

# **CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**210566Orig1s000**

## **MULTI-DISCIPLINE REVIEW**

**Summary Review**

**Office Director**

**Cross Discipline Team Leader Review**

**Clinical Review**

**Non-Clinical Review**

**Statistical Review**

**Clinical Pharmacology Review**

NDA/BLA Multi-disciplinary Review and Evaluation for NDA 210566  
 TRADENAME (halobetasol propionate) foam, 0.05%

NDA/BLA Multi-disciplinary Review and Evaluation

|                                                         |                                                                                                  |
|---------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| Application Type                                        | NDA                                                                                              |
| Application Number(s)                                   | NDA 210566                                                                                       |
| Priority or Standard                                    | Standard                                                                                         |
| Submit Date(s)                                          | 7-28-17                                                                                          |
| Received Date(s)                                        | 7-28-17                                                                                          |
| PDUFA Goal Date                                         | 5-28-18                                                                                          |
| Division/Office                                         | DDDP                                                                                             |
| Review Completion Date                                  | 4-4-18                                                                                           |
| Established Name                                        | halobetasol propionate foam, 0.05%                                                               |
| (Proposed) Trade Name                                   |                                                                                                  |
| Pharmacologic Class                                     | Corticosteroid                                                                                   |
| Code name                                               |                                                                                                  |
| Applicant                                               | Therapeutics Inc.                                                                                |
| Formulation(s)                                          | foam                                                                                             |
| Dosing Regimen                                          | Twice daily for two weeks with a maximum recommended exposure of up to (b) (4) 50 grams per week |
| Applicant Proposed Indication(s)/Population(s)          | For the topical treatment of plaque psoriasis in patients 18 years of age and older              |
| Recommendation on Regulatory Action                     | Approval                                                                                         |
| Recommended Indication(s)/Population(s) (if applicable) | for the topical treatment of plaque psoriasis in patients eighteen (18) years of age and older   |

## Table of Contents

|                                                                                                                      |    |
|----------------------------------------------------------------------------------------------------------------------|----|
| Reviewers of Multi-Disciplinary Review and Evaluation .....                                                          | 7  |
| Additional Reviewers of Application .....                                                                            | 9  |
| Glossary .....                                                                                                       | 10 |
| 1 Executive Summary .....                                                                                            | 12 |
| 1.1. Product Introduction .....                                                                                      | 12 |
| 1.2. Conclusions on the Substantial Evidence of Effectiveness .....                                                  | 12 |
| 1.3. Benefit-Risk Assessment .....                                                                                   | 13 |
| 2 Therapeutic Context .....                                                                                          | 19 |
| 2.1. Analysis of Condition .....                                                                                     | 19 |
| 2.2. Analysis of Current Treatment Options .....                                                                     | 19 |
| 3 Regulatory Background .....                                                                                        | 22 |
| 3.1. U.S. Regulatory Actions and Marketing History .....                                                             | 22 |
| 3.2. Summary of Presubmission/Submission Regulatory Activity .....                                                   | 22 |
| 4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions<br>on Efficacy and Safety ..... | 25 |
| 4.1. Office of Scientific Investigations (OSI) .....                                                                 | 25 |
| 4.2. Product Quality .....                                                                                           | 25 |
| 4.3. Clinical Microbiology .....                                                                                     | 25 |
| 4.4. Devices and Companion Diagnostic Issues .....                                                                   | 25 |
| 5 Nonclinical Pharmacology/Toxicology .....                                                                          | 26 |
| 5.1. Executive Summary .....                                                                                         | 26 |
| 5.2. Referenced NDAs, BLAs, DMFs .....                                                                               | 27 |
| 5.3. Pharmacology .....                                                                                              | 27 |
| 5.4. ADME/PK .....                                                                                                   | 27 |
| 5.5. Toxicology .....                                                                                                | 28 |
| 5.5.1. General Toxicology .....                                                                                      | 28 |
| 5.5.2. Genetic Toxicology .....                                                                                      | 29 |
| 5.5.3. Carcinogenicity .....                                                                                         | 29 |
| 5.5.4. Reproductive and Developmental Toxicology .....                                                               | 29 |
| 5.5.5. Other Toxicology Studies .....                                                                                | 31 |

|                                                                                         |    |
|-----------------------------------------------------------------------------------------|----|
| 5.6. Labeling .....                                                                     | 32 |
| 6 Clinical Pharmacology .....                                                           | 34 |
| 6.1. Executive Summary .....                                                            | 34 |
| 6.1.1. Recommendations .....                                                            | 34 |
| 6.1.2. Post-Marketing Requirements.....                                                 | 34 |
| 6.1.3. Post-Marketing Commitment.....                                                   | 34 |
| 6.2. Summary of Clinical Pharmacology Assessment .....                                  | 35 |
| 6.2.1. Pharmacology and Clinical Pharmacokinetics .....                                 | 35 |
| 6.2.2. General Dosing and Therapeutic Individualization.....                            | 36 |
| 6.3. Comprehensive Clinical Pharmacology Review.....                                    | 37 |
| 6.3.1. General Pharmacology and Pharmacokinetic Characteristics .....                   | 37 |
| 6.3.2. Clinical Pharmacology Questions.....                                             | 38 |
| 7 Statistical and Clinical and Evaluation .....                                         | 40 |
| 7.1. Sources of Clinical Data and Review Strategy.....                                  | 40 |
| 7.1.1. Table of Clinical Studies.....                                                   | 40 |
| 7.1.2. Review Strategy .....                                                            | 44 |
| 7.2. Review of Relevant Individual Trials Used to Support Efficacy .....                | 45 |
| 7.2.1. Pivotal Phase 3 Trials (Trials 306 & 310).....                                   | 45 |
| 7.2.1.1. Trial Design and Endpoints .....                                               | 45 |
| 7.2.1.2. Statistical Methodologies .....                                                | 46 |
| 7.2.1.3. Subject Disposition, Demographics and Baseline Disease<br>Characteristics..... | 48 |
| 7.2.1.4. Results of the Primary Endpoint.....                                           | 49 |
| 7.2.1.5. Results of the Secondary Endpoints .....                                       | 50 |
| 7.2.1.6. Efficacy Over Time.....                                                        | 51 |
| 7.2.1.7. Patient Reported Outcomes (PROs).....                                          | 51 |
| 7.2.1.8. Findings in Special/Subgroup Populations.....                                  | 52 |
| 7.2.1.8.1. Sex, Race, Age and Baseline Disease Severity .....                           | 52 |
| 7.2.1.8.2. Center .....                                                                 | 53 |
| 7.2.2. Supportive Phase 3 Trial (Trial 305).....                                        | 54 |
| 7.2.2.1. Study Design, Endpoints and Statistical Methodologies .....                    | 54 |
| 7.2.2.2. Subject Disposition, Demographics and Baseline Disease<br>Characteristics..... | 55 |

|         |                                                                   |    |
|---------|-------------------------------------------------------------------|----|
| 7.2.3.  | Results of the Primary Endpoint.....                              | 56 |
| 7.3.    | Review of Safety .....                                            | 57 |
| 7.3.1.  | Safety Review Approach.....                                       | 57 |
| 7.3.2.  | Review of the Safety Database .....                               | 57 |
| 7.3.3.  | Adequacy of Applicant's Clinical Safety Assessments .....         | 59 |
| 7.3.4.  | Safety Results .....                                              | 59 |
| 7.3.5.  | Analysis of Submission-Specific Safety Issues .....               | 62 |
| 7.3.6.  | Safety Analyses by Demographic Subgroups .....                    | 63 |
| 7.3.7.  | Specific Safety Studies/Clinical Trials .....                     | 64 |
| 7.3.8.  | Safety in the Postmarket Setting .....                            | 71 |
| 7.3.9.  | Integrated Assessment of Safety .....                             | 71 |
|         | SUMMARY AND CONCLUSIONS .....                                     | 72 |
| 7.4.    | Summary and Conclusions .....                                     | 72 |
| 7.4.1.  | Statistical Issues .....                                          | 72 |
| 7.4.2.  | Conclusions and Recommendations.....                              | 73 |
| 8       | Advisory Committee Meeting and Other External Consultations ..... | 74 |
| 9       | Pediatrics.....                                                   | 75 |
| 10      | Labeling Recommendations .....                                    | 77 |
| 10.1.   | Prescribing Information .....                                     | 77 |
| 10.2.   | Patient Labeling .....                                            | 77 |
| 11      | Risk Evaluation and Mitigation Strategies (REMS) .....            | 78 |
| 12      | Postmarketing Requirements and Commitments.....                   | 78 |
| 13      | Appendices.....                                                   | 79 |
| 13.1.   | References .....                                                  | 79 |
| 13.2.   | Financial Disclosure .....                                        | 79 |
| 13.3.   | Clinical/Biostatistics .....                                      | 86 |
| 13.4.   | Nonclinical Pharmacology/Toxicology.....                          | 88 |
| 13.5.   | Clinical Pharmacology .....                                       | 90 |
| 13.5.1. | Clinical Pharmacology Studies.....                                | 90 |

## Table of Tables

|                                                                                                                                                     |    |
|-----------------------------------------------------------------------------------------------------------------------------------------------------|----|
| Table 1: Summary of Treatment Relevant to the Proposed Indication for Plaque Psoriasis.....                                                         | 19 |
| Table 2: Precision and accuracy of the bioanalytical method (Source: Table 2 in Summary of Biopharm Studies and Associated Analytical Methods)..... | 37 |
| Table 3: Listing of Clinical Trials Relevant to NDA 210566 .....                                                                                    | 41 |
| Table 4: Subject Disposition for Trials 306 and 310 .....                                                                                           | 48 |
| Table 5: Demographics for Trials 306 and 310 – ITT <sup>(1)</sup> .....                                                                             | 48 |
| Table 6: Baseline Disease Characteristics for Trials 306 and 310 – ITT <sup>(1)</sup> .....                                                         | 49 |
| Table 7: Missing Data for the Primary Endpoint by Day for Trials 306 and 310 – ITT <sup>(1)</sup> .....                                             | 50 |
| Table 8: Results of the Primary Endpoint at Day 15 for Trials 306 and 310 .....                                                                     | 50 |
| Table 9: Results of the Secondary Endpoints at Day 15 for Trials 306 and 310 .....                                                                  | 51 |
| Table 10: Subject Disposition for Trial 305.....                                                                                                    | 55 |
| Table 11: Demographics for Trial 305 – ITT <sup>(1)</sup> .....                                                                                     | 55 |
| Table 12: Baseline Disease Characteristics for Trial 305 – ITT <sup>(1)</sup> .....                                                                 | 56 |
| Table 13: Characterization of the Combined Safety Population .....                                                                                  | 57 |
| Table 14: Adverse Reactions Occurring in ≥ 1% of Subjects Treated with HBP foam for up to Two Weeks .....                                           | 61 |
| Table 15: TEAE Incidence Rates by Age, Gender and Race for the Combined Safety Pool.....                                                            | 63 |
| Table 16: Grading of responses (dermal safety study).....                                                                                           | 65 |
| Table 17: Subject Disposition for Trial 108.....                                                                                                    | 67 |
| Table 18: Scores for Subjects Demonstrating Skin Reactivity in Challenge/ Rechallenge Testing .....                                                 | 69 |
| Table 19: Covered Clinical Studies for Financial Disclosure: 108, 202, 203, 305, 306, 310 .....                                                     | 80 |
| Table 20: Investigator's Global Assessment (IGA).....                                                                                               | 86 |
| Table 21: Clinical Signs and Symptoms: Plaque Elevation .....                                                                                       | 87 |
| Table 22: Clinical Signs and Symptoms: Scaling .....                                                                                                | 87 |
| Table 23: Clinical Signs and Symptoms: Erythema.....                                                                                                | 87 |
| Table 24. Demographic information (Source: Table 11.2-1 of Study report 122-0551-202).....                                                          | 93 |
| Table 25. Summary of HPA axis response, dose and HBP AUC in Study #122-0551-202 .....                                                               | 93 |
| Table 26. Systemic PK parameters of HBP foam 0.05% (Source: Table 11.5-2 of Study report 122-0551-202) .....                                        | 94 |

## Table of Figures

|                                                                                                                                                                                     |    |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
| Figure 1: Individual subject PK profile on Day 14, mean plasma HBP concentration-time profile (in red) and systemic PK parameters of HBP foam 0.05% on Day 14.....                  | 38 |
| Figure 2: Results of IGA Response <sup>(1)</sup> over Time for Trials 306 and 310 - ITT <sup>(2)</sup> .....                                                                        | 51 |
| Figure 3: Forest Plot for the Treatment Effect at Day 15 by Age, Sex, Race and Baseline IGA Score for Trial 306 – ITT <sup>(1)</sup> .....                                          | 52 |
| Figure 4: Forest Plot for the Treatment Effect at Day 15 by Age, Sex, Race and Baseline IGA Score for Trial 310 – ITT <sup>(1)</sup> .....                                          | 53 |
| Figure 5: Results of the Primary Endpoint at Day 15 by Center for Trials 306 and 310 – ITT <sup>(1)</sup> .....                                                                     | 54 |
| Figure 6: 5-D Pruritus Scale .....                                                                                                                                                  | 88 |
| Figure 7: Vasoconstriction mean visual score (N = 36) (Reviewer's analysis) .....                                                                                                   | 91 |
| Figure 8: Comparison of systemic cortisol level vs AUC or Total dose (Reviewer's analysis) .....                                                                                    | 94 |
| Figure 9: Mean plasma HBP concentration-time profile on Day 14 in Study #122-0551-202 (Source: Figure 1 of 2.7.1 Summary of Biopharm Studies & Associated Analytical Methods) ..... | 95 |

## Reviewers of Multi-Disciplinary Review and Evaluation

| DISCIPLINE                   | REVIEWER                                        | OFFICE/DIVISION | SECTIONS AUTHORED/ ACKNOWLEDGED/ APPROVED                                                | AUTHORED/ ACKNOWLEDGED/ APPROVED                                                                                                                     |
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| Clinical Reviewer            | Amy S. Woitach, MS, DO                          | ODE III/DDDP    | Sections: 1.2, 1.3, 2, 3, 4.1, 4.3, 4.4, 7.1.1, 7.3, 7.4.2, 8, 9, 10, 11, 12, 13.1, 13.2 | Select one:<br><input checked="" type="checkbox"/> Authored<br><input type="checkbox"/> Acknowledged<br><input type="checkbox"/> Approved            |
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NDA/BLA Multi-disciplinary Review and Evaluation for NDA 210566  
 TRADENAME (halobetasol propionate) foam, 0.05%

|                                      |                           |              | ACKNOWLEDGED/<br>APPROVED     | APPROVED                                                                                                                                  |
|--------------------------------------|---------------------------|--------------|-------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|
| Biometrics Team<br>Leader            | Mohamed Alosch,<br>PhD    | OTS/OB/DBIII | Section(s): 7.2, 7.4,<br>13.3 | Select one:<br><input type="checkbox"/> Authored<br><input type="checkbox"/> Acknowledged<br><input checked="" type="checkbox"/> Approved |
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| Acting Division<br>Director (DBIII)  | Laura Lee<br>Johnson, PhD | OTS/OB/DBIII | Section(s): 7.2, 7.4,<br>13.3 | Select one:<br><input type="checkbox"/> Authored<br><input type="checkbox"/> Acknowledged<br><input checked="" type="checkbox"/> Approved |
|                                      | Signature:                |              |                               |                                                                                                                                           |
| Nonclinical<br>Reviewer              | Jill Merrill              | ODE III/DDDP | Sections:                     | Select one:<br><input checked="" type="checkbox"/> Authored<br><input type="checkbox"/> Acknowledged<br><input type="checkbox"/> Approved |
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|                                      | Signature:                |              |                               |                                                                                                                                           |
| Clinical<br>Pharmacology<br>Reviewer | Luke Oh                   |              | Sections:                     | Select one:<br><input checked="" type="checkbox"/> Authored<br><input type="checkbox"/> Acknowledged<br><input type="checkbox"/> Approved |

NDA/BLA Multi-disciplinary Review and Evaluation for NDA 210566  
 TRADENAME (halobetasol propionate) foam, 0.05%

|                                   |                        |         |  |                                                                                                                                           |
|-----------------------------------|------------------------|---------|--|-------------------------------------------------------------------------------------------------------------------------------------------|
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### Additional Reviewers of Application

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|              |                                           |
|--------------|-------------------------------------------|
| OPQ          | Yichun Sun, Sarah Ibrahim, Jeffrey Medwid |
| Microbiology |                                           |
| OPDP         |                                           |
| OSI          | n/a                                       |
| OSE/DEPI     | n/a                                       |
| OSE/DMEPA    |                                           |
| OSE/DRISK    | n/a                                       |
| Other        | PLT:                                      |

OPQ=Office of Pharmaceutical Quality  
 OPDP=Office of Prescription Drug Promotion  
 OSI=Office of Scientific Investigations  
 OSE= Office of Surveillance and Epidemiology  
 DEPI= Division of Epidemiology  
 DMEPA=Division of Medication Error Prevention and Analysis  
 DRISK=Division of Risk Management

## Glossary

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|            |                                                                         |
|------------|-------------------------------------------------------------------------|
| AC         | advisory committee                                                      |
| ADME       | absorption, distribution, metabolism, excretion                         |
| AE         | adverse event                                                           |
| BLA        | biologics license application                                           |
| BPCA       | Best Pharmaceuticals for Children Act                                   |
| BRF        | Benefit Risk Framework                                                  |
| <b>BSA</b> | <b>Body Surface Area</b>                                                |
| CBER       | Center for Biologics Evaluation and Research                            |
| CDER       | Center for Drug Evaluation and Research                                 |
| CDRH       | Center for Devices and Radiological Health                              |
| CDTL       | Cross-Discipline Team Leader                                            |
| CFR        | Code of Federal Regulations                                             |
| CMC        | chemistry, manufacturing, and controls                                  |
| <b>CMH</b> | <b>Cochran-Mantel-Haenszel</b>                                          |
| COSTART    | Coding Symbols for Thesaurus of Adverse Reaction Terms                  |
| CRF        | case report form                                                        |
| CRO        | contract research organization                                          |
| CRT        | clinical review template                                                |
| CSR        | clinical study report                                                   |
| CSS        | Controlled Substance Staff                                              |
| DHOT       | Division of Hematology Oncology Toxicology                              |
| DMC        | data monitoring committee                                               |
| ECG        | electrocardiogram                                                       |
| eCTD       | electronic common technical document                                    |
| ETASU      | elements to assure safe use                                             |
| FDA        | Food and Drug Administration                                            |
| FDAAA      | Food and Drug Administration Amendments Act of 2007                     |
| FDASIA     | Food and Drug Administration Safety and Innovation Act                  |
| GCP        | good clinical practice                                                  |
| GRMP       | good review management practice                                         |
| <b>HBP</b> | <b>Halobetasol Propionate</b>                                           |
| ICH        | International Conference on Harmonization                               |
| <b>IGA</b> | <b>Investigator Global Assessment</b>                                   |
| IND        | Investigational New Drug                                                |
| ISE        | integrated summary of effectiveness                                     |
| ISS        | integrated summary of safety                                            |
| ITT        | intent to treat                                                         |
| MedDRA     | Medical Dictionary for Regulatory Activities                            |
| <b>MI</b>  | <b>multiple imputation</b>                                              |
| NCI-CTCAE  | National Cancer Institute-Common Terminology Criteria for Adverse Event |

NDA/BLA Multi-disciplinary Review and Evaluation for NDA 210566  
TRADENAME (halobetasol propionate) foam, 0.05%

|       |                                         |
|-------|-----------------------------------------|
| NDA   | new drug application                    |
| NME   | new molecular entity                    |
| NRI   | non-responder imputation                |
| OCS   | Office of Computational Science         |
| OPQ   | Office of Pharmaceutical Quality        |
| OSE   | Office of Surveillance and Epidemiology |
| OSI   | Office of Scientific Investigation      |
| PBRER | Periodic Benefit-Risk Evaluation Report |
| PD    | pharmacodynamics                        |
| PI    | prescribing information                 |
| PK    | pharmacokinetics                        |
| PMC   | postmarketing commitment                |
| PMR   | postmarketing requirement               |
| PP    | per protocol                            |
| PPI   | patient package insert                  |
| PREA  | Pediatric Research Equity Act           |
| PRO   | patient reported outcome                |
| PSUR  | Periodic Safety Update report           |
| REMS  | risk evaluation and mitigation strategy |
| SAE   | serious adverse event                   |
| SAP   | statistical analysis plan               |
| SGE   | special government employee             |
| SOC   | standard of care                        |
| SPA   | Special Protocol Assessment             |
| TEAE  | treatment emergent adverse event        |

## 1 Executive Summary

---

### 1.1. Product Introduction

This NDA for halobetasol propionate foam, 0.05% for the treatment of psoriasis in adults is submitted as a 505(b)(1) application by Therapeutics Inc. Therapeutics Inc. obtained the right from Sun Pharma Company to reference the following two NDAs to support this application: NDA 19967 [Ultravate<sup>®</sup> (halobetasol propionate) cream, 0.05%] and NDA 19968 [Ultravate<sup>®</sup> (halobetasol propionate) ointment, 0.05%].

Halobetasol propionate foam is proposed for the topical treatment of plaque psoriasis in patients eighteen (18) years of age and older. The active pharmaceutical ingredient (API), halobetasol propionate, is a corticosteroid.

The drug product, halobetasol propionate foam, 0.05%, (HBP foam), contains 0.05% w/w halobetasol propionate as the active ingredient. The inactive ingredients used in the drug product include ethanol, water and propylene glycol as (b) (4) for the API; emulsifying wax, polyoxyl 20 cetostearyl ether, and cetostearyl alcohol as (b) (4) and benzoic acid (b) (4) isobutane and propane at the ratio of (b) (4) (w/w), is used as the propellant for the foam. The drug product will be supplied as physician samples (17 g) in 35×70 mm aluminum cans with (b) (4) actuator assemblies and as the commercial configuration (50 g) in 38×106 mm aluminum cans with (b) (4) actuator assemblies. The recommended expiration dating period of the drug product is 36 months when stored at USP controlled room temperature (20° - 25°C).

