alternate sites (up to two) were used if the test articles evoked a strong reaction (score of 2 or greater).

Rest Period
Subjects did not receive any application of test articles for approximately 14-17 days.

Challenge Period
A 48-hour (±2 hrs.) challenge patch application of the test articles (control test articles were not patched in the Challenge phase) occurred 14 to 17 days following the final induction visit. Challenge patch applications were to the right para-spinal region of the upper back. Test articles were applied on Monday and left on the back for 48 hours. After the 48 hour wear, patches were removed and the test sites were evaluated 30 minutes (±5 mins.) later, and again 24 (±2 hrs.) and 48 (±2 hrs.) hours after patch removal. If reactivity increased from the 24- to the 48-hour time point then the subject returned at 72 (±2 hrs.) hours after patch removal for scoring for irritation.

Re-challenge Period
Allergic contact dermatitis (ACD) reactions at Challenge would generally be more intense and persistent than Induction reactions. ACD may present as a papulovesicular, edematous eczematous eruption. Borderline responses were re-challenged. At least a 4-week interval was allowed before re-challenge testing to avoid the "angry-back syndrome." Re-challenge testing consisted of a 48-hour (±2 hrs) patch application of the test article associated with the questionable challenge reaction. Patches were removed after 48 hours, and the test sites were evaluated for any reaction 30 minutes (±5 mins.) after patch removal and 48 hours (±2 hrs.) after patch removal.

Study Population: The study enrolled males and females,18 through 65 years of age, and in good health.

Investigational Products:

- HBP Lotion
- VEH Lotion
- Aqueous Sodium Lauryl Sulfate (0.05%, w/v) (SLS; Positive Irritant Control)
- Aqueous Sodium Chloride (0.9%) (Low Irritant Control)

Assessment of Contact Sensitization: The primary measure of the induction of contact sensitization was determined through assessments of the application sites during the Challenge and Re-challenge phases of the study. Observed responses (e.g., erythema) were graded according to a protocol-specified grading scale in Table 27. Individual subject scores were reported by treatment and visit.

Dermal irritation was scored according to the following scale:

Table 27: Grading of responses (dermal safety study)
(Source: protocol for study 103)

Grade	Definition
Irritation Signs	
0	No visible reaction
1	Mild erythema (pink)
2	Moderate erythema (definite redness)
3	Strong erythema (very intense redness)

Definition of letter grades appended to a numerical grade	
E	Edema – swelling, spongy feeling when palpated
P	Papule – red, solid, pinpoint elevation
V	Vesicle – small elevation containing fluid
B	Bulla reaction – fluid-filled lesion (blister)

S	Spreading – evidence of the reaction beyond the Webril pad area
W	Weeping – result of a vesicular or bulla reaction - serous exudate
I	Induration – solid, elevated, hardened, thickened skin
Superficial effects	
G	Glazing
Y	Peeling
K	Scab, dried film of serous exudate of vesicular or bulla reaction
D	Hyperpigmentation (reddish-brown discoloration of test site)
H	Hypopigmentation (loss of visible pigmentation at test site)
F	Fissuring – grooves in the superficial layers of the skin
Symbols used in tabulating data (in addition to scoring grades)	
M	Adjacent site for application after first strong reaction during induction
M-1	Second adjacent site for application after second strong reaction during induction
NP	Not patched
Symbols used to document deviation from experimental plan	
X	Patch omitted due to previous strong reaction
XR	Patch omitted for reasons unrelated to the test

Applications were either terminated or moved to naïve adjacent sites if an accumulated score of 2 or greater was observed. For this purpose, the letter grades assigned to the inflammatory responses were considered to be equal to 1. Under superficial effects, fissuring or scabbing an meaningful degrees of glazing or peeling (as determined by the investigator or designee) were also considered to be equal to 1.

Subject Disposition

A total of 262 subjects were enrolled in the study, and 204 subjects completed the study and were evaluable for determining induced contact sensitization. Fifty-eight (58) subjects were discontinued from the study for the following reasons:

Table 28: Subject Disposition (dermal safety)
(Source: p. 31 of clinical study report for study 103)

Subject Number	Reason for Discontinuation
172 and 256	Discontinued due to tape reaction (tape dermatitis) at the test sites
34 and 230	Discontinued due to non-serious adverse event
199 and 232	Discontinued due to serious adverse event
21, 25, 27, 28, 35, 40, 46, 48, 51, 57, 59, 80, 88, 96, 101, 107, 120, 123, 132,133,136,150, 151, 161, 190, 204, 219, 220, 244, 246, 254, and 260	Discontinued due to noncompliance (e.g., excessive missed visits or unwillingness to follow procedures outlined in the protocol)
102, 114, 211, 252, and 262	Subjects could not be contacted to determine the reason for their discontinuation; therefore, these subjects were considered “lost to follow-up”