### 1.2. Conclusions on the Substantial Evidence of Effectiveness

To establish the efficacy of halobetasol propionate (HBP) foam, 0.05% for the topical treatment of plaque psoriasis, the applicant submitted data from two multicenter, randomized, double-blind, vehicle-controlled, parallel-group, pivotal Phase 3 trials (Trials 306 and 310). The trials enrolled adult subjects who had moderate to severe plaque psoriasis, based on the Investigator's Global Assessment (IGA) score, involving 2%-12% BSA. The design of the trials was identical, except from the sample size. The primary efficacy endpoint was the proportion of subjects achieving an IGA score of 0 or 1 at Day 15, with at least a 2-grade improvement from baseline. HBP foam was statistically superior to vehicle foam for the primary endpoint (p-value<0.001).

The applicant has demonstrated that HBP Foam is effective for its intended use in the target population, and has met the evidentiary standard required by 21 CFR 314.126(a)(b) to support approval.

### 1.3. Benefit-Risk Assessment

#### Benefit-Risk Summary and Assessment

Halobetasol propionate Foam, 0.05% (HBP Foam) is a corticosteroid, which the applicant proposes for topical treatment of plaque psoriasis in adults. Psoriasis is a common, chronic, immune-mediated skin disorder. The characteristic lesion is a sharply demarcated scaly, erythematous plaque with scale, and the plaques may be localized or widespread in distribution symmetrically distributed. These plaques commonly involve the extensor surfaces of the extremities, but may present anywhere from the scalp to the soles of the feet. The extent of the body surface area affected may vary from limited to extensive. The extent of involvement is one consideration in the approach to patient management. Disease of limited extent may be effectively managed with topical treatment.

Current topical therapeutic options include synthetic vitamin D3 derivatives, retinoids and corticosteroids. There are several approved topical corticosteroids available for treatment of psoriasis, including other halobetasol propionate products, marketed in cream, ointment, and lotion dosage forms. The applicant's product provides for a new foam dosage form for halobetasol propionate. Approval of this application would add to the treatment armamentarium for plaque psoriasis by providing a new dosage form of a super-potent corticosteroid.

Substantial efficacy was demonstrated from two adequate and well-controlled studies, 306 and 310. The studies were conducted under identical protocols and evaluated HBP Foam and its vehicle foam in adult subjects with moderate to severe plaque psoriasis.

Adult subjects with plaque psoriasis, with disease severity defined by a BSA of 2-12% (excluding face, scalp, groin, axillae and other intertriginous areas) and a baseline Investigator's Global Assessment (IGA) score of at least three (3 =moderate) were enrolled. The protocol-specified primary efficacy endpoint was the proportion of subjects achieving an IGA "Treatment Success" defined as a score of 0 (clear) or 1 (almost clear) with at least a two-grade improvement measured at Day 15.

In Study 306, 25.3% (19/73) subjects in the HBP Foam group achieved "treatment success" at Day 15 compared to 3.9% (3/72) subjects in the vehicle group; the results were statistically significant ( $p < 0.001$ ). In Study 310, 30.7% (56/184) subjects in the HBP Foam group achieved "treatment success" at Day 15 compared to 7.4 % (14/184) subjects in the vehicle group; the results were again statistically significant ( $p < 0.001$ ). The applicant has established that HBP Foam is effective in the treatment of plaque psoriasis.

The safety population for the foam formulation comprised 704 subjects 351 subjects were randomized to treatment with HBP Foam (351/704, 49.9%). Adult subjects with plaque psoriasis were exposed to up to approximately 50-60 grams/week of study product for two weeks. Adverse events did not identify a new safety signal. 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. All adrenal-suppressed subjects who received post-treatment follow-up testing showed a normal adrenal response at follow-up testing. There was a correlation between the dose and HPA axis suppression.

There were no deaths reported and the one subject that experienced a serious adverse event was in the VEH foam group. Overall, the incidence of treatment emergent adverse events (TEAEs) was low and TEAEs were typically mild in severity across both treatment groups. TEAEs that occurred in  $\geq 1\%$  of subjects and that occurred at a higher incidence in the HBP Foam group (incidences are for the HBP Foam group) were: application site pain (1%) and headache (1%).

A maximal use PK and HPA axis suppression study conducted using the to-be-marketed formulation demonstrated abnormal Cosyntropin stimulation tests (CST) in 24% (6/25) of the subjects. Subjects did not report clinical symptoms and CST returned to normal at follow-up. 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.

Adverse events were generally consistent with those that may be seen with corticosteroid use. The applicant established the safety of HBP Foam in the treatment of plaque psoriasis. Prescription and patient labeling, as well as routine pharmacovigilance are adequate to manage the risk of HBP Foam in the postmarketing setting.

The available safety and efficacy data supports the approval.

| Dimension                                 | Evidence and Uncertainties                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Conclusions and Reasons                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|-------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <a href="#">Analysis of Condition</a>     | <ul style="list-style-type: none"> <li>Psoriasis is a common, chronic, inflammatory multi-system disorder which primarily affects the skin and joints and is associated with substantial impairment of quality of life. The prevalence of psoriasis in the US is approximately 2-3 %, of which an estimated 20% have moderate to- severe disease.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | <p>Plaque psoriasis can be a serious disease because of its chronicity and impact on quality of life.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <a href="#">Current Treatment Options</a> | <ul style="list-style-type: none"> <li>Mild disease is commonly treated with topical corticosteroids or synthetic vitamin D products, but systemic treatments may be needed for more widespread disease. Systemic agents include adalimumab, etanercept, infliximab (TNF antagonists), secukinumab, ixekizumab (IL 17 antagonists), brodalumab (an IL 17 receptor antagonist), and ustekinumab, an IL12/23 antagonist. Other approved systemic psoriasis therapies include acitretin, methotrexate, cyclosporine, and apremilast. Phototherapy, either PUVA (UVA light combined with the psoralen methoxsalen) or UVB light therapy (narrow or broadband) may also be appropriate first line or adjunctive treatment for patients with moderate to severe psoriasis.</li> <li>FDA approved topical drugs for the treatment of psoriasis include synthetic vitamin D3 derivatives, retinoids and corticosteroids. Topical products come in a variety of formulations. Other halobetasol propionate products are marketed in cream, ointment, and lotion dosage forms.</li> </ul> | <p>There are a number of FDA-approved products with an acceptable risk-benefit profile for the treatment of plaque psoriasis in adults. None of these treatments provides a permanent cure.</p> <p>There are multiple topical corticosteroid products with various potencies that can be prescribed for psoriasis. Multiple dosage forms are available, and include creams, lotions, sprays, foams, gels, ointments, oils, shampoos, solutions, and medicated tapes. The dosage form may affect potency, adverse events, and patient acceptance.</p> <p>For topical formulations, patients have preferences for various vehicles. Preference depends on many factors including the size and location of the affected area and the time of day the treatment will be applied. Foam</p> |

NDA/BLA Multi-disciplinary Review and Evaluation for NDA 210566  
 TRADENAME (halobetasol propionate) foam, 0.05%

| Dimension               | Evidence and Uncertainties                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Conclusions and Reasons                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|-------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | formulations spread readily and are easier to apply to hairy areas. Approval of this application would add to the treatment armamentarium for plaque psoriasis by providing a new dosage form of a super-potent corticosteroid.                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <a href="#">Benefit</a> | <ul style="list-style-type: none"> <li>Data from two multicenter, randomized, double-blind, vehicle-controlled, parallel-group, pivotal Phase 3 trials (Trials 306 and 310) provide substantial evidence of the effectiveness of HBP foam for the treatment of plaque psoriasis. The trials enrolled adult subjects, who had moderate to severe plaque psoriasis based on the Investigator's Global Assessment (IGA) score, involving 2%-12% BSA. The design of the trials was identical, except from the sample size. The primary efficacy endpoint was the proportion of subjects achieving an IGA score of 0 or 1 at Day 15, with at least a 2-grade improvement from baseline. HBP foam was statistically superior to vehicle foam for the primary endpoint (p-value&lt;0.001).</li> <li>In Study 306, 25.3% (19/73) subjects in the HBP Foam group achieved "treatment success" at Day 15 compared to 3.9% (3/72) subjects in the vehicle group. In Study 310, 30.7% (56/184) subjects in the HBP Foam group achieved "treatment success" at Day 15 compared to 7.4 % (14/184) subjects in the vehicle group.</li> </ul> | <p>The data submitted by the applicant met the evidentiary standard for provision of substantial evidence of effectiveness under the proposed conditions of use. The trials were adequate and well-controlled. The results are persuasive.</p> <p>Both the clinical and biostatistics reviews concluded that there was adequate demonstration of efficacy.</p> <p>Achievement of clear or almost-clear skin is an intrinsically meaningful outcome for a cutaneous disease such as psoriasis. The data suggest that a patient with moderate-to-severe plaque psoriasis treated with topical HBP foam twice daily for up to 2 weeks may achieve clear or almost clear skin.</p> |
| <a href="#">Risk</a>    | <ul style="list-style-type: none"> <li>The safety assessment did not identify a new safety signal compared to marketed formulations of halobetasol. Local adverse reactions of application site pain, telangiectasias, skin atrophy and contact dermatitis were consistent with those that may be seen with topical corticosteroid use. Adrenal suppression was observed in the HPA axis study in 24% (6/25) of the subjects.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | <p>The safety profile of HBP Foam has been adequately characterized and appears to be similar to other marketed halobetasol products. The rate of HPA axis suppression is at a level expected for a super-potent corticosteroid.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                           |

| Dimension                       | Evidence and Uncertainties                                                                                                                                                                                                                                                                                                                             | Conclusions and Reasons                                                                                                                                              |
|---------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <a href="#">Risk Management</a> | <ul style="list-style-type: none"> <li>• A PREA PMR to characterize the safety of HBP foam in adolescents is recommended.</li> <li>• To address the PMR, the applicant should conduct a safety pharmacokinetic (PK) and HPA axis suppression study under maximal use conditions in subjects 12 years to &lt; 17 years of age with psoriasis</li> </ul> | Prescription labeling, patient labeling and routine pharmacovigilance are adequate to manage the risks of the product. A REMS is not recommended by the review team. |

## 1.4 Patient Experience Data

Patient experience data pertaining and submitted with this application are outlined in Table 1.

**Table 1: Patient Experience Data Relevant to this Application**

|   |                                                                                                                                      |                                        |
|---|--------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|
| x | The patient experience data that was submitted as part of the application include:                                                   | Section where discussed, if applicable |
|   | x Clinical outcome assessment (COA) data, such as                                                                                    |                                        |
|   | x Patient reported outcome (PRO)                                                                                                     | Section 7.2.1.1<br>Appendix 13.3       |
|   | □ Observer reported outcome (ObsRO)                                                                                                  |                                        |
|   | x Clinician reported outcome (ClinRO)                                                                                                | Section 7.2.1.1<br>Appendix 13.3       |
|   | □ Performance outcome (PerfO)                                                                                                        |                                        |
|   | □ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.) |                                        |
|   | □ Patient-focused drug development or other stakeholder meeting summary reports                                                      |                                        |
|   | □ Observational survey studies designed to capture patient experience data                                                           |                                        |
|   | □ Natural history studies                                                                                                            |                                        |

NDA/BLA Multi-disciplinary Review and Evaluation for NDA 210566  
 TRADENAME (halobetasol propionate) foam, 0.05%

|                          |                                                                                                         |                                                                                 |  |
|--------------------------|---------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|--|
| <input type="checkbox"/> | <input type="checkbox"/>                                                                                | Patient preference studies (e.g., submitted studies or scientific publications) |  |
|                          | <input type="checkbox"/>                                                                                | Other: (Please specify)                                                         |  |
| <input type="checkbox"/> | Patient experience data that were not submitted in the application, but were considered in this review: |                                                                                 |  |
|                          | <input type="checkbox"/>                                                                                | Input informed from participation in meetings with patient stakeholders         |  |
|                          | <input type="checkbox"/>                                                                                | Patient-focused drug development or other stakeholder meeting summary reports   |  |
|                          | <input type="checkbox"/>                                                                                | Observational survey studies designed to capture patient experience data        |  |
|                          | <input type="checkbox"/>                                                                                | Other: (Please specify)                                                         |  |
| <input type="checkbox"/> | Patient experience data was not submitted as part of this application.                                  |                                                                                 |  |

## 2 Therapeutic Context

### Analysis of Condition

Psoriasis is a common, chronic, immune-mediated skin disorder. The characteristic lesion is a sharply demarcated scaly, erythematous plaque with scale, and the plaques may be localized or widespread in distribution symmetrically distributed. These plaques commonly involve the extensor surfaces of the extremities, but may present anywhere from the scalp to the soles of the feet. The natural history of psoriasis is chronic with intermittent remissions. A diagnosis of psoriasis can typically be made by history and physical examination, though skin biopsy can provide confirmation if needed.

The extent of body surface area affected may vary from 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.

The prevalence of psoriasis in the US is approximately 2-3 %, of which an estimated 20% have moderate to- severe disease.

### 2.2. Analysis of Current Treatment Options

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 includes those listed in Table 2Error! Reference source not found. below:

**Table 2: Summary of Treatment Relevant to the Proposed Indication for Plaque Psoriasis**

| Product Class<br>Corticosteroid           |                                                                     |                                                                                                                                |                                                                                                                                                                                                                                              |                                                                                                                                                                |
|-------------------------------------------|---------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Example Product /year approved            | Relevant Indication*                                                | Dosage & Admin                                                                                                                 | Efficacy Information                                                                                                                                                                                                                         | Important Safety and Tolerability Issues                                                                                                                       |
| Olux E (clobetasol propionate) Foam/ 2007 | CSRD (one trial was done in mild to moderate plaque-type Psoriasis) | Apply a thin layer twice daily. Treatment should be limited to 2 consecutive weeks and patients should not use greater than 50 | In a randomized study of subjects 12 years of age and older with mild to moderate plaque psoriasis, 253 subjects were treated with Olux-E Foam and 123 subjects were treated with Vehicle Foam. 41 of 253 subjects (16%) treated with Olux-E | Use in pediatric patients under 12 years of age is not recommended because of numerically high rates of hypothalamic-pituitary-adrenal (HPA) axis suppression. |

NDA/BLA Multi-disciplinary Review and Evaluation for NDA 210566  
 TRADENAME (halobetasol propionate) foam, 0.05%

|                                                                                                                                                                                                                                  |                     | grams per week                  | Foam compared with 5 of 123 (4%) treated with Vehicle Foam achieved treatment success. Treatment success was defined by an Investigator's Static Global Assessment (ISGA) score of clear (0) or almost clear (1) with at least 2 grades improvement from baseline, scores of none or faint/minimal (0 or 1) for erythema and scaling, and a score of none (0) for plaque thickness. |                                                     |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|---------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|
| *Some corticosteroids are indicated for the "treatment (or relief) of inflammatory and pruritic manifestations of moderate to severe corticosteroid-responsive dermatoses (CSR), which is inclusive of the psoriasis indication. |                     |                                 |                                                                                                                                                                                                                                                                                                                                                                                     |                                                     |
| Product Class<br>Synthetic vitamin D3 derivative                                                                                                                                                                                 |                     |                                 |                                                                                                                                                                                                                                                                                                                                                                                     |                                                     |
| Example Product /year approved                                                                                                                                                                                                   | Relevant Indication | Dosage & Admin                  | Efficacy Information                                                                                                                                                                                                                                                                                                                                                                | Important Safety and Tolerability Issues            |
| Dovonex (Calcipotriene cream)/ 1996                                                                                                                                                                                              | plaque psoriasis    | Apply a thin layer twice daily. | Adequate and well-controlled trials have demonstrated improvement usually beginning after 2 weeks of therapy. This improvement continued with approximately 50% of patients showing at least marked improvement in the signs and symptoms of psoriasis after 8 weeks of therapy, but only approximately 4% showed complete clearing.                                                | Reversible elevation of serum calcium has occurred. |
| Product Class<br>Synthetic vitamin D3 derivative/corticosteroid combination product                                                                                                                                              |                     |                                 |                                                                                                                                                                                                                                                                                                                                                                                     |                                                     |
| Example Product /year                                                                                                                                                                                                            | Relevant            | Dosage                          | Efficacy Information                                                                                                                                                                                                                                                                                                                                                                | Important Safety and                                |

NDA/BLA Multi-disciplinary Review and Evaluation for NDA 210566  
 TRADENAME (halobetasol propionate) foam, 0.05%

| approved                                                               | Indication                                             | & Admin                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Tolerability Issues                                                                                                                                                                                                               |
|------------------------------------------------------------------------|--------------------------------------------------------|-----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Taclonex (Calcipotriene and betamethasone dipropionate) Ointment/ 2006 | plaque psoriasis in patients 12 years of age and older | Use once daily for up to 4 weeks. | <p>1603 subjects with mild to very severe plaque psoriasis on trunk and limbs were treated once daily for 4 weeks. Subjects were randomized to one of four treatment arms: Taclonex Ointment, calcipotriene hydrate 50 mcg/g in the same vehicle, betamethasone dipropionate 0.64 mg/g in the same vehicle, and vehicle alone. Treatment effect was 48%, 16.5%, 23.3% and 7.6%, respectively.</p> <p>Efficacy was assessed as the proportion of subjects with absent or very mild disease according to the Investigator's Global Assessment of Disease Severity at end of treatment (4 weeks).</p> | <p>Hypercalcemia and hypercalciuria and HPA axis suppression have been observed.</p> <p>Patients ages 12 to 17 years should not use more than 60 g per week. Treatment of more than 30% body surface area is not recommended.</p> |
| Product Class<br>Retinoid                                              |                                                        |                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                   |
| Example Product /year approved                                         | Relevant Indication                                    | Dosage & Admin                    | Efficacy Information                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Important Safety and Tolerability Issues                                                                                                                                                                                          |
| Tazorac (tazarotene cream) 0.05%, 0.1%/ 2000                           | plaque psoriasis                                       | Apply a thin film once daily.     | Improvements in plaque elevation, scaling, and erythema were generally significantly greater with tazarotene 0.05% and 0.1% than with vehicle. The number of patients with none, minimal or mild overall disease was significantly greater with tazarotene 0.05%                                                                                                                                                                                                                                                                                                                                   | Retinoids may cause fetal harm when administered to a pregnant woman.                                                                                                                                                             |

|  |  |  |                      |  |
|--|--|--|----------------------|--|
|  |  |  | and 0.1% vs vehicle. |  |
|--|--|--|----------------------|--|

Systemic treatments may be required for more widespread, chronic, or advanced disease and/or where topical therapy may not be sufficient or appropriate.. These include adalimumab, etanercept, infliximab (all TNF blockers), secukinumab and ixekizumab, IL 17 inhibitors, brodalumab, an IL 17 receptor antagonist, and ustekinumab, an IL12/23 inhibitor, guselkumab, and tildrakizumab. Other approved systemic psoriasis therapies include acitretin, methotrexate, cyclosporine, and apremilast. Phototherapy, either PUVA (UVA light combined with the psoralen methoxsalen) or UVB light therapy (narrow or broadband) is also an appropriate first line or adjunctive treatment for moderate to severe psoriasis patients.

### 3 Regulatory Background

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#### 3.1. U.S. Regulatory Actions and Marketing History

Halobetasol propionate is a corticosteroid, (b) (4)

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). A lotion dosage form was approved for “the topical treatment of plaque psoriasis in patients 18 years of age and older” on November 6, 2015 (Ultravate® lotion; NDA 208183). In addition to the innovators, several generic cream and ointment products are currently marketed.

The applicant’s foam represents a new dosage form for this moiety and is not currently marketed in the United States.

#### 3.2. Summary of Presubmission/Submission Regulatory Activity

The applicant opened IND 107302 on 11/25/2009 with a protocol for a Phase 1 single-point vasoconstriction assay. During the development of HBP Foam, the Sponsor met with the Agency on several occasions to discuss the clinical program (VCA, HPA axis suppression, and Phase 2). A pre-IND meeting was not held. The key meetings and relevant meeting points are as follows:

- An End-of-Phase 2 Meeting was held on Aug 21, 2013

- o trial design is acceptable
  - o primary endpoint, defined as the proportion of subjects who achieved “treatment success,” (defined as IGA score 0 to 1 with at least a 2-grade decrease in severity score relative to baseline) is acceptable
  - o recommend revising the IGA scale to a 5-point scale where the grades are non-overlapping and sufficiently defined to appropriately and unambiguously represent each severity grade on the scale
  - o the spectrum and timing of safety evaluation appears adequate
  - o the proposal to actively assess application site reactions for teleangiectasia, skin atrophy, burning/stinging and folliculitis and report them as mild, moderate or severe is acceptable Based on the report of 270-700 nm Wavelength Scan of Halobetasol Propionate foam 0.05% dated 7/5/2013, it is appropriate to request the waiver from conducting phototoxicity and photoallergenicity testing in humans
  - o irritancy potential of the final to-be-marketed formulation should be established in humans. Cumulative irritation testing can be combined with sensitization testing in a single trial
- SPA Agreement Letters 13 May 2014 and 21 May 2014
  - o agree with the general design of the trials 305 and 306
  - o agree with the category descriptions of the proposed IGA scale
  - o agree with the primary endpoint
  - o agree that the secondary efficacy endpoints defined as the proportion of subjects rated as a “treatment success” at Day 15 for each of the clinical signs of psoriasis (scaling, erythema, and plaque elevation) are appropriate. Utility for eventual product labeling will be determined during review of the complete NDA application proposed
  - o statistical analysis plan is generally acceptable, but the protocol should pre-specify the complete details on how the randomization will be carried out including block size
  - o recommend that you consider an alternate multiplicity testing strategy that uniformly controls the Type I error rate
- PSP Amended Agreement Letter 09 Feb 2017
  - o includes a partial waiver from conducting clinical studies in the pediatric population (birth to 11 years of age) and the deferral of a planned Hypothalamic-Pituitary-Adrenal (HPA)/pharmacokinetics (PK) postmarketing study (in children 12 to <17 years of age)
  - o Refer to section 9 Pediatrics for a detailed discussion of the regulatory history of pediatric development
- Pre-NDA Meeting: June 14, 2017
  - o the studies proposed for NDA submission appear reasonable for the filing of an NDA
  - o vasoconstrictor assay (study 122-0551-101) was conducted with an older

formulation and the results were inconclusive. Provide a justification in the NDA to support applicability of this study.

- o Include with the Integrated Summary of Safety (ISS) a pooled analyses that does not include Study 202 and Study 203.

The applicant has obtained a right-of-reference to the ULTRAVATE Cream and Ointment NDAs (19-967 [cream] and 19-968 [ointment]) and is submitting this NDA via the 505(b)(1) registration path.

## **4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety**

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### **4.1. Office of Scientific Investigations (OSI)**

The overall quality of the clinical information contained in this submission is adequate. The Division did not request that the Office of Scientific Investigations (OSI) conduct clinical inspections. A review of the data did not identify issues for inspection of any specific clinical study sites. .

### **4.2. Product Quality**

The complete OPQ review is archived in the CDER Informatics Platform. Final recommendation for approval is pending final agreement on labeling.

The executive summary, by Dr. Yichun Sun, concludes,

“The applicant of this NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug substance and drug product. The facility review ... team from the Office of Process and Facility (OPF) has issued an “Acceptable” recommendation for the facilities involved in this application. The consult review on the device component of the container closure system of the drug product has been conducted .....by the Office of Device Evaluation, Center for Devices and Radiological Health (CDRH). The ..... device constituent part of this combination product is recommended for approval by CDRH. However, the issues on labels/labeling are not completely resolved at this time.”

Novel excipients: No.  
Any impurity of concern: No.

### **4.3. Clinical Microbiology**

Not applicable.

### **4.4. Devices and Companion Diagnostic Issues**

Not applicable.

## 5 Nonclinical Pharmacology/Toxicology

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### 5.1. Executive Summary

The applicant has developed a novel foam formulation of halobetasol propionate (HBP) as a topical treatment for (b) (4) plaque psoriasis. They have obtained a letter of authorization for Ultravate Cream and Ultravate Ointment. Therefore, this NDA is a 505(b)(1) NDA from a Pharmacology/Toxicology perspective because the applicant has obtained right-of-reference to all the nonclinical studies conducted to support approval of Ultravate Cream and Ultravate Ointment and has conducted additional nonclinical studies to support the safety of their new HBP foam, 0.05% formulation. The active ingredient, HBP, is well characterized and the concentration (0.05%) is known to be safe and effective as an anti-inflammatory and antipruritic agent in different topical dosage forms. HBP is a super high potency corticosteroid, known to cause hypothalamic-pituitary adrenal axis suppression and immunosuppression.

The cause of psoriasis is not known, but is believed to involve external or environmental factors that initiate an exaggerated inflammatory response in the skin of genetically predisposed individuals. Following the initial insult an innate immune response is triggered which results in an increase in the production of numerous cytokines. These cytokines promote the accumulation of inflammatory cells in the skin and keratinocyte proliferation (adaptive or acquired immune response). Keratinocytes produce additional inflammatory cytokines, exaggerating the local inflammatory response in the skin of susceptible individuals.

The systemic toxicity of HBP has been previously addressed in studies to support the approval of Ultravate Cream (NDA 19967, approved 12-27-1990) for which the applicant has obtained the right-of-reference. (b) (4)

(b) (4). Local toxicity associated with topical use of HBP foam (0.05%) was addressed in a 4-week repeat-dose dermal minipig study with separate studies for acute ocular and dermal irritation. In support of a potential dermal carcinogenicity study, HBP foam (0.005%, 0.01%, or 0.05%) was applied once daily to rats for 13 weeks. Reduced body weight and histopathological changes resulting from test article-induced immunosuppression occurred in males and females at  $\geq 0.005\%$ . Therefore, the carcinogenicity study was waived since rats would not be able to tolerate long term topical treatment with HBP foam.

HBP Foam, 0.05% is approvable from a pharmacology/toxicology perspective.

## 5.2. Referenced NDAs, BLAs, DMFs

IND 107302, indicated for (b) (4) plaque psoriasis

NDA 19967, Ultravate® Cream, 0.05%, approved 12-27-1990, Ranbaxy

NDA 19968, Ultravate® Ointment, 0.05%, approved 12-17-1990, Ranbaxy

The sponsor has provided a letter authorizing FDA to refer to the relevant data for both NDA 19967 and NDA 19968 to support the current NDA.

DMF (b) (4) halobetasol propionate. The sponsor has provided a letter authorizing FDA to refer to all pages of the DMF from the holder of the DMF, (b) (4)

## 5.3. Pharmacology

### Primary pharmacology

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

### Secondary Pharmacology

Systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Manifestations of Cushing's syndrome, hyperglycemia and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on treatment.

### Safety Pharmacology

No safety pharmacology studies have been conducted with HBP foam, 0.05%. However, no adverse effects on the auditory or cardiovascular systems were observed in a 3-month oral toxicity study performed in dogs (80-5264). In the 28-day dermal minipig study (1246-009), no effects on ECG parameters were observed with HBP foam, 0.05 and 0.15% when applied twice daily to 10% body surface area.

## 5.4. ADME/PK

| Type of Study                                                          | Major Findings                                       |
|------------------------------------------------------------------------|------------------------------------------------------|
| Halobetasol propionate 0.05% and 0.15% foams: a 4-week dermal toxicity | <u>Minipig</u><br>All of the plasma HBP samples were |

| Type of Study                          | Major Findings                                     |
|----------------------------------------|----------------------------------------------------|
| study in Gottingen minipigs (1246-009) | below the limit of quantitation (BLQ<0.500 ng/mL). |

## 5.5. Toxicology

### 5.5.1. General Toxicology

Study title/ number: Halobetasol propionate 0.05% and 0.15% foams: a 4-week dermal toxicity study in Gottingen minipigs (1246-009)

Based on the long history of clinical use of halobetasol propionate, a 4-week dermal toxicity study in Gottingen Minipigs was conducted with only two doses instead of a standard 9-month repeat-dose toxicity study. Twice daily dermal administration of halobetasol propionate foam at concentrations of 0.05% or 0.15% (0.15, 0.46 mg/kg/day) for 28 or 29 days produced changes consistent with dermal application of corticosteroids with no new or unique toxicities occurring. Observations included minimal decreases in body weight, adrenal gland atrophy, bone marrow hypocellularity, lymphoid depletion, and hepatocellular hypertrophy. Minimal skin atrophy was observed in both treated and untreated skin regions and was characterized by a diffuse, generalized thinning of the epidermis with reduced size and or numbers of hair follicles and associated adnexa. All plasma samples were below the limit of quantitation (<0.500 ng/mL) and no toxicokinetic evaluation could be performed.

Study title/ number: A 13-week study of halobetasol propionate foam by dermal administration in rats (20069816)

Dermal administration of halobetasol propionate foam once a day to Sprague Dawley rats for up to 92 days at concentrations of 0.005%, 0.01%, or 0.05% (0.011, 0.022, 0.11 mg/kg/day) resulted in 1 early death at 0.05%, marked reductions in body weight gain with corresponding reductions in feed consumption, changes in hematology and clinical chemistry parameters, gross pathology changes, organ weight differences, and histopathology changes at  $\geq 0.005\%$  in males and females. The findings observed following topical administration were consistent with corticosteroid exposure with no new or unique toxicities occurring. Based on these results, a maximum tolerated dose could not be determined in male or female rats. The results of this study were

the basis for granting a waiver for conduct of a dermal carcinogenicity study with halobetasol propionate foam. Refer to Section 5.5.3.

### **5.5.2. Genetic Toxicology**

The sponsor has obtained the right of reference to the genetic toxicology studies conducted to support Ultravate® Cream, 0.05% (NDA 19967). The following information appears in the Mutagenesis section of the label for Ultravate® Cream, 0.05% (NDA 19967).

Positive mutagenicity effects were observed in two genotoxicity assays. Halobetasol propionate was positive in a Chinese hamster micronucleus test, and in a mouse lymphoma gene mutation assay in vitro. In other genotoxicity testing, halobetasol propionate was not found to be genotoxic in the Ames/Salmonella assay, in the sister chromatid exchange test in somatic cells of the Chinese hamster, in chromosome aberration studies of germinal and somatic cells of rodents, and in a mammalian spot test to determine point mutations.

### **5.5.3. Carcinogenicity**

Data from a 13-week rat dermal study (20069816) showed that HBP foam at concentrations of 0.005%, 0.01%, or 0.05% (0.011, 0.022, 0.11 mg/kg/day) caused marked immunosuppression resulting in the development of opportunistic infections as well as significant toxicity in multiple organ systems. The low dose used in this dermal rat toxicity study was 10-fold lower than the clinical concentration of halobetasol propionate foam. Given the decreases noted in white blood cell counts, the decreases in body weights, the effect on immune system organ weights, and corresponding histopathological effects on immune system organs, a 2-year dermal carcinogenicity would not be tolerated in rats and the sponsor's waiver request for conduct of the 2-year dermal carcinogenicity study for HBP foam was granted. The results of the 13-week dermal rat study should be incorporated into Section 13.1 of the HBP foam label.

Long-term animal studies have not been performed to evaluate the carcinogenic potential of halobetasol propionate.

### **5.5.4. Reproductive and Developmental Toxicology**

The sponsor has obtained the right of reference to the fertility and embryofetal development studies conducted to support Ultravate® Cream, 0.05% (NDA 19967). The following information appears in the corresponding sections of the label for Ultravate® Cream, 0.05% (NDA 19967).

(b) (4)

Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. Halobetasol propionate has been shown to be teratogenic in SPF rats and chinchilla-type rabbits when given systemically during gestation at doses of 0.04 to 0.1 mg/kg in rats and 0.01 mg/kg 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 rats.

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

*Reviewer's comment: It is unclear how the above multiples of human exposure were calculated, but they appear to be incorrect based on body surface area comparisons. If the multiples of human exposure are calculated based on body surface area comparisons (see below), then all the multiples are much less than one. Since there is minimal systemic exposure in humans after topical administration of HBP, 0.05% foam, then no comparisons of animal exposure with human exposure may be calculated.*

(b) (4)

Multiples of human exposure calculations based on body surface area comparison

Maximum recommended human dose: 50 gram HBP foam (0.05 % HBP) /week

$50 \text{ g/week} \times 0.5 \text{ mg/g} = 25 \text{ mg/week HBP}$

$25 \text{ mg/7 days} = 3.57 \text{ mg/day}$

$3.57 / 60 \text{ kg} = 0.06 \text{ mg/kg}$

Rat LOAEL in embryofetal development study (EFD)= 0.04 mg/kg

Human equivalent dose (HED):  $0.04 \text{ mg/kg} \times 6/37 = 0.0065 \text{ mg/kg}$

Multiple of clinical dose:  $0.0065 / 0.06 = 0.1$

Rat high dose in EFD= 0.1 mg/kg

HED:  $0.1 \text{ mg/kg} \times 6/37 = 0.016 \text{ mg/kg}$

Multiple of clinical dose:  $0.016 / 0.06 = 0.27$

Rabbit LOAEL in EFD = 0.01 mg/kg

HED:  $0.01 \text{ mg/kg} \times 12/37 = 0.003 \text{ mg/kg}$

Multiple of clinical dose:  $0.003 / 0.06 = 0.05$

#### **5.5.5. Other Toxicology Studies**

Study title/ number: Primary eye irritation study in rabbits (0421LT28.004)

The applicant has performed a primary eye irritation study in rabbits. Under the conditions of this study halobetasol propionate foam 0.05% was found to be slightly irritating in rabbits (Maximum mean Total Score = 18.7 at 1 hour and complete resolution of irritation by 72 hours).

Study title/ number: Primary dermal irritation study in rabbits (042LT28.012)

The applicant has performed a primary dermal irritation study in rabbits. Under the conditions of this study halobetasol propionate glycol foam and halobetasol propionate alcohol foam were not considered to be irritants when applied topically to rabbits.

Study title/ number: Delayed contact hypersensitivity in guinea pigs (0424GT28.005)

The 0.05% halobetasol propionate foam was tested for delayed contact hypersensitivity in guinea pigs (Buehler Method). Ten guinea pigs per sex were treated with the test article once a week for 3 weeks with a six-hour occluded dermal application of halobetasol propionate foam 0.05% in an attempt to induce sensitization at subsequent challenge. An additional 5 animals per sex were treated in the same manner with halobetasol propionate foam placebo. A positive control group of 3 animals per sex was induced with a known dermal sensitizer: 1-chloro-2,4-dinitrobenzene (DNCB) in 80% ethanol.

Fourteen days after the last induction, all animals were dermally challenged with occluded applications at naïve test sites. Animals in both the test article and vehicle groups were challenged with halobetasol propionate 0.05% foam and halobetasol propionate foam placebo. Animals in the positive control group were challenged with DNCB (0.2% in acetone). On the day following the challenge, all animals were depilated and approximately three hours later were scored for dermal irritation (24 hour). Scoring was repeated at 48 hours.

There were no signs of systemic toxicity and all animals gained weight during the study. Halobetasol propionate 0.05% foam did not elicit a delayed contact hypersensitivity

response in guinea pigs. The positive control group, induced and challenged with DNCB, exhibited the anticipated positive responses at challenge, indicating that the methods employed in the study were valid.

## 5.6. Labeling

Revisions to the applicant's proposed wording for the nonclinical and related sections of the label are provided below. The clinical reviewer will determine appropriate modifications to the clinical portions of Section 8 of the label. With the exception of titles which are underlined based on the label template, nonclinical recommendations are shown as underlined text. It is recommended that the underlined wording be inserted into and the ~~strikeout~~ wording be deleted from the HBP foam, 0.05% label text. A clean copy of these revised labeling sections is provided in Section 13.3 Appendices.

### HIGHLIGHTS OF PRESCRIBING INFORMATION INDICATIONS AND USAGE

TRADENAME is a corticosteroid indicated for the topical treatment of plaque psoriasis in patients eighteen (18) years of age and older.

#### 8 Use in Specific Populations

##### 8.1 Pregnancy

##### Risk Summary

There are no available data on (b) (4) TRADENAME use in pregnant women to inform of (b) (4) drug-associated risk (b) (4) for (b) (4) adverse developmental outcomes. In animal reproduction studies, increased malformations, including cleft palate and omphalocele, were observed after oral administration of halobetasol propionate (b) (4) during organogenesis to pregnant rats (b) (4)

(b) (4) No comparisons of animal exposure with human exposure may be calculated due to minimal systemic exposure in humans after topical administration of TRADENAME [see Clinical Pharmacology (12.3)].

##### Data

##### *Animal Data*

Halobetasol propionate has been shown to (b) (4) cause malformations in rats and rabbits when given (b) (4) orally during organogenesis at doses of 0.04 to 0.1 mg/kg/day in rats and 0.01 mg/kg/day in rabbits. (b) (4)

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.

## 12 Clinical Pharmacology

### 12.1 Mechanism of Action

(b) (4)

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

## 13 Nonclinical Toxicology

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of halobetasol propionate.

In a 90-day repeat-dose toxicity study in rats, topical administration of ~~TRADENAME~~ halobetasol propionate foam at dose concentrations from 0.005% to 0.05% or from 0.011 to 0.11 mg/kg/day of halobetasol propionate resulted in a toxicity profile consistent with long-term exposure to corticosteroids including adrenal atrophy, histopathological changes in several organ systems indicative of severe immune suppression, and opportunistic fungal and bacterial infections. A no observable adverse effect level (b) (4) could not be determined in this study. Although the clinical relevance of the findings in animals to humans is not clear, sustained glucocorticoid-related immune suppression may increase the risk of infection and possibly the risk of carcinogenesis.

Halobetasol propionate was not found to be genotoxic in the Ames/Salmonella assay, in the Chinese hamster CHO/HGPRT assay, in the mouse micronucleus test, in the sister chromatid exchange test in somatic cells of the Chinese hamster, or in the chromosome aberration test in somatic cells of Chinese hamsters. Positive mutagenicity effects were observed in two genotoxicity assays: Chinese hamster nuclear anomaly test and mouse lymphoma gene mutation assay in vitro.

Studies in the rat following oral administration at dose levels up to (b) (4) 0.05 mg/kg/day indicated no impairment of fertility or general reproductive performance.

## 6 Clinical Pharmacology

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### 6.1. Executive Summary

The purpose of this NDA is to seek the approval for an alternative dosage form (i.e., foam) for halobetasol propionate (HBP) to treat plaque psoriasis. Halobetasol propionate, a super-potent corticosteroid, is currently being marketed in three formulations: cream, ointment, and lotion under the brand name Ultravate®. All marketed HBP products including generics contain HBP 0.05% and the proposed new product is of the same strength. Similar to other topical corticosteroids, HBP has anti-inflammatory and antipruritic activity. The mechanism of action of HBP is thought to be by the induction of phospholipase A2 inhibitory proteins which are related to modulation of the biosynthesis of inflammatory mediators such as prostaglandins and leukotrienes.

The applicant conducted a maximal use pharmacokinetic (PK) and hypothalamic-pituitary- adrenal (HPA) axis suppression study in adult subjects with psoriasis following twice daily application of the HBP 0.05% foam for 2 weeks. The results indicated that 24% of subjects who received HBP 0.05% foam manifested an HPA axis suppression which returned to normal during 4-8 week follow-up period and the mean  $\pm$  SD  $C_{max}$  and AUC on day 14 were  $199.7 \pm 217.3$  pg/mL and  $1434.9 \pm 1310.6$  pg·h/mL, respectively.

#### 6.1.1. Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds NDA 210566 acceptable, provided that the applicant adequately addresses the labeling comments.

#### 6.1.2. Post-Marketing Requirements

Conduct a maximal use pharmacokinetic (PK) and HPA axis suppression study in subjects 12 to less than 17 years of age with plaque psoriasis.

#### 6.1.3. Post-Marketing Commitment

Conduct a single point vasoconstrictor assay with adequate bracketing using visual assessment to determine the topical corticosteroid potency classification of your commercial formulation.

## 6.2. Summary of Clinical Pharmacology Assessment

This submission includes study reports from seven clinical studies which included two clinical pharmacology studies as follows:

- Phase 1 vasoconstrictor assay (VCA) study
- Phase 2 maximal use PK/HPA axis suppression study

Phase 1 VCA study did not use the to-be-marketed formulation and furthermore, the results of the current study failed to show significant difference between the reference products of Class I and Class III making the study results, inconclusive. As a result of this, a post-marketing commitment (PMC) will be issued to conduct a VCA study with final commercial formulation to identify the potency class of the HBP foam product using visual assessment as a primary end-point. The PMC is being requested because the VCA information is being used by the physicians as an initial guide to narrow down their prescribing choices from the realm of available topical corticosteroids and this information can be submitted as PMC.

The Phase 2 PK/HPA study demonstrated that the systemic exposure of HBP was quantifiable in 23 subjects and systemic concentrations were at steady state by Day 14. The mean  $\pm$  SD  $C_{\max}$  and AUC on Day 14 were  $199.7 \pm 217.3$  pg/mL and  $1434.9 \pm 1310.6$  pg·h/mL, respectively and 6 out of 25 subjects (24%) with plaque psoriasis developed a HPA axis suppression by the end of treatment (i.e., Day 14).

The incident of HPA axis suppression in adults was sufficiently low to allow for further assessment in pediatric subjects, which will be requested as a post marketing requirement (PMR). Hence, assessment of maximal use PK and HPA axis suppression is being requested in pediatric subjects from 12 to less than 17 year old as a PMR. This study is being requested as a PMR because clinical experience in adults was needed to support pediatric assessment for HBP foam as currently approved HBP products are considered in the range of potent to super-potent topical corticosteroids.

### 6.2.1. Pharmacology and Clinical Pharmacokinetics

Study 122-0551-202 (N = 25) was conducted to evaluate HPA axis suppression potential and PK profile of HBP foam in subjects with moderate to severe plaque psoriasis under maximal use conditions. The dose was limited to approximately 50g HBP foam, 0.05% foam per week. Six out of 25 (24%) subjects exhibited a decreased serum cortisol level  $\leq 18$  mcg/dL indicating a HPA-axis suppression at the end of treatment. All six subjects had cortisol level returned to normal range at the follow-up visit at 4 – 8 weeks post last dose. Systemic concentrations of HBP were at steady state by Day 14 and were quantifiable in 23 subjects. The mean  $\pm$  SD  $C_{\max}$  and AUC on Day 14 were  $199.7 \pm 217.3$  pg/mL and  $1434.9 \pm 1310.6$  pg·h/mL, respectively. Topical application of twice daily of the HBP foam did not elicit any systemic drug accumulation during the treatment period of two weeks. The study results suggest a trend that

showed higher systemic exposure of HBP in subjects with HPA axis suppression although data variability was too high to draw any statistical significance of this finding. Furthermore, there was also a trend indicating higher dose producing HPA axis suppression and the dosing limit of 50g/week in the label is justified.

### **6.2.2. General Dosing and Therapeutic Individualization**

#### **General Dosing**

The applicant's proposed dosing regimen of the HBP foam, 0.05% is twice daily to be applied topically for up to two weeks and maximum recommended dose is up to (b) (4) 50g per week. This dose limitation of 50g/week and duration of up to 2 weeks is identical with the other approved and marketed HBP topical products such as Ultravate® cream, ointment and lotion.

#### **Therapeutic Individualization**

The applicant did not conduct studies for therapeutic individualization of the proposed HBP 0.05% foam product.

#### **Outstanding Issues**

The Applicant's VCA study data failed to demonstrate statistically significant difference between Class I and Class III reference products due to which the study results became inconclusive towards identifying the potency classification of their product. Furthermore, the formulations used in the VCA study did not include the final to-be-marketed formulation.

Due to the aforementioned reasons, the Agency cannot include potency class information of the proposed HBP 0.05% foam in the product label. The Agency considers the potency classification of topical corticosteroid products to serve as an initial guide to prescribers in helping them narrow down their choice of treatment from the range of topical corticosteroids that are available. Based on this, the Agency recommends the applicant to conduct another single point VCA study using the commercial formulation with adequate bracketing as a PMC.

In the maximal use PK study the applicant studied subjects with at least 15% body surface area (BSA) involved. The Agency recommends at least 20% of BSA involved in adult subjects with psoriasis. The mean BSA in the maximal use study was 18.4% and this is acceptable because at the time of study protocol review 15% BSA was considered reasonable. Later the minimum % BSA recommended was at least 20% in adult subjects with psoriasis.

### 6.3. Comprehensive Clinical Pharmacology Review

#### 6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Dermal penetration of HBP following topical application of HBP foam formulations were evaluated in non-clinical studies using rats and minipigs and in clinical pharmacology studies. Non-clinical pharmacology studies using rats demonstrated rapid dermal penetration of HBP following topical application of foam formulations of HBP in 0.005 % – 0.05 % strength. In contrast, a study in minipigs did not demonstrate the detectable levels of HBP following twice daily topical application of HBP foam formulations. Non-clinical oral PK studies demonstrated that HBP was widely distributed to tissues, highly metabolized and primarily excreted via the feces.