75, 95, and 214	Discontinued due to violation of the inclusionary criteria (patches fell off, too much dryness present on the back to accommodate patching)
20, 26, 41, 64, 105, 110, 128, 134, 173, 192, 243, and 248	Discontinued due to other reasons (did not want to continue the study)

Table 29: Worst Score Calculated in Completed Subjects
(Source: Text Table 13-1 of clinical study report for study 103)

		Worst Score Calculated*		
Sponsor's Test Article Codes	RCTS' Test Article Codes	Calculated Irritation Score	Subject Number	Testing Condition
Halobetasol Propionate Lotion 0.05%	2812.8972	3	12, 22, 55, 63, 82, 94, 103, 127, 139, 148, 160, 206, 210, 234, 237, 239, 251	Occlusive patches
Halobetasol Propionate Lotion Vehicle	2812.8973	4	22	
Sodium Lauryl Sulfate 0.05%**	2812.8974	3	160, 168, 206, 251, 255	
Aqueous Sodium Chloride 0.9%	2812.8975	5	22	

*The data shown reflect the calculated erythema scores, not the observed scores, for all subjects who completed the study.
**Patches were discontinued once an erythema score of a 2 level or greater was observed.

Conclusions:
HBP Lotion produced mild (Grade 1) to strong (Grade 3) patch test/patch test irritant responses in 95.6% (195/204) of the study population. The investigator did not consider the reactions to be clinically meaningful in the context of study, where study product was applied under occlusion for 21 days. No evidence of contact sensitization was observed. The reviewer notes that the "worst score calculated" was 3 for both HBP Lotion and SLS. There were more such scores with HBP Lotion than with SLS, the positive irritant control. However, this may be because the SLS patches were discontinued if an erythema score ≥ 2 was observed. The reviewer identified no significant irritancy signal in the Safety Population, where subjects used the product under intended, non-occlusive conditions.

VEH Lotion produced mild (1-level) to strong (3-level) irritant responses in 97.5% (199/204) of the test population. Reactions at VEH Lotion sites were also not considered clinically meaningful, given the occlusive test conditions.

One subject (# 22) exhibited a reaction suspicious for sensitization to VEH Lotion during the challenge phase. The reaction was scored "2EP" ("Moderate erythema," "edema," "papule"). However, on rechallenge (which also included HBP Lotion), the subject exhibited no reactivity.

The study revealed no signal for contact sensitization for HBP Lotion nor VEH Lotion.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

No pattern for dose dependency for adverse events was observed.

7.5.2 Time Dependency for Adverse Events

No pattern for time dependency for adverse events was observed.

7.5.3 Drug-Demographic Interactions

No safety signals were identified when age, gender, or race demographic subgroups were examined.

Table 30 TEAE Incidence Rates by Age, Gender, and Race (Safety Population) (Source: Table 4.2-1 of the Integrated Summary of Safety)

Subjects with any TEAE	HBP Lotion n (%) N=277		VEH Lotion n (%) N=259	
By Age				
<65 Years	n=234	28 (12.0%)	n=213	12 (5.6%)
≥65 Years	n=43	4 (9.3%)	n=46	4 (8.7%)
By Gender				
Male	n=164	21 (12.8%)	n=142	9 (6.3%)
Female	n=113	11 (9.7%)	n=117	7 (6.0%)
By Race				
White	n=238	28 (11.8%)	n=222	14 (6.3%)
Non-White	n=39	4 (10.3%)	n=37	2 (5.4%)

7.5.4 Drug-Disease Interactions

Drug-disease interaction analyses were not done. HBP Lotion 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

No malignancies were reported in the Safety Population.

7.6.2 Human Reproduction and Pregnancy Data

Protocols for all clinical studies excluded pregnant and/or nursing women. There is no information on the use of HBP Lotion in pregnant or lactating women.

The Pregnancy (8.1) and Lactation (8.2) sections of the label will be in the format dictated by the Pregnancy and Lactation Labeling Rule (PLLR). Leyla Sahin, M.D. of the Division of Pediatric and Maternal Health, Maternal Health Team participated in the development of for language for these sections of the label. Draft language follows:

8.1 Pregnancy

Risk Summary

There are no data on topical halobetasol propionate use in pregnant women to inform any drug-associated risks for birth defects or miscarriage. In animal reproduction studies, halobetasol propionate administered systemically during organogenesis to pregnant rats at 13 and 33 times the human topical dose and to pregnant rabbits at 3 times the human topical dose resulted in teratogenic and embryotoxic effects *[see Data]*. The clinical relevance of the animal findings is not clear.

The background risk of major birth defects and miscarriage for the indicated population are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Halobetasol propionate has been shown to be teratogenic in rats and rabbits when given systemically during organogenesis at doses of 0.04 to 0.1 mg/kg/day in rats and 0.01 mg/kg/day in rabbits. These doses are approximately 13, 33, and 3 times, respectively, the human topical dose of halobetasol propionate, 0.05%. Halobetasol propionate was embryotoxic in rabbits but not in rats.