Initial foam formulations tested in non-clinical studies did not include the final to-be-marketed formulation. Subsequently, the applicant (b) (4)

in the final foam formulation. The Agency agreed that the minor change was acceptable (*End of Phase 2 meeting minutes, Dated August 21, 2013*). Subsequently, the applicant conducted a 13-week dermal toxicity study in rats using the final to-be-marketed foam formulation

HBP is not a new molecular entity. This product is a new formulation (foam) at the same strength (0.05%) as the other approved HBP products (i.e., cream, ointment and lotion). Furthermore, the dosing regimen and indication is also similar to other approved halobetasol products. The sponsor has conducted clinical trials and obtained safety and efficacy data of this product and the HPA axis suppression potential under maximal use conditions was 24%; which was sufficiently low to allow for further assessment in pediatric subjects as a PMR (see 7 Statistical and Clinical and Evaluation for further information on safety and efficacy of this product). All this information, would support the risk-benefit of this product and the foam formulation will serve as a new dosage form providing patients with more treatment choices. The HBP level in human plasma was determined using a validated liquid chromatographic-mass spectrometry (LC-MS/MS) method. The linear concentration range was 20 pg/mL to 4000 pg/mL HBP with performance characteristics as shown in Table 3. The HBP standards were stable in human plasma for minimum 532 days at -20°C and this long-term stability duration was adequate to support the storage stability of the PK plasma samples. The bioanalytical method for cortisol was well validated and the long-term storage stability data supported the duration of storage for minimum 240 days below -16°C of the serum cortisol samples.

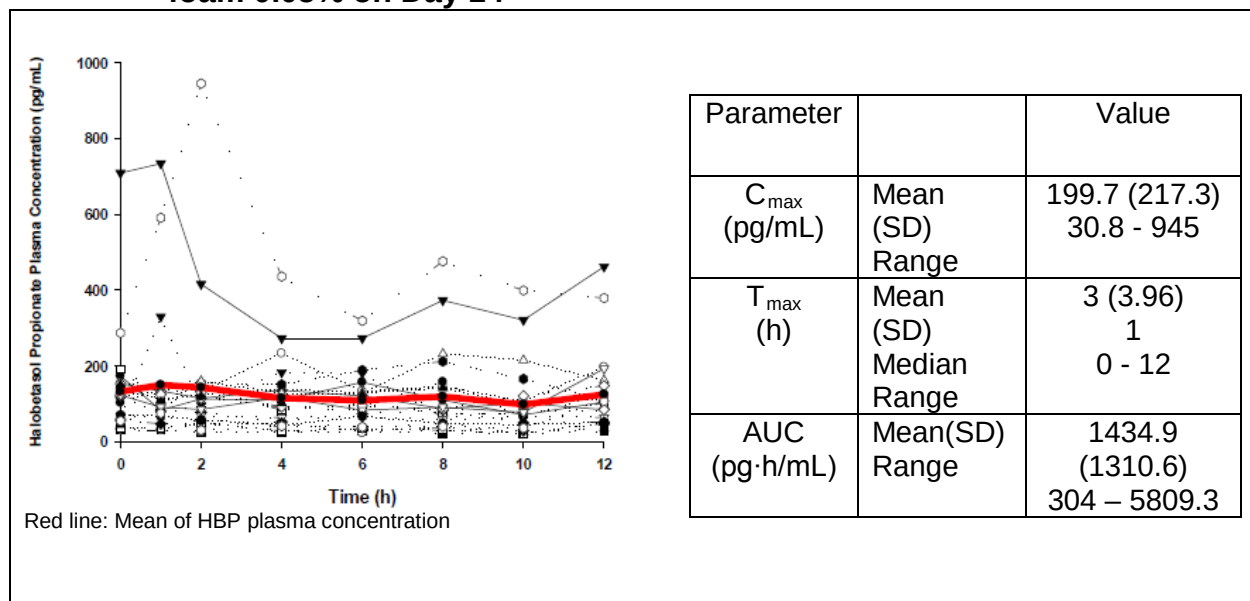
**Table 3: Precision and accuracy of the bioanalytical method (Source: Table 2 in Summary of Biopharm Studies and Associated Analytical Methods)**

|  |
|--|
|  |
|--|

| Variable              | Range (% of relative error) | N     |
|-----------------------|-----------------------------|-------|
| Inter-Assay Precision | 7.2 to 11.5                 | 17-18 |
| Inter-Assay Accuracy  | -1.5 to 3.4                 | 17-18 |
| Intra-Assay Precision | 3.9 to 8.6                  | 6     |
| Intra-Assay Accuracy  | 3.0 to 7.1                  | 6     |

The clinical PK/HPA study results indicated that the systemic concentrations on Day 14 were at steady state. The mean 12-hour post-dose HBP concentration differed by less than 9 % between trough blood collections (i.e., Days 8, 14, and 15). At steady state, the mean  $\pm$  SD peak plasma concentration ( $C_{max}$ ) of  $199.7 \pm 217.3$  pg/mL was reached at a median of 1 hour post-dose ( $T_{max}$ ). The  $C_{max}$  of 23 subjects ranged from 30.8 pg/mL to 945 pg/mL exhibiting a high inter-subject variability (Figure 1). The mean  $\pm$  SD AUC was  $1434.9 \pm 1310.6$  pg·h/mL.

**Figure 1: Individual subject PK profile on Day 14, mean plasma HBP concentration-time profile (in red) and systemic PK parameters of HBP foam 0.05% on Day 14**



### 6.3.2. Clinical Pharmacology Questions

**Does the clinical pharmacology program provide supportive evidence of effectiveness?**

No. For topical products, PK assessed under maximal use conditions support systemic safety and not efficacy.

**Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?**

Yes. HPA axis suppression was observed in subjects with higher systemic exposure, although the trend was not very clear due to high inter-subject variability. There was also a correlation between the dose and HPA axis suppression which justifies the dosing limitation of 50g/week which is similar to other HBP products that are approved. HPA axis suppression was observed in 24% of adult subjects and was reversible in all the subjects after discontinuing the drug. The incident of HPA axis suppression was sufficiently low to allow for further assessment in pediatric subjects as a PMR.

**Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?**

No. The effect of intrinsic factors on the PK of HBP foam was not evaluated.

**Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?**

Food-drug interactions are not applicable for topical products. Drug-drug interaction was not evaluated.

## **7 Statistical and Clinical and Evaluation**

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### **7.1. Sources of Clinical Data and Review Strategy**

#### **7.1.1. Table of Clinical Studies**

Seven clinical studies have been conducted with Halobetasol Propionate Foam, 0.05% (HBP Foam): two Phase 1, two Phase 2, and three Phase 3 studies. All seven studies were conducted in the US and under IND 107,302. Six of the studies supporting the safety and efficacy of HBP Foam in the treatment of psoriasis are listed in Table 4.

NDA/BLA Multi-disciplinary Review and Evaluation for NDA 210566  
 TRADENAME (halobetasol propionate) foam, 0.05%

**Table 4: Listing of Clinical Trials Relevant to NDA 210566**

| Trial Identity                                           | Trial Design                                                                                          | Regimen/<br>schedule/ route                                                                                                                         | Study Endpoints                                                                                                                                                                                            | No. of<br>subject<br>s<br>enrolle<br>d | Study Population                                                                                                                                                                  |
|----------------------------------------------------------|-------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Controlled Studies to Support Efficacy and Safety</i> |                                                                                                       |                                                                                                                                                     |                                                                                                                                                                                                            |                                        |                                                                                                                                                                                   |
| <b>122-0551-306</b>                                      | Vehicle-controlled, safety and efficacy study, reviewed under a SPA                                   | Subjects applied the randomized test article twice daily for two weeks with a maximum recommended exposure of up to approximately 50 grams per week | Primary efficacy endpoint was the proportion of subjects achieving an IGA "Treatment Success" defined as a score of 0 (clear) or 1 (almost clear) with at least a two-grade improvement measured at Day 15 | 151                                    | Adult subjects with plaque psoriasis, with disease severity defined by a BSA of 2-12% and a baseline Investigator's Global Assessment (IGA) score of at least three (3 =moderate) |
| <b>122-0551-310</b>                                      | Vehicle-controlled, safety and efficacy study with the same study design as the other pivotal studies | Subjects applied the randomized test article twice daily for two weeks with a maximum recommended exposure of up to approximately 50 grams per week | Primary efficacy endpoint was the proportion of subjects achieving an IGA "Treatment Success" defined as a score of 0 (clear) or 1 (almost clear) with at least a two-grade improvement measured at Day 15 | 409                                    | Adult subjects with plaque psoriasis, with disease severity defined by a BSA of 2-12% and a baseline Investigator's Global Assessment (IGA) score of at least three (3 =moderate) |
| <b>122-0551-305</b>                                      | Vehicle-controlled, safety and efficacy                                                               | Subjects applied the randomized test                                                                                                                | Primary efficacy endpoint was the                                                                                                                                                                          | 144                                    | Adult subjects with plaque psoriasis, with disease severity                                                                                                                       |

NDA/BLA Multi-disciplinary Review and Evaluation for NDA 210566  
 TRADENAME (halobetasol propionate) foam, 0.05%

|                                  |                                                                                                                                                       |                                                                                                                             |                                                                                                                                                                          |     |                                                                                                                       |
|----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|-----------------------------------------------------------------------------------------------------------------------|
|                                  | study, reviewed under a SPA                                                                                                                           | article twice daily for two weeks with a maximum recommended exposure of up to approximately 50 grams per week              | proportion of subjects achieving an IGA "Treatment Success" defined as a score of 0 (clear) or 1 (almost clear) with at least a two-grade improvement measured at Day 15 |     | defined by a BSA of 2-12% and a baseline Investigator's Global Assessment (IGA) score of at least three (3 =moderate) |
| <i>Studies to Support Safety</i> |                                                                                                                                                       |                                                                                                                             |                                                                                                                                                                          |     |                                                                                                                       |
| <b>122-0551-202</b>              | Open label, HPA/PK study under maximal use conditions                                                                                                 | Subjects applied twice daily for 2 weeks; max dosage of 60 g/week                                                           | -HPA axis responses to cosyntropin<br>-Plasma concentration of HBP                                                                                                       | 25  | Adult subjects with moderate to severe plaque psoriasis [>15% BSA]                                                    |
| <b>122-0551-203</b>              | Phase 2, double-blind, vehicle-controlled, safety and efficacy study                                                                                  | Subjects applied twice daily for 2 weeks; max dosage of 60 g/week                                                           | Primary efficacy endpoint was the proportion of subjects achieving an Overall Disease Severity Score of 0 (clear) or 1 (almost clear) measured at Day 15                 | 44  | Adult subjects with moderate to severe plaque psoriasis [2-10% BSA]                                                   |
| <b>122-0551-108</b>              | Human Repeat Insult Patch Test (HRIPT) and Cumulative Irritation Test (CIT) study; Double-blind; randomized; vehicle and reference controlled; within | Applied 9 applications of HBP Foam, VEH Foam, and reference controls over 3 weeks under occlusion for 24-72 hr with a 48 hr | Tolerability was evaluated by objective assessments of the application sites. Observed dermal responses were graded                                                      | 245 | Healthy male and female subjects aged 18-65 years                                                                     |

NDA/BLA Multi-disciplinary Review and Evaluation for NDA 210566  
TRADENAME (halobetasol propionate) foam, 0.05%

|  |         |                                          |                                                    |  |  |
|--|---------|------------------------------------------|----------------------------------------------------|--|--|
|  | subject | challenge/re-challenge after 2 week rest | according to the protocol-specified scoring scale. |  |  |
|--|---------|------------------------------------------|----------------------------------------------------|--|--|

### 7.1.2. Review Strategy

#### Data Sources

The sources of data used for the evaluation of the efficacy and safety of halobetasol foam for the proposed indication included final study reports submitted by the applicant, datasets [Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM)] and literature references.

This application was submitted in eCTD format and entirely electronic. The electronic submission including the protocol, the statistical analysis plan (SAP), the clinical study report, SAS transport datasets in legacy, Study Data Tabulation Modal (SDTM), and Analysis Data Model (ADaM) format were in the following network path:

- Original submission: [\\cdsesub1\evsprod\NDA210566\0001\m5\datasets](#)

## **7.2. Review of Relevant Individual Trials Used to Support Efficacy**

### **7.2.1. Pivotal Phase 3 Trials (Trials 306 & 310)**

#### **7.2.1.1. Trial Design and Endpoints**

The applicant conducted two multicenter, randomized, double-blind, vehicle-controlled, parallel-group, pivotal Phase 3 trials (Trials 306 and 310) to evaluate the safety and efficacy of halobetasol propionate (HBP) foam, 0.05%, for the topical treatment of plaque psoriasis. For both trials, the key inclusion criteria that defined the trial population were identical and are as follows:

- Male or non-pregnant female aged 18 years or older
- Have a clinical diagnosis of stable plaque psoriasis involving 2%-12% body surface area (BSA), excluding the face, scalp, groin, axillae and other intertriginous areas
- Have an Investigator's Global Assessment (IGA) score of at least 3 (moderate) at baseline; refer to Appendix 13.3 for details on the IGA scale

It should be noted that the applicant originally planned to conduct two Phase 3 trials, Trial 305 and Trial 306, to establish the safety and efficacy of the proposed product. However, after the completion of these trials, the results of the analysis for Trial 305 did not meet its objective and the applicant decided to conduct a third pivotal Phase 3 trial (Trial 310) with a larger sample size of 400 subjects to serve as the second pivotal trial. Consequently, the applicant considered Trials 306 and 310 to be pivotal and Trial 305 to be supportive.

The design of the submitted trials was identical (except from the sample size). The protocols specified randomization to be conducted on the center level, using a block size of 6, along with randomizing subjects in a 1:1 ratio to either HBP foam, 0.05% or vehicle foam.

Subjects were instructed to apply the assigned product to all psoriatic plaques (excluding the face, scalp, groin, axillae and other intertriginous areas) twice daily for two weeks (maximum of approximately 50 grams per week). Subjects had scheduled visits at baseline (Day 1), Day 8, and Day 15.

The protocol-specified primary endpoint was the proportion of subjects with overall treatment success at Day 15, defined as achieving an IGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade reduction from baseline.

The protocols listed the proportion of subjects with treatment success on the individual signs of psoriasis (plaque elevation, scaling, and erythema) at Day 15 as the secondary endpoints, where treatment success was defined as achieving a score of 0 (clear) or 1 (almost clear) with at least a 2-grade reduction from their corresponding baseline scores. Refer to Appendix 13.3 for details on the Clinical Signs and Symptoms scales.

The protocols also listed the following “other” endpoints:

- The proportion of subjects with overall treatment success based on the IGA at Day 8
- The proportion of subjects with treatment success for each of the individual clinical signs of psoriasis (scaling, erythema, and plaque elevation) at Day 8
- Change from baseline in pruritus score at Day 15, based on the 5-D Pruritus scale; Refer to Appendix 13.3 for the 5-D Pruritus scale
- Change in % BSA with active psoriasis at Days 8 and 15

As these “other” endpoints were not adjusted for multiplicity, therefore, their results are considered exploratory and are not included in this review.

#### **7.2.1.2. Statistical Methodologies**

The primary efficacy analysis population specified in the protocols was the intent-to-treat (ITT) population, defined as all subjects who are randomized and dispensed study medication. The protocols also specified supportive analysis using the per-protocol (PP) population. The PP population was defined as subjects in the ITT population who satisfy the following criteria:

- Meet the inclusion/exclusion criteria, specifically with a clinical diagnosis of stable plaque psoriasis involving a minimum of 2% and no more than 12% BSA in the treatment area
- Have baseline IGA score of at least 3 (moderate)
- Have not taken or applied any interfering concomitant medications
- Completed Visit 3 / Day 15 ( $\pm$  3 days) and the Day 15 procedures
- Must have applied at least 80% of expected applications with no evidence of material dosing non-compliance

For the analysis of the primary endpoint (i.e., the proportion of subjects achieving an IGA score of 0 or 1 at Day 15 with at least a 2-grade reduction from baseline), the protocols specified using the Cochran-Mantel-Haenszel (CMH) test stratified by center.

The protocols specified that the trials were to be conducted in such a manner as to have a minimum of eight (8) ITT subjects enrolled in each treatment group at each center. It should be noted that in the advice letter dated October 15, 2014, the Agency recommended that the protocols include a pooling algorithm for centers that do not enroll the specified minimum number of subjects, as in practice, it is generally expected that not all centers will enroll the specified minimum. The letter also stated that investigation of consistency of treatment effect across centers should be based on the original enrollment, as pooling could mask differences in treatment effect among the centers.

The protocols specified investigating treatment-by-center interaction for the primary endpoint using the Breslow Day test. This testing for interaction was to be carried out for centers that enrolled at least 8 subjects in each treatment arm. If the Breslow-Day test

was significant at  $\alpha=0.10$  level, the applicant planned to conduct a sensitivity analysis that excludes the centers with “extreme efficacy results”. The identification of an extreme center was to be done by analyzing all subsets that can be created excluding one center. If one or more of the subsets resulted in a Breslow Day test p-value  $>0.10$ , then the center excluded from the subset with the largest p-value was considered to be the extreme center. If all subset p-values were  $\leq 0.10$ , the process was repeated by excluding two centers. If one or more of these subsets resulted in a Breslow Day test p-value  $> 0.10$ , then the centers excluded from the subset with the largest p-value were considered to be the extreme centers. This process that creates subsets by increasing the number of centers was repeated until the p-value exceeded 0.10. Upon identification of the extreme center(s), the primary endpoint was to be analyzed excluding these centers.

The protocols specified analyzing the three secondary endpoints (all binary endpoints) using the same approach as that for analyzing the primary endpoint (i.e. using CMH test stratified by center). According to the protocols, “subjects with a baseline score of 0 or 1 will be excluded unless the corresponding sign score at Day 15 is  $>1$ ”.

To control the Type I error rate, the protocols specified using a sequential gatekeeping approach in the order listed in Section 7.2.1.1. The first secondary endpoint was to be tested only if the primary endpoint was significant at the 0.05 significance level, and the subsequent secondary endpoint(s) were to be tested only if the current secondary endpoint was significant at the 0.05 significance level.

The primary imputation method for handling the missing data specified in the protocols was the non-responder imputation (NRI). For the primary endpoint, the protocols specified the following sensitivity analyses for the handling of missing data:

- Impute missing data as responders
- Worst Case Scenario: Impute missing data for the vehicle arm as responders and imputing missing data for the HBP arm as non-responders
- Not imputing missing data and analyzing only observed data
- Multiple Imputation (MI)

For the sensitivity analysis based on MI, the protocols specified using a logistic regression model with treatment and plaque elevation as covariates in order to impute the missing values of the primary endpoint. However, the Statistical Analysis Plan (SAP) for Trial 310 specified that the logistic regression will additionally include the covariate of baseline IGA. The protocols stated that “a minimum of 10 imputed data sets will be generated for this analysis”. The SAP for Trial 310 stated that 25 imputed data sets will be generated using a seed of 122310.

### 7.2.1.3. Subject Disposition, Demographics and Baseline Disease Characteristics

Trial 306 enrolled and randomized a total of 151 subjects (74 subjects to HBP foam and 75 subjects to vehicle foam) from 8 centers in the U.S. Trial 310 enrolled and randomized a total of 409 subjects (205 subjects to HBP foam and 204 subjects to vehicle foam) from 21 centers in the U.S. Table 5 presents the disposition of subjects for Trials 306 and 310. The discontinuation rates were low in both trials, ranging from 1% to 4%. The discontinuation rates were balanced across the two treatment arms in each trial.

**Table 5: Subject Disposition for Trials 306 and 310**

|                       | Trial 306     |                   | Trial 310      |                    |
|-----------------------|---------------|-------------------|----------------|--------------------|
|                       | HBP<br>(N=75) | Vehicle<br>(N=76) | HBP<br>(N=205) | Vehicle<br>(N=204) |
| Completed             | 74 (99%)      | 75 (99%)          | 199 (97%)      | 196 (96%)          |
| Discontinued          | 1 ( 1%)       | 1 ( 1%)           | 6 ( 3%)        | 8 ( 4%)            |
| Lost to follow-up     | 0             | 0                 | 4              | 4                  |
| Withdrawal by Subject | 1             | 0                 | 2              | 2                  |
| Adverse Event         | 0             | 1                 | 0              | 2                  |
| Other                 | 0             | 0                 | 0              | 0                  |

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis)

Table 6 presents the demographics for both trials. The demographics were generally balanced between the treatment arms within each trial and across the two trials. Approximately 82% of the enrolled subjects were below the age of 65 years old in both trials. In Trial 306, a slightly larger proportion of subjects were males compared to females. The majority of subjects were White (approximately 90%) with smaller proportions of Black, Asian, or other ethnicity.

**Table 6: Demographics for Trials 306 and 310 – ITT<sup>(1)</sup>**

|      |                                           | Trial 306     |                   | Trial 310      |                    |
|------|-------------------------------------------|---------------|-------------------|----------------|--------------------|
|      |                                           | HBP<br>(N=75) | Vehicle<br>(N=76) | HBP<br>(N=205) | Vehicle<br>(N=204) |
| Age  | Mean (SD)                                 | 54.0 (14.2)   | 55.1 (13.9)       | 50.3 (13.9)    | 50.1 (14.0)        |
|      | Median                                    | 54            | 54                | 51             | 52                 |
|      | Range                                     | 23 – 78       | 21 – 83           | 18 – 80        | 19 – 85            |
|      | < 65 years                                | 57 (76%)      | 56 (74%)          | 172 (84%)      | 174 (85%)          |
|      | ≥ 65 years                                | 18 (24%)      | 20 (26%)          | 33 (16%)       | 30 (15%)           |
| Sex  | Female                                    | 27 (36%)      | 22 (29%)          | 92 (45%)       | 86 (42%)           |
|      | Male                                      | 48 (64%)      | 54 (71%)          | 113 (55%)      | 118 (58%)          |
| Race | White                                     | 63 (84%)      | 68 (90%)          | 190 (93%)      | 185 (91%)          |
|      | Black or African American                 | 9 (12%)       | 6 ( 8%)           | 11( 5%)        | 15 ( 7%)           |
|      | American Indian or Alaska Native          | 0 ( 0%)       | 0 ( 0%)           | 1 (<1%)        | 0 ( 0%)            |
|      | Native Hawaiian or Other Pacific Islander | 0 ( 0%)       | 1 ( 1%)           | 0 ( 0%)        | 1 (<1%)            |
|      | Asian                                     | 3 ( 4%)       | 1 ( 1%)           | 2 ( 1%)        | 2 ( 1%)            |
|      | Other                                     | 0 ( 0%)       | 0 ( 0%)           | 1 (<1%)        | 1 (<1%)            |

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis)

(1) Intent-to-Treat (ITT) population: all randomized subjects

Table 7 presents the baseline disease characteristics for the two pivotal trials. For enrollment, subjects should have an IGA score of 3 (moderate) or 4 (severe). In general, more subjects had an IGA score of 3 (approximately 87%) at baseline compared to IGA score of 4 (approximately 13%), in the two trials. In both trials, the majority of subjects had moderate to severe individual signs of psoriasis (plaque elevation, scaling, and erythema), with a larger proportion of subjects with moderate signs of psoriasis compared to severe. A small number subjects had signs of psoriasis of mild severity in the two trials, while in Trial 310, a few subjects were clear or almost clear in plaque elevation and scaling.

**Table 7: Baseline Disease Characteristics for Trials 306 and 310 – ITT<sup>(1)</sup>**

|                         |                  | Trial 306     |                   | Trial 310      |                    |
|-------------------------|------------------|---------------|-------------------|----------------|--------------------|
|                         |                  | HBP<br>(N=75) | Vehicle<br>(N=76) | HBP<br>(N=205) | Vehicle<br>(N=204) |
| <b>IGA</b>              | 3 - Moderate     | 67 (89%)      | 65 (86%)          | 176 (86%)      | 180 (88%)          |
|                         | 4 - Severe       | 8 (11%)       | 11 (14%)          | 29 (14%)       | 24 (12%)           |
| <b>Plaque Elevation</b> | 0 - Clear        | 0 ( 0%)       | 0 ( 0%)           | 0 ( 0%)        | 0 ( 0%)            |
|                         | 1 - Almost Clear | 0 ( 0%)       | 0 ( 0%)           | 3 ( 1%)        | 1 (<1%)            |
|                         | 2 - Mild         | 1 ( 1%)       | 3 ( 4%)           | 13 ( 6%)       | 13 ( 6%)           |
|                         | 3 - Moderate     | 65 (87%)      | 65 (86%)          | 166 (81%)      | 164 (80%)          |
|                         | 4 - Severe       | 9 (12%)       | 8 (10%)           | 23 (11%)       | 26 (13%)           |
| <b>Scaling</b>          | 0 - Clear        | 0 ( 0%)       | 0 ( 0%)           | 2 ( 1%)        | 0 ( 0%)            |
|                         | 1 - Almost Clear | 0 ( 0%)       | 0 ( 0%)           | 2 ( 1%)        | 0 ( 0%)            |
|                         | 2 - Mild         | 6 ( 8%)       | 1 ( 1%)           | 10 ( 5%)       | 13 ( 6%)           |
|                         | 3 - Moderate     | 59 (79%)      | 62 (82%)          | 161 (78%)      | 170 (83%)          |
|                         | 4 - Severe       | 10 (13%)      | 13 (17%)          | 30 (15%)       | 21 (10%)           |
| <b>Erythema</b>         | 0 - Clear        | 0 ( 0%)       | 0 ( 0%)           | 0 ( 0%)        | 0 ( 0%)            |
|                         | 1 - Almost Clear | 0 ( 0%)       | 0 ( 0%)           | 0 ( 0%)        | 0 ( 0%)            |
|                         | 2 - Mild         | 5 ( 7%)       | 8 (10%)           | 13 ( 6%)       | 15 (7%)            |
|                         | 3 - Moderate     | 59 (79%)      | 60 (79%)          | 166 (81%)      | 162 (79%)          |
|                         | 4 - Severe       | 11 (15%)      | 8 (10%)           | 26 (13%)       | 27 (13%)           |
| <b>% BSA</b>            | Mean (SD)        | 5.7 (3.1)     | 5.7 (3.2)         | 5.4 (3.2)      | 5.1 (2.8)          |
|                         | Median           | 5             | 4.5               | 4              | 4                  |
|                         | Range            | 2 – 12        | 2 – 12            | 2 – 12         | 2 – 12             |

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis)

(1) Intent-to-Treat (ITT) population: all randomized subjects

#### 7.2.1.4. Results of the Primary Endpoint

Table 8 displays the rate of missing data for the primary endpoint by day of study visit, treatment arm, and trial. Overall, the rate of missing data at Day 15 (primary time point) was relatively low in the two trials (1% in Trial 306 and 3% in Trial 310).

**Table 8: Missing Data for the Primary Endpoint by Day for Trials 306 and 310 – ITT<sup>(1)</sup>**

|                             | Trial 306     |                   | Trial 310      |                    |
|-----------------------------|---------------|-------------------|----------------|--------------------|
|                             | HBP<br>(N=75) | Vehicle<br>(N=76) | HBP<br>(N=205) | Vehicle<br>(N=204) |
| Baseline                    | 0             | 0                 | 0              | 0                  |
| Day 8                       | 1 (1%)        | 0 (0%)            | 5 (2%)         | 5 (2%)             |
| Day 15 (Primary Time Point) | 1 (1%)        | 1 (1%)            | 6 (3%)         | 8 (4%)             |

Source: Statistical Reviewer's Analysis

(1) Intent-to-Treat (ITT) population: all randomized subjects

As stated earlier in Section 7.2.1.2, the primary method of handling missing data specified in the protocols was non-responder imputation (NRI). The protocols also specified the following sensitivity analyses for the handling of missing data: (i) impute missing data as treatment success, (ii) worst case scenario (i.e., missing data for the vehicle is imputed as responders and missing data for the HBP is imputed as non-responders), (iii) observed cases (i.e., missing data is not imputed), and (iv) multiple imputation (MI). Table 9 presents the results of the primary endpoint in both trials using various imputation methods. For both trials, the results of the analyses were similar across the various methods of handling the missing data. In the extreme case (i.e., worst case scenario), HBP foam remained statistically significant to vehicle foam (p-values < 0.001) for the primary endpoint. Table 9 also presents the results of the primary endpoint using the PP population. The results for the ITT and PP populations were very similar.

**Table 9: Results of the Primary Endpoint at Day 15 for Trials 306 and 310**

|                                         | Trial 306   |           |                        | Trial 310    |              |                        |
|-----------------------------------------|-------------|-----------|------------------------|--------------|--------------|------------------------|
|                                         | HBP         | Vehicle   | P-value <sup>(7)</sup> | HBP          | Vehicle      | P-value <sup>(7)</sup> |
| ITT <sup>(1)</sup> - NRI <sup>(2)</sup> | 19/75 (25%) | 3/76 (4%) | < 0.001                | 63/205 (31%) | 15/204 (7%)  | < 0.001                |
| Sensitivity Analyses                    |             |           |                        |              |              |                        |
| Responder Imputation <sup>(1,3)</sup>   | 20/75 (27%) | 4/76 (5%) | < 0.001                | 69/205 (34%) | 23/204 (11%) | < 0.001                |
| Worst Case Scenario <sup>(1,4)</sup>    | 19/75 (25%) | 4/76 (5%) | < 0.001                | 63/205 (31%) | 23/204 (11%) | < 0.001                |
| MI <sup>(1,5)</sup>                     | 26%         | 4%        | < 0.001                | 32%          | 8%           | < 0.001                |
| Observed cases                          | 19/74 (26%) | 3/75 (3%) | < 0.001                | 63/199 (32%) | 15/196 (8%)  | < 0.001                |
| PP <sup>(6)</sup>                       | 19/73 (26%) | 3/72 (4%) | < 0.001                | 56/184 (30%) | 14/184 (8%)  | < 0.001                |

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis)

(1) Intent-to-Treat (ITT) population: all randomized subjects

(2) Missing data was imputed using non-responder imputation (NRI)

(3) Missing data was imputed as responders

(4) Missing data for the HBP foam was imputed as non-responders and missing data for vehicle was imputed as responders

(5) Missing data was imputed using Multiple Imputation (MI). Data imputed using a logistic regression model with treatment group, baseline IGA, and plaque elevation. The rates displayed are the averages over the 25 imputed datasets.

(6) Per-Protocol (PP) population (see Section 7.2.1.2 for definition)

(7) P-values based on CMH test stratified by analysis center.

### 7.2.1.5. Results of the Secondary Endpoints

Table 10 presents the results of the secondary endpoints listed in Section 7.2.1.1. Subjects with baseline score of 0 or 1 were excluded from the analysis. The primary

method for handling the missing data was the non-responder imputation (NRI). In both trials, HBP foam was statistically superior to vehicle foam for all secondary endpoints (p-values < 0.001).

**Table 10: Results of the Secondary Endpoints at Day 15 for Trials 306 and 310**

| Secondary Endpoints | Trial 306   |                |                        | Trial 310    |                 |                        |
|---------------------|-------------|----------------|------------------------|--------------|-----------------|------------------------|
|                     | HBP (N=75)  | Vehicle (N=76) | P-value <sup>(2)</sup> | HBP (N=205)  | Vehicle (N=204) | P-value <sup>(2)</sup> |
| Plaque Elevation    | 20/75 (27%) | 3/76 ( 4%)     | <0.001                 | 71/202 (35%) | 20/203 (10%)    | <0.001                 |
| Scaling             | 21/75 (28%) | 4/76 ( 5%)     | <0.001                 | 68/201 (34%) | 20/204 (10%)    | <0.001                 |
| Erythema            | 16/75 (21%) | 2/76 (11%)     | <0.001                 | 59/205 (29%) | 17/204 ( 8%)    | <0.001                 |

Source: Statistical Reviewer's Analysis (similar to Applicant's Analysis)

(1) Intent-to-Treat (ITT) population: all randomized subjects; Missing data was imputed using non-responder imputation (NRI)

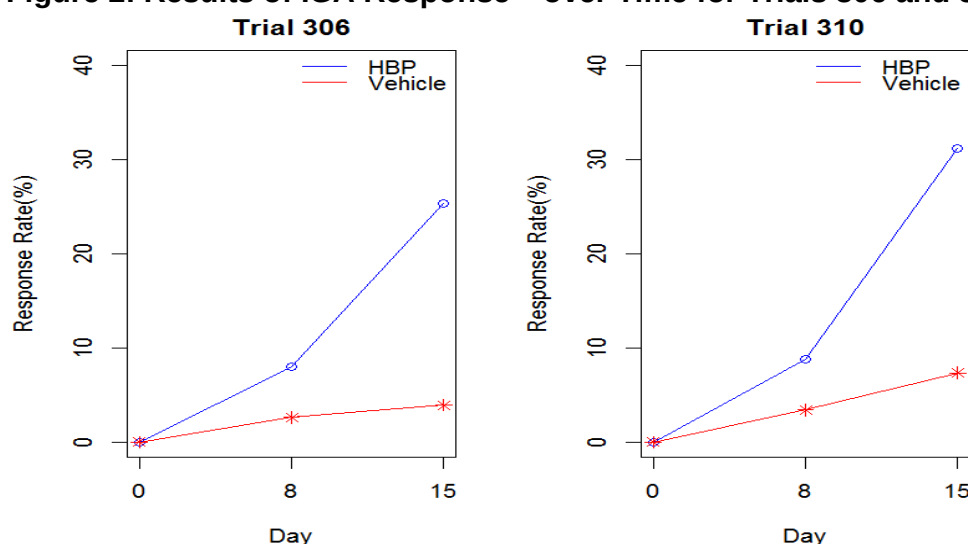
(2) P-values were calculated using CMH test stratified by analysis center

Note: Subjects with baseline scores of 0 or 1 were excluded from the analysis

### 7.2.1.6. Efficacy Over Time

Figure 2 presents the results of IGA response (i.e., IGA score of 0 or 1 with at least a 2-grade reduction from baseline) over time for the two pivotal Phase 3 trials. The results were similar across the two trials.

**Figure 2: Results of IGA Response<sup>(1)</sup> over Time for Trials 306 and 310 - ITT<sup>(2)</sup>**



Source: Statistical Reviewer's Analysis

(1) IGA response is defined as an IGA score of 0 or 1 with at least 2-grade reduction from baseline

(2) Intent-to-Treat (ITT) population: all randomized subjects; Missing data was imputed using non-responder imputation (NRI)

### 7.2.1.7. Patient Reported Outcomes (PROs)

As previously noted in Section 7.2.1.1, the protocols for Trials 306 and 310 included assessment of the 5-D Pruritus Scale PRO. As the endpoint of change from baseline in pruritus score was designated as "other" endpoint and was not included in the multiplicity testing strategy, the results of this endpoint are not presented in this review.

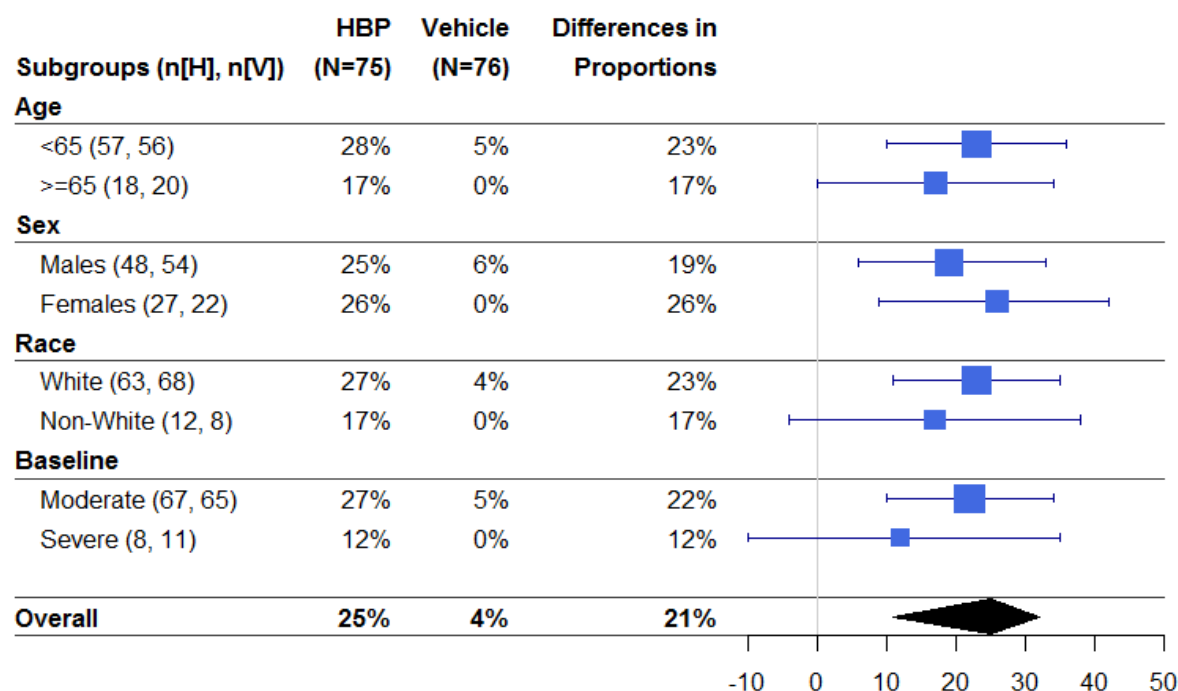
## 7.2.1.8. Findings in Special/Subgroup Populations

### 7.2.1.8.1. Sex, Race, Age and Baseline Disease Severity

Figure 3 and Figure 4 present the results of the primary endpoint (i.e., IGA score of 0 or 1 at Day 15 with at least a 2-grade reduction from baseline) by age (<65 and ≥65), sex, race and baseline IGA score (3-moderate, 4-severe) for Trial 306 and Trial 310, respectively. The forest plots in these figures contain 95% confidence intervals for the difference in proportions of success between HBP arm and the vehicle arm for the ITT population using the non-responder imputation method for handling the missing data.

It should be noted that subgroup analyses by age and race may not be meaningful due to the small number of subjects in the subgroups of ≥65 years of age and non-white, in both trials. For sex, while the response rates were consistent for males and females in Trial 306; the response rate was slightly larger in males compared to females in Trial 310. For subgroups defined based on baseline IGA scores, the response rate was greater for the subgroup with baseline severity score of 3 (moderate) compared to that with baseline severity score of 4 (severe); however, a small number of subjects with severe IGA score were enrolled in the trials. Generally, the treatment effects for the various subgroups are comparable between the two trials.

**Figure 3: Forest Plot for the Treatment Effect at Day 15 by Age, Sex, Race and Baseline IGA Score for Trial 306 – ITT<sup>(1)</sup>**



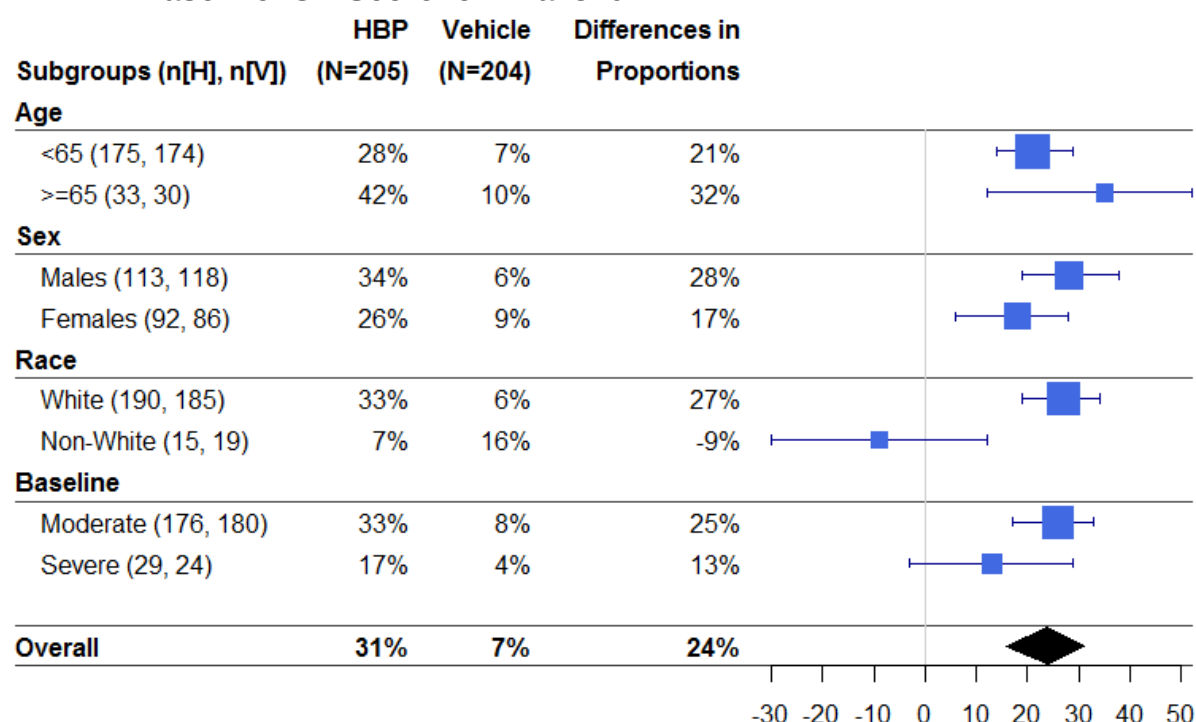
Source: Statistical Reviewer's Analysis

(1) Intent-to-Treat (ITT) population: all randomized subjects; Missing data was imputed using non-responder imputation (NRI)

n[H] = subgroup sample size for HBP foam arm; n[V] = subgroup sample size in vehicle foam arm

Forest Plot: 95% asymptotic confidence interval for the difference in proportions

**Figure 4: Forest Plot for the Treatment Effect at Day 15 by Age, Sex, Race and Baseline IGA Score for Trial 310 – ITT<sup>(1)</sup>**



Source: Statistical Reviewer's Analysis

(1) Intent-to-Treat (ITT) population: all randomized subjects; Missing data was imputed using non-responder imputation (NRI)

n[H] = subgroup sample size for HBP foam arm; n[V] = subgroup sample size in vehicle foam arm

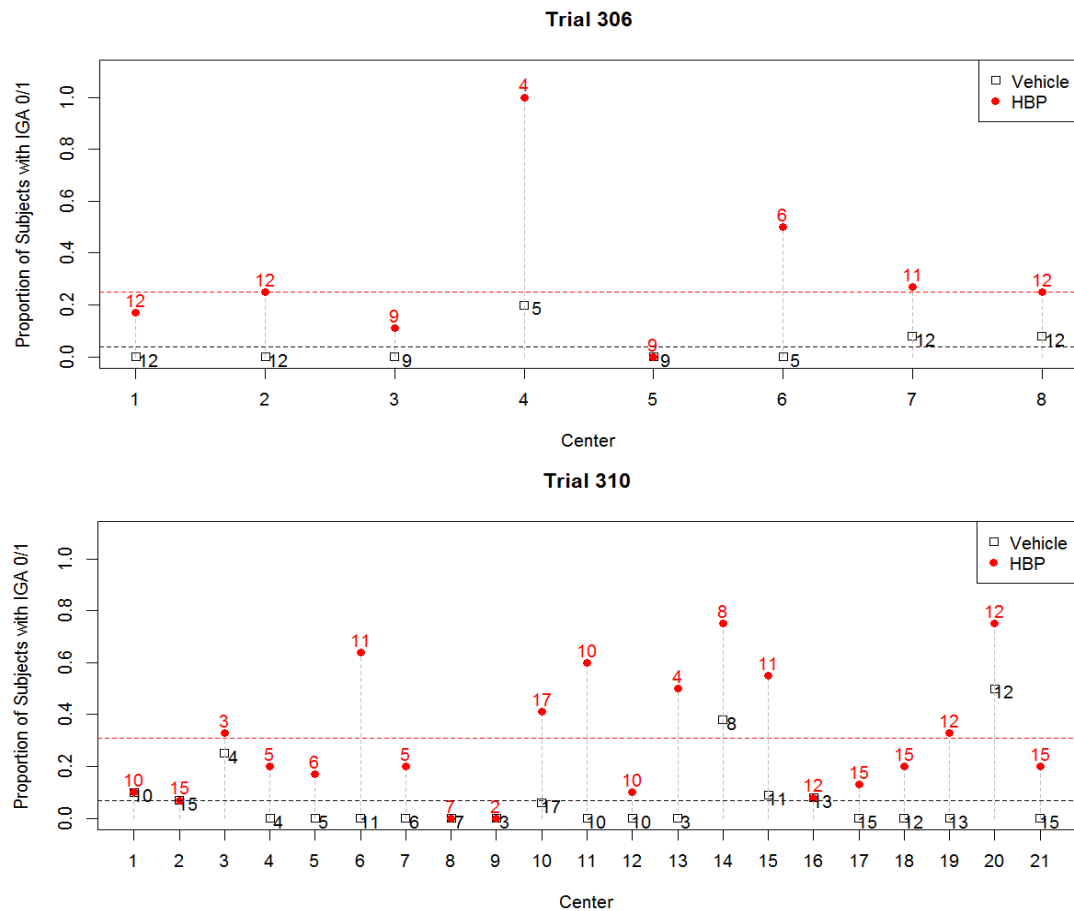
Forest Plot: 95% asymptotic confidence interval for the difference in proportions

#### 7.2.1.8.2. Center

Trial 306 enrolled 151 subjects from 8 centers and Trial 310 enrolled 409 subjects from 21 centers. All centers were located in the United States.