Cleft palate was observed in both rats and rabbits. Omphalocele was seen in rats, but not in rabbits.

8.2 Lactation

Risk Summary
There are no data on the presence of halobetasol propionate or its metabolites in human milk,, the effects on the breastfed infant, or the effects on milk production after topical application to women who are breastfeeding.
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 corticosteroids 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 ULTRAVATE lotion and any potential adverse effects on the breastfed infant from ULTRAVATE lotion or from the underlying maternal condition.

Clinical Considerations
Advise breastfeeding women not to apply ULTRAVATE lotion directly to the nipple and areola to avoid direct infant exposure.

7.6.3 Pediatrics and Assessment of Effects on Growth

The applicant will be required to conduct a postmarketing pediatric study under PREA; see Section 1.3 for discussion of the PREA PMR.

The Division issued an Agreed initial Pediatric Study Plan (iPSP) letter on May 15, 2014. The pediatric development plan presented in the Agreed iPSP was for a partial waiver for children from birth to 11 years of age and a deferral to initiate a safety PK/HPA axis suppression study in adolescents 12 to 17 years of age (the upper bound age limit is formally 16 years 11 months in the PMR; see Section 1.4).

The applicant submitted the protocol for the pediatric study on October 7, 2014. This study will be conducted to address the PREA PMR. The timeline for PMR schedule milestones is presented in Section 1.3.

The halobetasol moiety has not been studied in subjects younger than 18 years of age.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

According to the protocol, subject kits (cartons containing the labeled test articles for each subject) were packaged with three bottles of test article. However, subjects were to have been dispensed two bottles, with instructions to use Bottle 2 only if Bottle 1 were misplaced. Bottle 3 was to have been retained at the investigational site, for use only in the event of loss, spillage, or damage to Bottles 1 and 2.

The applicant reported that 9 subjects (4.1%) in the Phase 3 studies (304 and 305), applied >150 grams of HBP Lotion during the two week treatment period. Therefore, apparently, some subjects were dispensed all three 60gm bottles of test article.

On review of Listing 16.2.5.1 ("Study Medication Dosing Irregularities, Intent-to-Treat Population") of the study reports for both pivotal trials (304 and 305), the reviewer identified 13 subjects who were reported to have exceeded the 50gm per week dosing limitation (a 14th was said to have applied an "extra dose" each treatment week). However, these listings did not specifically identify those subjects who dosed >150 grams of HBP Lotion during the treatment period. Four subjects were specifically reported to have exceeded 50gm of HBP Lotion each week of the 2-week treatment period. Of these 13 subjects, TEAEs were reported for one (subject 305-08-018): "burning (mild) post application" and "application site pain"). However, HPA-axis evaluation was not done in the pivotal studies, so it is not known whether any of these subjects (or any other subjects) experienced adrenal suppression in the pivotal studies.

7.7 Additional Submissions / Safety Issues

The applicant submitted the four-month Safety Update on May 6, 2015. The submission consisted of a cover letter in which the applicant stated:

"The original NDA contains all safety data obtained from the completed clinical and nonclinical studies. No new nonclinical, or clinical studies have initiated or completed by Ferndale.

A search for safety information in the literature, TOXLINE, and the FAERS database on adverse reactions to halobetasol propionate has been conducted from July 1, 2014 (last date covered in original NDA) to March 8, 2015, and no new information that would affect the safety of Halobetasol Propionate Lotion, 0.05% was identified. As a result, an update to the integrated summary of safety provided in Section 5.3.5.3 is not warranted at this time."

8 Postmarket Experience

HBP Lotion has not been marketed in any country.

9 Appendices

9.1 Literature Review/References

The reviewer did not perform a literature review for this application.

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.

Clinical Investigator Financial Disclosure
Review Template

Application Number: 208183

Submission Date(s): January 8, 2015

Applicant: Ferndale Laboratories, Inc.

Product: halobetasol propionate lotion, 0.05%

Reviewer: Brenda Carr, M.D.

Date of Review: September, 17, 2015

Covered Clinical Study (Name and/or Number): Study (b) (6)

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from applicant)
Total number of investigators identified: one		
Number of investigators who are sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): one		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Significant payments of other sorts: X Proprietary interest in the product tested held by investigator: X Significant equity interest held by investigator in sponsor of covered study: X		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes X	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes X	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) None		
Is an attachment provided with the reason:	Yes X	No ☐ (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.[2] Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

The applicant appears to have adequately disclosed financial arrangements with clinical investigators. The applicant took reasonable steps to minimize any potential investigator bias by the design of the study:

- (b) (6)

The disclosed financial interests/arrangements do not affect approvability of the application.

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

/s/

BRENDA CARR
10/28/2015

JILL A LINDSTROM
10/29/2015