Figure 5 presents the results of the primary endpoint (i.e., IGA score of 0 or 1 at Day 15 with at least a 2-grade reduction from baseline) by center for both trials. Treatment effects varied somewhat across the centers, but no one center had extreme results. The same argument is supported by the Breslow-Day test performed on the ITT population, where missing data was imputed as non-responders. The test failed to reject the hypothesis of homogeneity of treatment effects across the centers (p-value= 0.69 for Trial 306 and p-value= 0.47 for Trial 310).

**Figure 5: Results of the Primary Endpoint at Day 15 by Center for Trials 306 and 310 – ITT<sup>(1)</sup>**



Source: Statistical Reviewer's Analysis

(1) Intent-to-Treat (ITT) population: all randomized subjects; Missing data was imputed using non-responder imputation (NRI)

Note: The dotted horizontal line denotes the overall efficacy for each treatment arm.

The numbers on the plot denote the sample size of each treatment arm within each site.

## 7.2.2. Supportive Phase 3 Trial (Trial 305)

### 7.2.2.1. Study Design, Endpoints and Statistical Methodologies

As discussed in Section 7.2.1.1, Trial 305 was designed to be a pivotal trial along with Trial 306, however, as findings from this trial did not meet the trial objective, the applicant conducted another trial (Trial 310) of larger sample size compared to Trial 306. The design and statistical analysis for Trial 305 were similar to those of Study 306 discussed in Sections 7.2.1.1 and 7.2.1.2, respectively. In the next sections, we summarize the findings from Trial 305 to provide a supportive evidence for the findings of the pivotal trials 306 and 310.

### 7.2.2.2. Subject Disposition, Demographics and Baseline Disease Characteristics

Trial 305 enrolled and randomized a total of 144 subjects (71 subjects to HBP foam and 73 subjects to vehicle foam) from 9 centers in the U.S. Table 11 presents the disposition of subjects for Trial 305. The discontinuation rates were low in Trial 305 (7% in the HBP foam arm and 6% in the vehicle foam arm).

**Table 11: Subject Disposition for Trial 305**

|                       | Trial 305     |                   |
|-----------------------|---------------|-------------------|
|                       | HBP<br>(N=71) | Vehicle<br>(N=73) |
| <b>Completed</b>      | 66 (93%)      | 69 (94%)          |
| <b>Discontinued</b>   | 5 ( 7%)       | 4 ( 6%)           |
| Lost to follow-up     | 2             | 2                 |
| Withdrawal by Subject | 3             | 2                 |
| Adverse Event         | 0             | 0                 |
| Other                 | 0             | 0                 |

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis)

The demographics for Trial 305 are presented in Table 12. The demographics were generally balanced between the treatment arms. Approximately 80% of the enrolled subjects were below the age of 65 years old. The majority of the subjects were White (approximately 90%) with smaller proportions of Black, Asian, or other ethnicity.

**Table 12: Demographics for Trial 305 – ITT<sup>(1)</sup>**

|             |                                           | Trial 305     |                   |
|-------------|-------------------------------------------|---------------|-------------------|
|             |                                           | HBP<br>(N=75) | Vehicle<br>(N=76) |
| <b>Age</b>  | Mean (SD)                                 | 52.4 (13.4)   | 52.0 (13.8)       |
|             | Median                                    | 54            | 49                |
|             | Range                                     | 18 – 78       | 27 – 78           |
|             | < 65 years                                | 58 (82%)      | 56 (77%)          |
|             | ≥ 65 years                                | 13 (18%)      | 17 (23%)          |
| <b>Sex</b>  | Female                                    | 35 (49%)      | 36 (49%)          |
|             | Male                                      | 36 (51%)      | 37 (51%)          |
| <b>Race</b> | White                                     | 68 (96%)      | 64 (88%)          |
|             | Black or African American                 | 2 ( 3%)       | 7 (10%)           |
|             | American Indian or Alaska Native          | 0 ( 0%)       | 0 ( 0%)           |
|             | Native Hawaiian or Other Pacific Islander | 0 ( 0%)       | 0 ( 0%)           |
|             | Asian                                     | 1 ( 1%)       | 2 ( 3%)           |
|             | Other                                     | 0 ( 0%)       | 0 ( 0%)           |

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis)

(1) Intent-to-Treat (ITT) population: all randomized subjects.

Table 13 presents the baseline disease characteristics for Trial 305. In general, more subjects had an IGA score of 3 (approximately 88%) at baseline compared to IGA score

of 4 (approximately 12%). In addition, the majority of subjects had moderate to severe individual signs of psoriasis (plaque elevation, scaling, and erythema), with a larger proportion of subjects with moderate signs of psoriasis compared to severe. Only a few subjects had signs of psoriasis of mild severity in Trial 305, while none of the subjects was clear or almost clear in severity.

**Table 13: Baseline Disease Characteristics for Trial 305 – ITT<sup>(1)</sup>**

|                         |                  | Trial 305     |                   |
|-------------------------|------------------|---------------|-------------------|
|                         |                  | HBP<br>(N=75) | Vehicle<br>(N=76) |
| <b>IGA</b>              | 3 - Moderate     | 63 (89%)      | 64 (88%)          |
|                         | 4 - Severe       | 8 (11%)       | 9 (12%)           |
| <b>Plaque Elevation</b> | 0 - Clear        | 0 ( 0%)       | 0 ( 0%)           |
|                         | 1 - Almost Clear | 0 ( 0%)       | 0 ( 0%)           |
|                         | 2 - Mild         | 1 ( 1%)       | 0 ( 0%)           |
|                         | 3 - Moderate     | 64 (90%)      | 65 (89%)          |
|                         | 4 - Severe       | 6 ( 8%)       | 8 (11%)           |
| <b>Scaling</b>          | 0 - Clear        | 0 ( 0%)       | 0 ( 0%)           |
|                         | 1 - Almost Clear | 0 ( 0%)       | 0 ( 0%)           |
|                         | 2 - Mild         | 4 ( 6%)       | 0 ( 0%)           |
|                         | 3 - Moderate     | 59 (83%)      | 64 (88%)          |
|                         | 4 - Severe       | 8 (11%)       | 9 (12%)           |
| <b>Erythema</b>         | 0 - Clear        | 0 ( 0%)       | 0 ( 0%)           |
|                         | 1 - Almost Clear | 0 ( 0%)       | 0 ( 0%)           |
|                         | 2 - Mild         | 1 ( 1%)       | 5 ( 7%)           |
|                         | 3 - Moderate     | 66 (93%)      | 62 (85%)          |
|                         | 4 - Severe       | 4 ( 6%)       | 6 ( 8%)           |
| <b>% BSA</b>            | Mean (SD)        | 5.7 (3.2)     | 5.3 (2.9)         |
|                         | Median           | 5             | 5                 |
|                         | Range            | 2 – 12        | 2 – 12            |

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis)

(1) Intent-to-Treat (ITT) population: all randomized subjects

### 7.2.3. Results of the Primary Endpoint

HBP foam failed to demonstrate statistical superiority against vehicle foam for the primary endpoint (i.e., IGA score of 0 or 1 at Day 15 with at least a 2-grade reduction from baseline) in Trial 305 (18% response rate in the active arm and 10% response rate in the vehicle arm; p-value=0.8805).

### 7.3. Review of Safety

#### 7.3.1. Safety Review Approach

The primary review of safety of HBP foam for the treatment of for the topical treatment of plaque psoriasis in adults focuses on the evaluation of pooled data from 3 Trials (referred to as the Phase 3 Safety Pool): 305, 306, and 310. All Phase 3 trials were identical with regard to design, study population, dosing regimen and key primary and secondary endpoints. Additional analyses (referred to as the Combined Safety Pool) included data from the aforementioned Phase 3 studies and include Phase 2 trial 203 and maximal use PK/ HPA Axis trial 202.

Dermal safety was assessed in the Phase 3 trials as well as a separate Human Repeat Insult Patch Test (HRIPT) and Cumulative Irritation Test (CIT) study (108).

#### 7.3.2. Review of the Safety Database

##### Overall Exposure

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

- Phase 2 studies: Studies 202 (PK/HPA axis evaluation) and 203 (supportive)
- Phase 3 studies: 305 and 310 (pivotal studies) and 306 (supportive)

The five studies enrolled 773 subjects: 399 subjects were randomized to treatment with HBP foam and 364 subjects were randomized to treatment with VEH foam.

Subjects in these five studies constituted the Safety Population. Adult subjects with plaque psoriasis were exposed to up to approximately 50-60 grams/week of study product for two weeks. All subjects applied the test article at least once with a mean number of days dosed of 14.8 days and 14.6 days for the HBP Foam and VEH Foam groups, respectively. The mean total amount of test article used during the studies was 71.71 grams of HBP Foam and 66.74 grams of VEH Foam

This reviewer concurs with the applicant's pooled safety population. The number of subjects contributed per study and disposition of the safety population are shown in Table 14

**Table 14: Characterization of the Combined Safety Population**

|                    | HBP Foam<br>n | VEH Foam<br>n | All<br>n |
|--------------------|---------------|---------------|----------|
| Safety Population  | n=399         | n=374         | n=773    |
| Study 122-0551-202 | 25            | 0             | 25       |
| Study 122-0551-203 | 23            | 21            | 44       |
| Study 122-0551-305 | 71            | 73            | 144      |
| Study 122-0551-306 | 75            | 76            | 151      |

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 TRADENAME (halobetasol propionate) foam, 0.05%

| Study 122-0551-310    | 205               | 204               | 409          |
|-----------------------|-------------------|-------------------|--------------|
|                       | HBP Foam<br>n (%) | VEH Foam<br>n (%) | All<br>n (%) |
| Completed Study       | 387 (97%)         | 360 (96.3%)       | 747 (96.6%)  |
| Discontinued          | 12 (3%)           | 14 (3.7%)         | 26 (3.4%)    |
| Adverse Event         | 0                 | 3 (0.8 %)         | 3 (0.4%)     |
| Lost to Follow-Up     | 6 (1.5%)          | 6 (1.6%)          | 12 (1.6%)    |
| Withdrawal by subject | 6 (1.5%)          | 4 (1.1%)          | 10 (1.3%)    |
| Other                 | 0                 | 1 (0.3%)          | 1 (0.1%)     |
|                       |                   |                   |              |

The applicant also conducted analyses with Phase 3 Safety pool. Safety results were pooled for the three Phase 3 studies (Study 305, Study 306, and Study 310). All 3 trials have the same trial design. Combining them adds to understanding of safety and is the recommended population for safety labeling.

Relevant characteristics of the safety population:

Demographic characteristics of the subject population in the HBP foam development program are presented in greater detail in Section 7.2.1.3 of this review. A brief summary of demographic information relevant to the evaluation of safety will be presented here.

The Safety population comprised more male subjects than female subjects: 454 males (454/773, 58.7%) and 319 females (319/773, 41.3%). The majority of subjects were White (699/773, 90.4%) and not of Hispanic or Latino origin (598/773, 77.4%). Overall, the average age of subjects was 51.4 years with a range from 18 years to 85 years. The majority of subjects (635/773, 82.1%) were between the ages of 18-64, with the remaining subjects (138/773, 17.9%) being 65 years old or older.

The majority of subjects had moderate IGA (HBP Foam: 348/399, 87.2% and VEH Foam: 327/374, 87.4%) and the remaining subjects had severe IGA (HBP Foam: 51/399, 12.8% and VEH Foam: 47/374, 12.6%). The mean percent BSA affected at Baseline was  $6.3 \pm 5.01\%$  for the HBP Foam group and  $5.2 \pm 2.90\%$  for the VEH Foam group, with a range of 2% to 60% for the HBP Foam group and 2% to 12% for the VEH Foam group.

Results of the Phase 3 studies were generally consistent with the Combined Safety pool with the exception of the BSA. The large range of BSA in the HBP Foam group of the safety pool was due to the inclusion of Study 202 in the Combined Safety pool, which allowed subjects with  $\geq 15\%$  BSA affected with psoriasis at Baseline. For Phase 3 studies, baseline BSA affected was limited to 2% to 12%.

Adequacy of the safety database:

The total subject exposure to HBP foam, 0.05% for up to two weeks treatment, not to exceed 50 grams per week, provides adequate data for the evaluation of safety. The demographics of the study population are sufficiently representative of the target

population. Therefore, the safety database presented by the applicant is sufficient to characterize the safety profile of HPB foam for the topical treatment of plaque psoriasis.

### **7.3.3. Adequacy of Applicant's Clinical Safety Assessments**

#### Issues Regarding Data Integrity and Submission Quality

Overall the quality of the data submitted is adequate to characterize the safety of HBP foam.

#### 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). Integrated safety data is presented in MedDRA version 19.0. Individual study data that were coded in prior versions was reviewed and recoded where necessary to bring the coding current with version 19.0.

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 PT for the safety population. TEAE's are defined as those adverse events occurring after the first dose of study treatment.

The definition of AE, TEAE, and SAE are acceptable. The classification system used by investigators to describe the severity of AE as well as the causal relationship between AE and study product are also acceptable. The applicant's identification and presentation of AEs appears appropriate.

#### Routine Clinical Tests

The applicant performed laboratory evaluations in the Phase 2 Study 202. In this study, HPA axis suppression from treatment under maximal use conditions with HBP Foam was assessed. In addition, the evaluation for, hematology, chemistry, and urinalysis tests were performed in this study at Screening and EOT. See Section 6.2.1 for the discussion of HPA axis testing.

There were no clinically significant shifts in hematology, chemistry, or urinalysis test parameters identified in the treatment group.

### **7.3.4. Safety Results**

#### Deaths

No deaths occurred in the clinical development program.

#### Serious Adverse Events

There was one subject reporting a serious adverse event (SAE). Subject (b) (6) (VEH Foam) experienced a gastric ulcer hemorrhage on Study Day 5; the SAE was deemed unrelated to test article, the test article dose was not modified, and the SAE recovered/resolved by the end of the study.

#### Dropouts and/or Discontinuations Due to Adverse Effects

In the safety population, no subjects treated with HPB foam discontinued the study due to an adverse event.

There were three subjects from the VEH Foam group who had TEAEs (application site pain, application site pruritus, and psoriasis) that led to study drug withdrawal and study Discontinuation:

- Subject (b) (6) experienced a TEAE of moderate application site pain on Study Day 3
- Subject (b) (6) experienced a TEAE of severe application site pruritus on Study Day 1
- Subject (b) (6) experienced a TEAE of moderate psoriasis on Study Day 6

All three TEAEs were considered treatment related. The TEAEs of application site pain and application site pruritus recovered/resolved at the end of the study but the TEAE of psoriasis was not recovered/not resolved at the end of the study.

#### Significant Adverse Events

Of the 51 subjects with any TEAEs, no subjects treated with HBP foam reported severe TEAEs. Four subjects (VEH Foam) had six TEAEs that were considered severe: gastric ulcer hemorrhage, application site pain, application site pruritus, hand fracture, radius fracture, and fracture pain.

#### Treatment Emergent Adverse Events and Adverse Reactions

Overall, the incidence of treatment emergent adverse events (TEAEs) was low and TEAEs were typically mild in severity across both treatment groups. In the combined Safety pool, there were 51 subjects (28/399, 7.0% HBP Foam and 23/374, 6.1% VEH Foam) with any TEAE. Of the 51 total subjects with any TEAE, 16 subjects (9 HBP Foam and 7 VEH Foam) had TEAEs that were considered to be treatment related.

The majority of TEAEs occurred in the Phase 3 studies (Phase 3 Safety Pool: Study 305, 306, and 310) which includes 351 and 353 subjects treated with HPB foam and

VEH foam, respectively. In this safety population, TEAEs that occurred in  $\geq 1\%$  of subjects and that occurred at a higher incidence in the HBP foam group (subjects treated for up to two weeks) are presented in Table 15. It should be noted that Adverse Reactions with an incidence of 0.9% were rounded up to 1%.

**Table 15: Adverse Reactions Occurring in  $\geq 1\%$  of Subjects Treated with HBP foam for up to Two Weeks**

|                                | <b>HBP Foam<br/>N=351</b> | <b>Vehicle Foam<br/>N=353</b> |
|--------------------------------|---------------------------|-------------------------------|
| <b><i>Adverse Reaction</i></b> | <b>%</b>                  | <b>%</b>                      |
| Application site pain          | 1%                        | <1%                           |
| Headache                       | 1%                        | <1%                           |

This table represents the recommendation for the presentation of adverse reactions in the label. Rounding the values and labeling application site pain as it was a notable adverse reaction is recommended. In the largest clinical trial (510) application site pain was reported at rates of 1% vs 0.5% for HBP foam and VEH foam, respectively. Additionally, in a prospective assessment of local skin reactions (LSR), burning/ stinging was the most frequently reported LSR. Evaluation of LSR is described further in Section 7.3.5 *Analysis of Submission-Specific Safety Issues*.

HPA axis suppression was reported as an TEAE only in Study 202, which evaluated this outcome. It is recommended that labeling describing HPA axis suppression will be included in section 12.3 of the prescribing information, as is customary for topical corticosteroids.

#### Laboratory Findings

Routine clinical laboratory evaluations (hematology, chemistry, and urinalysis) were performed only in the PK/HPA axis open-labelled study (Study 202). No clinically significant shift in laboratory parameters was observed with HBP Foam treatment.

#### Vital Signs

Vital signs were measured at baseline in studies that comprise the Safety Population dataset. No post-treatment evaluation of vital signs was performed.

#### Electrocardiograms (ECGs)/ QT

The applicant submitted sufficient information to support a conclusion that HBP foam does not present a risk for prolongation of cardiac repolarization. Observed systemic exposure to HBP at steady-state resulting from treatment with HBP Foam was minimal and appears similar to other halobetasol-containing topical products by cross-study comparison. The applicant is relying on historical corticosteroid use and has provided post-marketing pharmacovigilance data of drug products containing halobetasol propionate to support cardiac safety. The applicant cites the absence of any FARES

reports of cardiovascular safety signals, including QT/QTc prolongation and torsades de pointes, or any AEs possibly related to QT/QTc prolongation with halobetasol propionate. The applicant also conducted a literature search to identify any relevant clinical publications on corticosteroid-related arrhythmias and did not find any publications.

They also cite a 4-week repeat dose dermal minipig study for HBP foam which indicated no effects on ECG parameters.

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.

Immunogenicity

Not applicable for this application.

### **7.3.5. Analysis of Submission-Specific Safety Issues**

Refer to Section 6.2.1 for a discussion of HPA axis testing. The applicant adequately evaluated the potential for HPA axis suppression associated with use of their product in adults. Labeling should reflect this potential.

Local skin reactions (LSRs) were reported as an AE only if therapy or discontinuation of test article was required. Local safety was evaluated prospectively within the areas treated with test article at each study visit (Baseline, Day 8 and Day 15). LSR evaluations included assessment for telangiectasia, skin atrophy, folliculitis, edema, and burning/stinging within the treatment area. LSR evaluations were performed by the investigator at every study visit and rated by severity (none, mild, moderate, or severe).

Results of the Phase 3 Safety pool were similar to that of the Combined Safety pool, with a low incidence of LSRs throughout treatment. In the Phase 3 Safety pool, the majority of subjects had no LSRs at Baseline. For subjects with LSRs at Baseline, burning/stinging was the most frequently observed (HBP Foam: 41/351, 11.7% and VEH Foam: 44/353, 12.5%).

At Days 8 and 15, the most frequently reported LSR was burning/stinging with 23.1% of HBP Foam and 26.5% of VEH Foam subjects with burning/stinging at Day 8 and 15.5% of HBP Foam and 20.1% of VEH Foam subjects with burning/stinging at Day 15. At Day 15, the proportion of subjects who had treatment emergent (i.e. new onset or worsening) burning/stinging was 12.0% (41/343) of HBP Foam subjects and 14.8% (51/344) of VEH Foam subjects, respectively. There was one subject with a treatment emergent LSR of skin atrophy and two subjects with a treatment emergent telangiectasia; no subjects reported either of these treatment emergent LSRs in the VEH Foam group.

Local adverse skin reactions were consistent with those which may be seen with a topical corticosteroid and similar to those reported with marketed halobetasol products. This formulation contains ethanol which may contribute to the burning/ stinging noted. The following is recommended for the presentation of adverse skin reactions in the label:

*During these clinical trials, subjects were also assessed for local skin reactions including telangiectasia, skin atrophy, folliculitis, edema, and burning and stinging, at the site of application. Local skin reactions were reported as an adverse event only if therapy or discontinuation of test article was required. The most frequently reported local skin reaction was burning/stinging (incidence of 12.0% and 14.8% of patients treated with HBP foam and VEH foam, respectively), the majority of which were rated mild in severity. Cases of new onset skin atrophy (1) and telangiectasia (2) were reported with HBP foam, but not with VEH foam.*

### 7.3.6. Safety Analyses by Demographic Subgroups

Analyses of the safety data pools did not find substantial differences in the risk of adverse reactions based on age, gender, or race subgroups. However, because the sample sizes are small and the trials were not powered for these analyses, the data must be interpreted with caution.

TEAE incidence rates for HBP Foam and VEH Foam were similar for subjects <65 years and ≥65 years and for White and non-White subjects. For gender, incidence rates were higher for males treated with HBP Foam versus males treated with VEH Foam; whereas incidence was lower for females between the HBP Foam and VEH Foam groups. With the small sample sizes, it cannot be concluded that these differences are clinically meaningful.

These trends were the same for both the combined safety pool and the Phase 3 safety pool. Table 16 shows treatment emergent adverse events by demographic subgroups.

**Table 16: TEAE Incidence Rates by Age, Gender and Race for the Combined Safety Pool**

|           | HBP Foam<br>n (%)<br>N=39 |          | VEH Foam<br>n (%)<br>N=37 |          |
|-----------|---------------------------|----------|---------------------------|----------|
| By Age    |                           |          |                           |          |
| <65       | N=330                     | 26 (7.9) | N=305                     | 20 (6.6) |
| ≥65       | N=69                      | 2 (2.9)  | N=69                      | 3 (4.3)  |
| By Gender |                           |          |                           |          |
| Male      | N=231                     | 18 (7.8) | N=223                     | 9 (4.0)  |
| Female    | N=168                     | 10 (6.0) | N=151                     | 14 (9.3) |

|           |       |          |       |          |
|-----------|-------|----------|-------|----------|
| By Race   |       |          |       |          |
| White     | N=363 | 25 (6.9) | N=336 | 20 (6.0) |
| Non-White | N=36  | 3 (8.3)  | N=38  | 3 (7.9)  |

Source: applicant's ISS table 15

### 7.3.7. Specific Safety Studies/Clinical Trials

The applicant conducted a single dermal safety study to evaluate both contact sensitization and relative cumulative irritation potential.

**Title:** Sensitization and Cumulative Irritation Study of Halobetasol Propionate Foam 0.05% in Healthy Adult Subjects

**Study #:** 122-0551-108

**Study Objectives:**

- 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
- To determine the relative cumulative irritation potential of the test articles, in a sub population of subjects, by performing a 21-Day Cumulative Irritation Test (CIT).

**Study Design:**

This was a randomized, single site, double blind vehicle controlled study using a within-subject randomized design where each subject received the Halobetasol Propionate Foam and Vehicle (those that participated in the CIT also evaluated the positive and negative irritant controls). The trained skin evaluator was blinded to the identity of the test articles and controls and the previous scores. The study population was divided into two cells: (1) Subjects assigned to Cell 1 participated in the HRIPT portion of the study; and (2) Subjects in Cell 2 participated the 21-Day CIT portion of the study. Subjects in both cells were assessed for the ability of the Halobetasol Propionate Foam and Vehicle to induce contact sensitization using a challenge procedure.

For the HRIPT portion of the study (subjects assigned to Cell 1), the study involved nine consecutive applications of the Halobetasol Foam and Vehicle, for approximately 3 weeks, with evaluations occurring 48 to 72 hours after application (Induction Phase). Scoring was performed 15 minutes ( $\pm 5$  minutes) after patch removal at every visit by a qualified blinded grader.

For the CIT portion of the study (subjects assigned to Cell 2), the test articles (Halobetasol Propionate Foam and Vehicle), plus a positive irritant control of 0.2% sodium lauryl sulfate (SLS) in de-ionized water and a low irritant control of aqueous sodium chloride (0.9%), were applied under separate occlusive patches to the back of the subjects once daily (Monday through Sunday) for up to 21 days. Each application was observed after 24 hours for signs of irritation or inflammation. At each study visit,

scoring was performed 15 minutes ( $\pm 5$  minutes) after patch removal by a qualified blinded grader.

Following the Induction Phases for the HRIPT and CIT portions of the study, the subject then underwent a Rest Phase of 10-17 days in which no drug was applied, followed by a Challenge Phase, and Re-Challenge Phase (if necessary). For the Challenge Phase, Halobetasol Propionate Foam and Vehicle were applied for 48 hours ( $\pm 8$  hours) with evaluations 20 minutes ( $\pm 5$  minutes) after patch removal, and again 24 hours ( $\pm 8$  hours) and 48 hours ( $\pm 8$  hours) after patch removal. Total duration of the study for each subject was approximately 40 days. If necessary, a Re-Challenge Phase was conducted no sooner than 4 weeks after resolution of the original reactions.

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

**Investigational/ Test Products:**

- Halobetasol Propionate Foam 0.05%
- Halobetasol Propionate Foam Vehicle
- Control products were applied to subjects enrolled in the CIT and include:
  - o Aqueous Sodium Lauryl Sulfate (0.2%, w/v) (Positive Irritant Control)
  - o Aqueous Sodium Chloride (0.9%) (Low Irritant Control)

**Assessment of Cumulative Irritation:** The primary measure of the induction of cumulative irritation was determined through assessments of the application sites during the Induction Phase. Observed responses (e.g., erythema) were graded according to a protocol-specified grading scale in Table 17. Individual subject scores were reported by treatment and visit. For each test article the summation of irritation scores across the 21-day Induction Phase was determined. An individual Cumulative Irritancy Index (CII) was calculated for each subject and a mean CII value was calculated for each test article. Additionally, for each test article, the cumulative irritation score (sum total of subject irritation scores for all subjects) was calculated and each test article classified using the Berger and Bowman classification of the relative irritation potential.

**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 17. Individual subject scores were reported by treatment and visit.

**Table 17: Grading of responses (dermal safety study)**

| Grade                   | Definition          |
|-------------------------|---------------------|
| <b>Irritation Signs</b> |                     |
| 0                       | No visible reaction |

NDA/BLA Multi-disciplinary Review and Evaluation for NDA 210566  
 TRADENAME (halobetasol propionate) foam, 0.05%

|     |                                        |
|-----|----------------------------------------|
| 0.5 | Barely Perceptible (faint reactivity)  |
| 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 (+1)                                |
| D                                                               | Severe Dryness (+1)                                                                |
| P                                                               | Papule – red, solid, pinpoint elevation (+1)                                       |
| V                                                               | Vesicle – small elevation containing fluid (+1)                                    |
| B                                                               | Bulla reaction – fluid-filled lesion (blister) (+1)                                |
| S                                                               | Spreading – evidence of the reaction beyond the Webril pad area (+1)               |
| W                                                               | Weeping – result of a vesicular or bulla reaction - serous exudate (+1)            |
| I                                                               | Induration – solid, elevated, hardened, thickened skin (+1)                        |
| Superficial effects                                             |                                                                                    |
| G                                                               | Glazing (+2)                                                                       |
| Y                                                               | Peeling (+2)                                                                       |
| K                                                               | Scab, dried film of serous exudate of vesicular or bulla reaction (+2)             |
| R                                                               | Hyperpigmentation (reddish-brown discoloration of test site) (+1)                  |
| H                                                               | Hypopigmentation (loss of visible pigmentation at test site) (+1)                  |
| F                                                               | Fissuring – grooves in the superficial layers of the skin (+2)                     |
| 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 3 or greater was observed. To calculate the accumulated score, the letter grades assigned to the inflammatory responses were considered to be equal to 1. Under superficial effects, fissuring or scabbing and meaningful degrees of glazing or peeling (as determined by the investigator or designee) were also considered to be equal to 2. Hyper and hypopigmentation were considered equal to 1.

Source: protocol for study 108

### Subject Disposition

For the HRIPT portion (Cell 1), 197 subjects were enrolled of which 164 completed the

study and were evaluable for determining the contact sensitization potential of the test articles.

For the CIT portion (Cell 2), 48 subjects were enrolled of which 42 completed the study and were evaluable for determining both the cumulative irritation potential and the contact sensitization potential of the test articles.

There were a total of 206 subjects evaluable for contact sensitization (164 from Cell 1 [HRIPT] and 42 from Cell 2 [CIT]). A total of 39 subjects discontinued from the study. Subject disposition is summarized in Table 18. unrelated to test article for the 2 subjects who discontinued due to AEs

**Table 18: Subject Disposition for Trial 108**

| Subject Disposition            | HRIPT   |        | CIT   |        |
|--------------------------------|---------|--------|-------|--------|
| Disposition                    | N = 197 |        | N =48 |        |
|                                | N       | (%)    | N     | (%)    |
| Enrolled                       | 197     | 100.0% | 48    | 100.0% |
| ITT Population                 | 197     | 100.0% | 48    | 100.0% |
| Safety Population              | 197     | 100.0% | 48    | 100.0% |
| All Phases Population          | 164     | 83.3%  | 42    | 87.5%  |
| Completed Study                | 164     | 83.3%  | 42    | 87.5%  |
| Discontinued                   | 33      | 16.8%  | 6     | 12.5%  |
| Adverse Event                  | 2       | 1.0%   | 0     | 0.0%   |
| Withdrawal by subject          | 27      | 13.7%  | 5     | 10.4%  |
| Lost to follow-up              | 2       | 1.0%   | 0     | 0.0%   |
| Non-compliance with study drug | 1       | 0.5%   | 0     | 0.0%   |
| Other                          | 1       | 0.5%   | 1     | 2.1%   |
| ITT = Intent to Treat          |         |        |       |        |

### CIT (Cell 2) Outcome

The total subject irritation score varied across test articles. The positive irritant control (SLS) had the highest mean score (53.51), the low irritant control (saline) had the lowest mean score (13.76), and Halobetasol Propionate Foam and its Vehicle had intermediate scores (22.68 and

22.71, respectively), which were not significantly different. Similarly, the mean CII was highest for the positive irritant control (2.55), followed by Halobetasol Propionate Foam and its Vehicle (each, 1.08), and then the low irritant control (0.66). The range of worst irritant scores by

subject was similar across Halobetasol Propionate Foam (1.5 to 4.0), Vehicle (1.0 to 3.0), and the low irritant control (1.0 to 4.0), but tended to be higher in the positive irritant control (3.0 to 5.0).

The data indicate that the Halobetasol Propionate Foam and corresponding Vehicle were not significantly different from each other but were significantly less irritating than SLS, but more

irritating than the sodium chloride. Based on the Berger and Bowman calculation, (b) (4)

the positive and low irritant controls would be categorized as a 'Class IV-experimental cumulative irritant' and 'Class II-probably mild in use', respectively.

### **Contact Sensitization (Cell 1 + Cell 2) Outcome**

Seven subjects [Cell 1: Subject Numbers 64, 72, 83, 85, 151, and 189; Cell 2: Subject Number 541] exhibited skin reactivity to Halobetasol Propionate Foam and/or Vehicle during the Challenge Phase of the study, which may have been allergic in nature. Positive reactions, at challenge, were generally more intense and persistent than reactions noted during the induction period, and typically accompanied by some level of edema or papulovesicular response. One subject (Subject (b) (6)) experienced strong reactivity early in the Induction Phase. The subject showed reactivity (3-level erythema with edema) during Challenge; however, given the similar reactivity observed with this subject during the Induction Phase, this subject was not included in the sensitization analysis.

To determine the reproducibility of the reactivity, subjects underwent a Re-Challenge Phase a minimum of four weeks after the completion of the Challenge Phase/resolution of Challenge Phase reactivity. During Re-Challenge, the reactivity observed in six of the seven subjects [ Subject Numbers (b) (6) ] was confirmed, with subjects displaying persistent erythema (2 to 3-level erythema with edema).

One subject had sensitization reaction to Halobetasol Propionate Foam only, one subject to Vehicle only, and four subjects had sensitization reactions to both Halobetasol Propionate Foam and the Vehicle. The challenge/ rechallenge data for these 6 subjects is shown in Table 19.

**Table 19: Scores for Subjects Demonstrating Skin Reactivity in Challenge/Rechallenge Testing**

| Subject Number | Test Article Code                   | Evaluation Time (hr) | Challenge Phase    |                 |                     |                   | Re-Challenge Phase |                 |                     |                   | Sensitized |
|----------------|-------------------------------------|----------------------|--------------------|-----------------|---------------------|-------------------|--------------------|-----------------|---------------------|-------------------|------------|
|                |                                     |                      | Inflammatory Score | Letter Grade    | Superficial Effects | Accumulated Score | Inflammatory Score | Letter Grade    | Superficial Effects | Accumulated Score |            |
| (b) (6)        | Halobetasol Propionate Foam 0.05%   | 0.33                 | 0.5                | N/A             | N/A                 | 0.5               | 0.5                | N/A             | N/A                 | 0.5               | Yes        |
|                |                                     | 24                   | 0.5                | N/A             | N/A                 | 0.5               | 3                  | E (1)           | N/A                 | 4                 |            |
|                |                                     | 48                   | 0.5                | N/A             | N/A                 | 0.5               | 3                  | N/A             | N/A                 | 3                 |            |
|                | Halobetasol Propionate Foam Vehicle | 0.33                 | 1                  | N/A             | N/A                 | 1                 | 2                  | E (1) and W (1) | N/A                 | 4                 | Yes        |
|                |                                     | 24                   | 1                  | E (1)           | N/A                 | 2                 | 3                  | E (1) and D (1) | N/A                 | 5                 |            |
|                |                                     | 48                   | 2                  | E (1)           | N/A                 | 3                 | 3                  | N/A             | N/A                 | 3                 |            |
|                | Halobetasol Propionate Foam 0.05%   | 0.33                 | 0.5                | N/A             | N/A                 | 0.5               | 0.5                | N/A             | N/A                 | 0.5               | Yes        |
|                |                                     | 24                   | 3                  | E (1)           | N/A                 | 4                 | 3                  | E (1)           | N/A                 | 4                 |            |
|                |                                     | 48                   | 3                  | E (1) and D (1) | N/A                 | 5                 | 2                  | E (1)           | N/A                 | 3                 |            |
|                | Halobetasol Propionate Foam Vehicle | 0.33                 | 2                  | N/A             | N/A                 | 2                 | 2                  | E (1), V(1)     | Y (2)               | 6                 | Yes        |
|                |                                     | 24                   | 3                  | E (1)           | N/A                 | 4                 | 3                  | E (1)           | N/A                 | 4                 |            |
|                |                                     | 48                   | 3                  | E (1) and D (1) | N/A                 | 5                 | 2                  | E (1) and D (1) | N/A                 | 4                 |            |
|                | Halobetasol Propionate Foam 0.05%   | 0.33                 | 1                  | N/A             | N/A                 | 1                 | 0.5                | N/A             | N/A                 | 0.5               | No         |
|                |                                     | 24                   | 1                  | N/A             | N/A                 | 2                 | 1                  | N/A             | N/A                 | 1                 |            |
|                |                                     | 48                   | 2                  | N/A             | N/A                 | 2                 | 0.5                | N/A             | N/A                 | 0.5               |            |
|                | Halobetasol Propionate Foam Vehicle | 0.33                 | 1                  | N/A             | N/A                 | 1                 | 1                  | D (1)           | N/A                 | 2                 | No         |
|                |                                     | 24                   | 1                  | E (1)           | N/A                 | 2                 | 1                  | N/A             | N/A                 | 1                 |            |
|                |                                     | 48                   | 2                  | E (1)           | N/A                 | 3                 | 0.5                | N/A             | N/A                 | 0.5               |            |

| Subject Number | Test Article Code                   | Evaluation Time (hr) | Challenge Phase    |              |                     |                   | Re-Challenge Phase |                 |                     |                   | Sensitized |
|----------------|-------------------------------------|----------------------|--------------------|--------------|---------------------|-------------------|--------------------|-----------------|---------------------|-------------------|------------|
|                |                                     |                      | Inflammatory Score | Letter Grade | Superficial Effects | Accumulated Score | Inflammatory Score | Letter Grade    | Superficial Effects | Accumulated Score |            |
| (b) (6)        | Halobetasol Propionate Foam 0.05%   | 0.33                 | 0.5                | N/A          | N/A                 | 0.5               | 0.5                | N/A             | N/A                 | 0.5               | Yes        |
|                |                                     | 24                   | 1                  | N/A          | N/A                 | 1                 | 1                  | E (1)           | N/A                 | 2                 |            |
|                |                                     | 48                   | 1                  | N/A          | N/A                 | 1                 | 1                  | E (1)           | N/A                 | 2                 |            |
|                | Halobetasol Propionate Foam Vehicle | 0.33                 | 1                  | E (1)        | N/A                 | 2                 | 1                  | E (1)           | N/A                 | 2                 | Yes        |
|                |                                     | 24                   | 2                  | E (1)        | N/A                 | 3                 | 2                  | E (1)           | N/A                 | 3                 |            |
|                |                                     | 48                   | 1                  | E (1)        | N/A                 | 2                 | 2                  | E (1)           | N/A                 | 3                 |            |
|                | Halobetasol Propionate Foam 0.05%   | 0.33                 | 0.5                | N/A          | N/A                 | 0.5               | 0.5                | N/A             | N/A                 | 0.5               | Yes        |
|                |                                     | 24                   | 1                  | E (1)        | N/A                 | 2                 | 0.5                | P (1)           | N/A                 | 1.5               |            |
|                |                                     | 48                   | 1                  | E (1)        | N/A                 | 2                 | 2                  | E (1)           | N/A                 | 3                 |            |
|                | Halobetasol Propionate Foam Vehicle | 0.33                 | 0.5                | N/A          | N/A                 | 0.5               | 2                  | E (1)           | N/A                 | 3                 | Yes        |
|                |                                     | 24                   | 0.5                | P (1)        | N/A                 | 1.5               | 2                  | E (1) and D (1) | N/A                 | 4                 |            |
|                |                                     | 48                   | 0.5                | E (1)        | N/A                 | 1.5               | 3                  | E (1)           | N/A                 | 4                 |            |

NDA/BLA Multi-disciplinary Review and Evaluation for NDA 210566  
 TRADENAME (halobetasol propionate) foam, 0.05%

| Subject Number | Test Article Code                   | Evaluation Time (hr) | Challenge Phase    |              |                     |                   | Re-Challenge Phase |                 |                     |                   | Sensitized |
|----------------|-------------------------------------|----------------------|--------------------|--------------|---------------------|-------------------|--------------------|-----------------|---------------------|-------------------|------------|
|                |                                     |                      | Inflammatory Score | Letter Grade | Superficial Effects | Accumulated Score | Inflammatory Score | Letter Grade    | Superficial Effects | Accumulated Score |            |
| (b) (6)        | Halobetasol Propionate Foam 0.05%   | 0.33                 | 0                  | N/A          | N/A                 | 0                 | 0.5                | D (1)           | N/A                 | 1.5               | Yes        |
|                |                                     | 24                   | 0                  | N/A          | N/A                 | 0                 | 2                  | E (1)           | N/A                 | 3                 |            |
|                |                                     | 48                   | 0                  | N/A          | N/A                 | 0                 | 1                  | E (1)           | N/A                 | 2                 |            |
|                | Halobetasol Propionate Foam Vehicle | 0.33                 | 0.5                | N/A          | N/A                 | 0.5               | 0.5                | D (1)           | N/A                 | 1.5               | No         |
|                |                                     | 24                   | 1                  | N/A          | N/A                 | 1                 | 1                  | N/A             | N/A                 | 1                 |            |
|                |                                     | 48                   | 1                  | E (1)        | N/A                 | 2                 | 1                  | K (2)           | N/A                 | 3                 |            |
|                | Halobetasol Propionate Foam 0.05%   | 0.33                 | 1                  | N/A          | N/A                 | 1                 | 1                  | N/A             | N/A                 | 1                 | No         |
|                |                                     | 24                   | 2                  | E (1)        | N/A                 | 3                 | 1                  | N/A             | N/A                 | 1                 |            |
|                |                                     | 48                   | 2                  | N/A          | N/A                 | 2                 | 1                  | E (1)           | N/A                 | 2                 |            |
|                | Halobetasol Propionate Foam Vehicle | 0.33                 | 1                  | D (1)        | N/A                 | 2                 | 2                  | E (1)           | N/A                 | 3                 | Yes        |
|                |                                     | 24                   | 2                  | N/A          | N/A                 | 2                 | 1                  | E (1)           | N/A                 | 2                 |            |
|                |                                     | 48                   | 1                  | N/A          | N/A                 | 1                 | 1                  | E (1) and D (1) | N/A                 | 3                 |            |

The reactivity observed to both the Halobetasol Propionate Foam and Vehicle in Subject Number (b) (6) during the Challenge Phase was not reproduced in the Re-Challenge Phase and, therefore, not considered evidence of induced contact sensitization. The results indicated that six subjects appear to have exhibited induced contact allergy to Halobetasol Propionate Foam and/or the corresponding Vehicle, as the reactivity observed tended to be persistent after patch removal (i.e., 24-48 hours into the Re-Challenge Phase) and was often times accompanied by edema.

### Conclusions:

HBP Foam produced and intermediary irritancy response between the positive irritant control and low irritant control, where study product was applied under occlusion for 21 days. The product did not produce significant irritancy signal in the Safety Population, where subjects used the product under intended, non-occlusive conditions.

The HRIPT study suggests the possibility of induced contact allergy with HBP foam (and VEH foam). The nature of these reactions appears to be based on the formulation. HBP Foam and/or its vehicle did not exhibit skin reactivity the majority of subjects exposed to over the course of the HBP Foam clinical development program. The applicant's proposed labeling describes allergic contact dermatitis in the Warnings and Precaution Section.

### Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No malignancies were reported in the Safety Population.

#### Pediatrics and Assessment of Effects on Growth

The applicant has not conducted an evaluation of the safety and efficacy of HPB foam in the pediatric population. Refer to section 9 *Pediatrics* regarding the Pediatric Study Plan.

#### Overdose, Drug Abuse Potential, Withdrawal, and Rebound

HBP Foam is to be applied twice daily to plaque psoriasis lesions on the skin with a maximum recommended exposure of up to (b) (4) 50 grams per week. In the Phase 3 studies, 20 subjects (20/704, 2.8%) applied >150 grams of the test article per the two week treatment period (HBP Foam: 14/351, 4.0%; VEH Foam 6/353, 1.7%). The incidence of AEs does not appear to be affected by the increased dosages. There was one subject (Subject (b) (6), HBP Foam) who used 157.7 grams and had an AE (sinus congestion unrelated to treatment) on Day 14

There is no data to support an association of topical halobetasol with the potential for addiction, abuse, withdrawal or rebound. Physical dependency to HBP Foam was not observed in any clinical or non-clinical studies. The applicant did not evaluate abuse potential.

#### **7.3.8. Safety in the Postmarket Setting**

##### Safety Concerns Identified Through Postmarket Experience

HBP Foam has not been marketed in any country.

##### Expectations on Safety in the Postmarket Setting

The postmarketing experience for HBP Foam is expected to be similar to that of other topical halobetasol-containing products.

#### **7.3.9. Integrated Assessment of Safety**

The safety population for the foam formulation comprised 704 subjects. In total, 351 subjects were randomized to treatment with HBP Foam (351/704, 49.9%). Adult subjects with plaque psoriasis were exposed to up to approximately 50-60 grams/week of study product for two weeks. Adverse events did not identify a new safety signal. 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. All adrenal-suppressed subjects who received post-treatment follow-up testing showed a normal adrenal response at follow-up testing. There was a correlation between the dose and HPA axis suppression.

There were no deaths reported and the one subject that experienced a serious adverse event was treated with VEH foam. Overall, the incidence of treatment emergent adverse events (TEAEs) was low and TEAEs were typically mild in severity across both treatment groups. The most frequent TEAE by preferred term were application site pain and headache. This formulation contains ethanol which may contribute to the burning/stinging and application site pain noted.

Routine clinical laboratory evaluations (hematology, chemistry, and urinalysis) were conducted in one study (PK/HPA axis study) and revealed no clinically significant shift in laboratory parameters with HBP Foam treatment.

The HRIPT study suggests the possibility of induced contact allergy with HBP foam (and VEH foam). The nature of these reactions appears to be based on the formulation. HBP Foam and/or its vehicle did not exhibit skin reactivity the majority of subjects exposed to over the course of the HBP Foam clinical development program.

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

Labeling is recommended to mitigate the identified safety issues. This includes:

- mitigation of HPA axis suppression risk by limiting dosing to 50g/week, similar to other approved HBP products
- mitigation of local skin adverse events by limiting duration of use (up to 2 weeks) and use on susceptible body locations such as the face, groin and axillae
- mitigation of allergic contact dermatitis by advising discontinuation of use if allergic contact dermatitis is established

## SUMMARY AND CONCLUSIONS

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### 7.4. Summary and Conclusions

#### 7.4.1. Statistical Issues

There were no major statistical issues affecting the overall conclusion. The treatment effects were large and consistent across the endpoints and trials.

The magnitude of missing data was small at Day 15 for both trials (i.e., 1% for Trial 306 and 3% for Trial 310). The primary method for handling the missing data was the non-responder imputation (NRI). The pre-specified sensitivity analyses for handling the missing data used the methods of responder imputation, worst case scenario, observed data and multiple imputation (MI). HBP foam, 0.05% was statistically superior to vehicle foam across the various method for handling the missing data (p-values < 0.001), even in the extreme case of 'worst case scenario'.

Subgroup classification led to small number of subjects in most of the subgroups, and therefore, subgroup analyses may not be meaningful for these subgroups. The treatment effects for the various subgroups were comparable across the two trials.

#### **7.4.2. Conclusions and Recommendations**

To establish the efficacy of halobetasol propionate (HBP) foam, 0.05% for the topical treatment of plaque psoriasis, the applicant submitted data from two multicenter, randomized, double-blind, vehicle-controlled, parallel-group, pivotal Phase 3 trials (Trials 306 and 310). The trials enrolled adult subjects, who had moderate to severe plaque psoriasis based on the Investigator's Global Assessment (IGA) score, involving 2%-12% BSA. The design of the trials was identical, except from the sample size. The primary efficacy endpoint was the proportion of subjects achieving an IGA score of 0 or 1 at Day 15, with at least a 2-grade improvement from baseline. HBP foam was statistically superior to vehicle foam for the primary endpoint ( $p$ -value $<0.001$ ; see Table 9 in Section 7.2.1.4).

The applicant conducted a comprehensive assessment of the safety of HBP Foam in the target population. The size of the safety database and the safety evaluations were adequate to identify local and systemic treatment-emergent adverse reactions.

Submitted safety and efficacy data support approval of this NLA for HBP Foam for the topical treatment of adults with plaque psoriasis.

## **8 Advisory Committee Meeting and Other External Consultations**

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This application was not discussed at an Advisory Committee Meeting. The review team determined early in the application review cycle that this new product for psoriasis presented no novel or complex regulatory issues that required the input of an advisory committee. No significant clinical issues that might have impacted approval were identified in the team's review.

## 9 Pediatrics

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The agreed upon PSP is 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 (b) (4) years of age. A significant safety concern for use of halobetasol, (b) (4) in the pediatric population is HPA axis suppression. Because of a higher ratio of skin surface area to body mass, children are at a greater risk than adults of HPA-axis-suppression when they are treated with topical corticosteroids. For HBP foam, 24% (6/25) of adult subjects demonstrated HPA axis suppression, which was similar to the rate for HPB lotion (25%; 5/20). The incidence of HPA axis suppression in adults was determined to be sufficiently low and similar to other corticosteroid products used in adolescents, that further assessment in pediatric subjects is not precluded and will be specified as a post-marketing requirement (PMR). The applicant will be required to conduct a postmarketing pediatric study under PREA to assess safety in this pediatric population; see Section 12 for discussion of the PREA PMR.

### Regulatory History on Pediatric Development

A discussion of the pediatric development program was initiated at End-of-Phase 2 (8/21/2013 meeting). The applicant proposed the intention to request a waiver from conducting pediatric studies due to the product, (b) (4) not being suitable for the pediatric population and does not provide a meaningful therapeutic benefit over existing therapies for this population. The Agency concurred that a waiver seemed reasonable based on HPA axis suppression rates seen in adults in PK trial 122-0551-202, but a final decision regarding a waiver would not be made until after the pediatric waiver request is reviewed.

The sponsor submitted an initial Pediatric Study Plan (iPSP) on 10/21/2013 proposing (b) (4). At the time of the submission, highly potent topical steroids, including halobetasol propionate cream and ointment, had been approved in the pediatric population 12 years of age and older. The Division concluded that there is sufficient rationale to support conducting studies with highly potent topical steroids in the pediatric population 12 to 17 years of age with plaque psoriasis. Also, due to the lower prevalence of psoriasis in children less than 12 years of age and potential for higher HPA axis suppression, no studies are recommended in children under 12 years of age.

The pediatric plan was presented to Pediatric Review Committee (PeRC) on 12/18/2013 and the committee concurred with the Division's recommendation that the iPSP should include a request for a partial waiver for studies in pediatric patients less than 12 years of age and a proposal for PK/ HPA axis suppression/safety study in adolescents (12 to (b) (4) years) with psoriasis. An agreed upon iPSP letter was sent to the sponsor on May 15, 2014.

The Partial Waiver/Deferral/Plan for the application was presented to the Pediatric Review Committee (PeRC) on 2/28/2018. This product triggers PREA as a new dosage form. PeRC agrees with the Division to grant a partial waiver in children less than 12 years the product would be ineffective or unsafe. Waivers < 12 years of age have generally been granted in the class of superpotent steroids because of effects on HPA axis. PeRC recommends that the agreed upon reason for the partial waive is as follows:

“the product would be ineffective and/or unsafe in one or more of the pediatric group(s) for which a waiver is being requested.”

PeRC agrees with the divisions plan to grant a deferral of studies in adolescents ages 12 to 17 years until adult studies are completed and ready for approval.

The applicant submitted a draft protocol for pediatric study (b) (4) to IND 107,302 on 12/30/2014 and a final protocol was submitted in on 02/22/2018. The intention of the study will be to address the PREA PMR. The applicant also requested that the protocol serve as the basis for a PPSR. The Agency issued a Pediatric Written Request (PWR) on November 29, 2017 (b) (4)

(b) (4)  
Amended protocol (b) (4) was also (b) (4)  
submitted on 02/22/2018 to NDA 210566 (b) (4) The  
protocol is currently under review.

## 10 Labeling Recommendations

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### 10.1. Prescribing Information

The applicant submitted proposed Prescribing Information (PI) and carton/container labels. The review team provided recommendations regarding PI which are provided throughout this review. Also added to the proposed labeling in Section 5 is a Warning pertaining to *visual disturbance*. The Division is currently updating topical corticosteroids with this class warning based on postmarketing experience.

Jina Kwak, PharmD from the Office of Prescription Drug Promotion (OPDP) provided comments regarding the PI (Review dated 3/15/2018).

Carlos M Mena-Grillasca, RPh. from the Division of Medication Error Prevention and Analysis (DMEPA) provided comments regarding the proposed carton and container labels (Review dated 3/21/2018).

Labeling negotiations are currently ongoing.

### 10.2. Patient Labeling

The applicant submitted a Patient Package Insert (PPI) and Instructions for Use (IFU). Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) reviewed and provided comments jointly on patient labeling. Refer to the Patient Labeling Review by Susan Redwood, MPH, BSN, RN (dated 3/19/2018)

## 11 Risk Evaluation and Mitigation Strategies (REMS)

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Routine pharmacovigilance and product labelling are recommended as methods for postmarket risk evaluation and mitigation. As no additional Risk Evaluation and Mitigation Strategy (REMS) is required, the subsequent subsections are not applicable for this review and are omitted.

## 12 Postmarketing Requirements and Commitments

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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 the following:

A safety pharmacokinetic (PK) and HPA axis suppression study under maximal use conditions in subjects 12 years to < 17 years of age with psoriasis.

The applicant submitted a draft protocol for pediatric study (b) (4) to IND 107,302 on 12/30/2014 and a final protocol was submitted in on 02/22/2018. The recommended timeline for the PMR is as follows:

- Final Protocol Submission: submitted on 02/2018
- Study/Trial Completion: 06/2020
- Final Report Submission: 12/2020

A postmarketing commitment (PMC) is recommended. This PMC should be a vasoconstrictor assay (VCA) to identify the potency classification of the commercialized product.

The Agency considers the potency classification of topical corticosteroids serves as an initial guide to prescribers in helping them narrow down their choice of treatment from the realm of topical corticosteroids that are available.

## 13 Appendices

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### 13.1. References

A literature review was not conducted for this application.

### 13.2. Financial Disclosure

In compliance with 21 CFR Part 54, the applicant provided Certification/Disclosure Forms from clinical investigators and sub-investigators who participated in covered clinical studies. Prior to trial initiation, the investigators certified the absence of certain financial interests or arrangements or disclosed, as required, those financial interests or arrangements as delineated in 21 CFR 54.4(a)(3)(i-iv).

The covered clinical studies as defined in 21 CFR 54.2(e) were Trials 108, 202, 203, 305, 306, and 310. Refer to Section 7.1.1 for a description of clinical trial design.

The applicant also included Certification/Disclosure Forms from the 2 clinical investigators for Trial 101 (A Randomized, Evaluator Blinded, Within Subject, Single-Center Evaluation of the Vasoconstrictive Properties of Halobetasol Propionate 0.05% Foam Formulations in Healthy Volunteers). One of the 2 investigators [REDACTED] (b) (6) [REDACTED] had disclosable financial arrangements. In SDN 3 (10/16/2017) the applicant addressed the steps taken to minimize potential bias and the information provided appears adequate. Furthermore, it is this reviewer's opinion that study 122-0551-101 does not meet covered clinical studies as defined in 21 CFR 54.2(e) and this study is not included in the template below. The review team has found issues with the manner in which study 101 was conducted and finds that the results do not contribute to the safety demonstration of the product. Refer to section 13.5.1 for the review of the study.

**Table 20: Covered Clinical Studies for Financial Disclosure: 108, 202, 203, 305, 306, 310**

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                         |                                                                  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|------------------------------------------------------------------|
| Was a list of clinical investigators provided:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request list from applicant)        |
| Total number of investigators identified:<br>Trial 108: 1<br>Trial 202: 3<br>Trial 203: 2<br>Trial 305: 9<br>Trial 306: 8<br>Trial 310: 21                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                         |                                                                  |
| Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                         |                                                                  |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                         |                                                                  |
| 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)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u><br>Significant payments of other sorts: <u>0</u><br>Proprietary interest in the product tested held by investigator: <u>0</u><br>Significant equity interest held by investigator in sponsor of covered study: <u>0</u> |                                         |                                                                  |
| Is an attachment provided with details of the disclosable financial interests/arrangements:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request details from applicant)     |
| Is a description of the steps taken to minimize potential bias provided:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request information from applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                         |                                                                  |
| Is an attachment provided with the reason:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request explanation from applicant) |

List of Investigators by Study Site:

|              |         |            |
|--------------|---------|------------|
| 122-0551-108 | (b) (6) | 245 (100%) |
|--------------|---------|------------|

NDA/BLA Multi-disciplinary Review and Evaluation for NDA 210566  
 TRADENAME (halobetasol propionate) foam, 0.05%

|              |         |  |  |               |
|--------------|---------|--|--|---------------|
| 122-0551-202 | (b) (6) |  |  | 8<br>(32.0%)  |
|              |         |  |  | 12<br>(48.0%) |
|              |         |  |  | 5<br>(20.0%)  |
| 122-0551-203 | (b) (6) |  |  | 26<br>(59.1%) |
|              |         |  |  | 18<br>(40.9%) |
| 122-0551-305 | (b) (6) |  |  | 24<br>(16.7%) |
|              |         |  |  | 13<br>(9.0%)  |
|              |         |  |  | 18<br>(12.5%) |

| Protocol No. | Site Number<br>Investigator Name | Address | Phone Number<br>Fax Number | Subjects<br>Enrolled (% of |
|--------------|----------------------------------|---------|----------------------------|----------------------------|
|              | (b) (6)                          |         |                            | 15<br>(10.4%)              |
|              |                                  |         |                            | 16<br>(11.1%)              |

NDA/BLA Multi-disciplinary Review and Evaluation for NDA 210566  
 TRADENAME (halobetasol propionate) foam, 0.05%

|              |         |               |
|--------------|---------|---------------|
|              | (b) (6) | 18<br>(12.5%) |
|              |         | 18<br>(12.5%) |
|              |         | 4<br>(2.8%)   |
|              |         | 18<br>(12.5%) |
|              |         | 24<br>(15.9%) |
| 122-0551-306 |         | 24<br>(15.9%) |

| Protocol No. | Site Number<br>Investigator Name | Address | Phone Number<br>Fax Number | Subject<br>Enrolled (% of |
|--------------|----------------------------------|---------|----------------------------|---------------------------|
|              | (b) (6)                          |         |                            | 18<br>(12.0%)             |
|              |                                  |         |                            | 9<br>(6.0%)               |

NDA/BLA Multi-disciplinary Review and Evaluation for NDA 210566  
 TRADENAME (halobetasol propionate) foam, 0.05%

|              |         |               |
|--------------|---------|---------------|
| 122-0551-310 | (b) (6) | 18<br>(12.0%) |
|              |         | 11<br>(7.3%)  |
|              |         | 23<br>(15.2%) |
|              |         | 24<br>(15.9%) |
|              |         | 20<br>(4.9%)  |
|              |         | 30<br>(7.3%)  |
|              |         | 7<br>(1.7%)   |
|              |         | 9<br>(2.2%)   |

| Protocol No. | Site Number<br>Investigator Name | Address | Phone Number<br>Fax Number | Subject<br>s<br>Enrolled (% of |
|--------------|----------------------------------|---------|----------------------------|--------------------------------|
|              | (b) (6)                          |         |                            | 18<br>(12.0%)                  |
|              |                                  |         |                            | 9<br>(6.0%)                    |

NDA/BLA Multi-disciplinary Review and Evaluation for NDA 210566  
 TRADENAME (halobetasol propionate) foam, 0.05%

|              |         |  |  |               |
|--------------|---------|--|--|---------------|
| 122-0551-310 | (b) (6) |  |  | 18<br>(12.0%) |
|              |         |  |  | 11<br>(7.3%)  |
|              |         |  |  | 23<br>(15.2%) |
|              |         |  |  | 24<br>(15.9%) |
|              |         |  |  | 20<br>(4.9%)  |
|              |         |  |  | 30<br>(7.3%)  |
|              | (b) (6) |  |  | 7<br>(1.7%)   |
|              |         |  |  | 9<br>(2.2%)   |

| Protocol No. | Site Number<br>Investigator Name | Address | Phone Number<br>Fax Number | Subject<br>s<br>Enrolled (% of |
|--------------|----------------------------------|---------|----------------------------|--------------------------------|
|              | (b) (6)                          |         |                            | 11<br>(2.7%)                   |
|              |                                  |         |                            | 22<br>(5.3%)                   |
|              |                                  |         |                            | 11<br>(2.7%)                   |

NDA/BLA Multi-disciplinary Review and Evaluation for NDA 210566  
 TRADENAME (halobetasol propionate) foam, 0.05%

|  |         |  |              |
|--|---------|--|--------------|
|  | (b) (6) |  |              |
|  |         |  | 14<br>(3.4%) |
|  |         |  | 5<br>(1.2%)  |
|  |         |  | 34<br>(8.3%) |
|  |         |  | 20<br>(4.9%) |
|  |         |  | 20<br>(4.9%) |
|  |         |  | 7<br>(1.7%)  |
|  |         |  | 16<br>(3.9%) |
|  |         |  | 22<br>(5.3%) |

| Protocol No. | Site Number<br>Investigator Name | Address | Phone Number<br>Fax Number | Subject<br>S<br>Enrolled (% of |
|--------------|----------------------------------|---------|----------------------------|--------------------------------|
|              | (b) (6)                          |         |                            | 25<br>(6.1%)                   |
|              |                                  |         |                            | 30<br>(7.3%)                   |
|              |                                  |         |                            | 27<br>(6.6%)                   |

|  |         |              |
|--|---------|--------------|
|  | (b) (6) | 25<br>(6.1%) |
|  |         | 24<br>(5.9%) |
|  |         | 30<br>(7.2%) |

### 13.3. Clinical/Biostatistics

#### 1) Scale Used to Evaluate Efficacy

**Table 21: Investigator's Global Assessment (IGA)**

| Scale |              | Description      |                                                                                                                                               |
|-------|--------------|------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| 0     | Clear        | Scaling          | No evidence of scaling                                                                                                                        |
|       |              | Erythema         | No erythema (hyperpigmentation may be present).                                                                                               |
|       |              | Plaque elevation | No evidence of plaque elevation above normal skin level.                                                                                      |
| 1     | Almost Clear | 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.                                                          |
| 2     | Mild         | 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 level, typically with edges that indistinct or sloped, on some of the plaques. |
| 3     | Moderate     | Scaling          | No more than somewhat coarser scales predominate; most plaques are partially covered.                                                         |
|       |              | Erythema         | No more than moderate red coloration.                                                                                                         |

NDA/BLA Multi-disciplinary Review and Evaluation for NDA 210566  
 TRADENAME (halobetasol propionate) foam, 0.05%

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

Source: Applicant's protocols

**Table 22: Clinical Signs and Symptoms: Plaque Elevation**

| Scale |              | Description                                                                                                                  |
|-------|--------------|------------------------------------------------------------------------------------------------------------------------------|
| 0     | Clear        | No evidence of plaque elevation above normal skin level.                                                                     |
| 1     | Almost Clear | Very slight elevation above normal skin level, easier felt than seen.                                                        |
| 2     | Mild         | Slight but definite elevation above normal skin level, typically with edges that distinct or sloped, on some of the plaques. |
| 3     | Moderate     | Moderate elevation with rounded or sloped edges on most of the plaques.                                                      |
| 4     | Severe       | Marked elevation with hard sharp edges on most of the plaques.                                                               |

Source: Applicant's protocols

**Table 23: Clinical Signs and Symptoms: Scaling**

| Scale |              | Description                                                                                          |
|-------|--------------|------------------------------------------------------------------------------------------------------|
| 0     | Clear        | No evidence of scaling                                                                               |
| 1     | Almost Clear | Limited amount of very fine scales partially covers some of the plaques.                             |
| 2     | Mild         | Mainly fine scales; some plaques are partially covered.                                              |
| 3     | Moderate     | Somewhat coarser scales predominate; most plaques are partially covered.                             |
| 4     | Severe       | Coarse, thick tenacious scales predominate; virtually all of the plaques are covered; rough surface. |

Source: Applicant's protocols

**Table 24: Clinical Signs and Symptoms: Erythema**

| Scale |              | Description                                     |
|-------|--------------|-------------------------------------------------|
| 0     | Clear        | No erythema (hyperpigmentation may be present). |
| 1     | Almost Clear | Faint red coloration.                           |
| 2     | Mild         | Light red coloration.                           |
| 3     | Moderate     | Moderate red coloration.                        |
| 4     | Severe       | Dusky to deep red coloration.                   |

Source: Applicant's protocols

**Figure 6: 5-D Pruritus Scale**



Source: Applicant's protocols

#### **13.4. Nonclinical Pharmacology/Toxicology**

Clean version of the recommended labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION  
INDICATIONS AND USAGE

TRADENAME is a corticosteroid indicated for the topical treatment of plaque psoriasis in patients eighteen (18) years of age and older.

## 8 Use in Specific Populations

### 8.1 Pregnancy

#### Risk Summary

There are no available data on TRADENAME use in pregnant women to inform of a drug-associated risk for adverse developmental outcomes. In animal reproduction studies, increased malformations, including cleft palate and omphalocele, were observed after oral administration of halobetasol propionate during organogenesis to pregnant rats and rabbits. No comparisons of animal exposure with human exposure may be calculated due to minimal systemic exposure in humans after topical administration of TRADENAME [see *Clinical Pharmacology* (12.3)].

#### Data

##### *Animal Data*

Halobetasol propionate has been shown to cause malformations in rats and rabbits when given orally during organogenesis at doses of 0.04 to 0.1 mg/kg/day in rats and 0.01 mg/kg/day in rabbits. 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.

## 12 Clinical Pharmacology

### 12.1 Mechanism of Action

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

## 13 Nonclinical Toxicology

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of halobetasol propionate.

In a 90-day repeat-dose toxicity study in rats, topical administration of halobetasol propionate foam at dose concentrations from 0.005% to 0.05% or from 0.011 to 0.11 mg/kg/day of halobetasol propionate resulted in a toxicity profile consistent with long-term exposure to corticosteroids including adrenal atrophy, histopathological changes in several organ systems indicative of severe immune suppression, and opportunistic fungal and bacterial infections. A no observable adverse effect level could not be determined in this study. Although the clinical relevance of the findings in animals to

humans is not clear, sustained glucocorticoid-related immune suppression may increase the risk of infection and possibly the risk of carcinogenesis.

Halobetasol propionate was not found to be genotoxic in the Ames/Salmonella assay, in the Chinese hamster CHO/HGPRT assay, in the mouse micronucleus test, in the sister chromatid exchange test in somatic cells of the Chinese hamster, or in the chromosome aberration test in somatic cells of Chinese hamsters. Positive mutagenicity effects were observed in two genotoxicity assays: Chinese hamster nuclear anomaly test and mouse lymphoma gene mutation assay in vitro.

Studies in the rat following oral administration at dose levels up to 0.05 mg/kg/day indicated no impairment of fertility or general reproductive performance.

## 13.5. Clinical Pharmacology

### 13.5.1. Clinical Pharmacology Studies

#### **Study 122-0551-101**

**Title:** A randomized, evaluator blinded, within subject, single-center evaluation of the vasoconstrictive properties of Halobetasol propionate (HBP) 0.05% foam formulations in healthy volunteers

**Objective:** To determine the relative vasoconstrictive potency of novel foam formulations containing halobetasol propionate in comparison with Ultravate® (halobetasol propionate) cream 0.05% (Ranbaxy) and Topicort® LP (desoximetasone) emollient cream 0.05% (Taro Pharmaceuticals Inc).

**Study design:** The study enrolled 36 healthy male and female subjects aged 18 -65 years with skin condition on the forearms that allowed vasoconstriction assay (VCA). The subject's skin on the forearms must have a positive skin-blanching response to topical corticosteroids. There are five test articles as following:

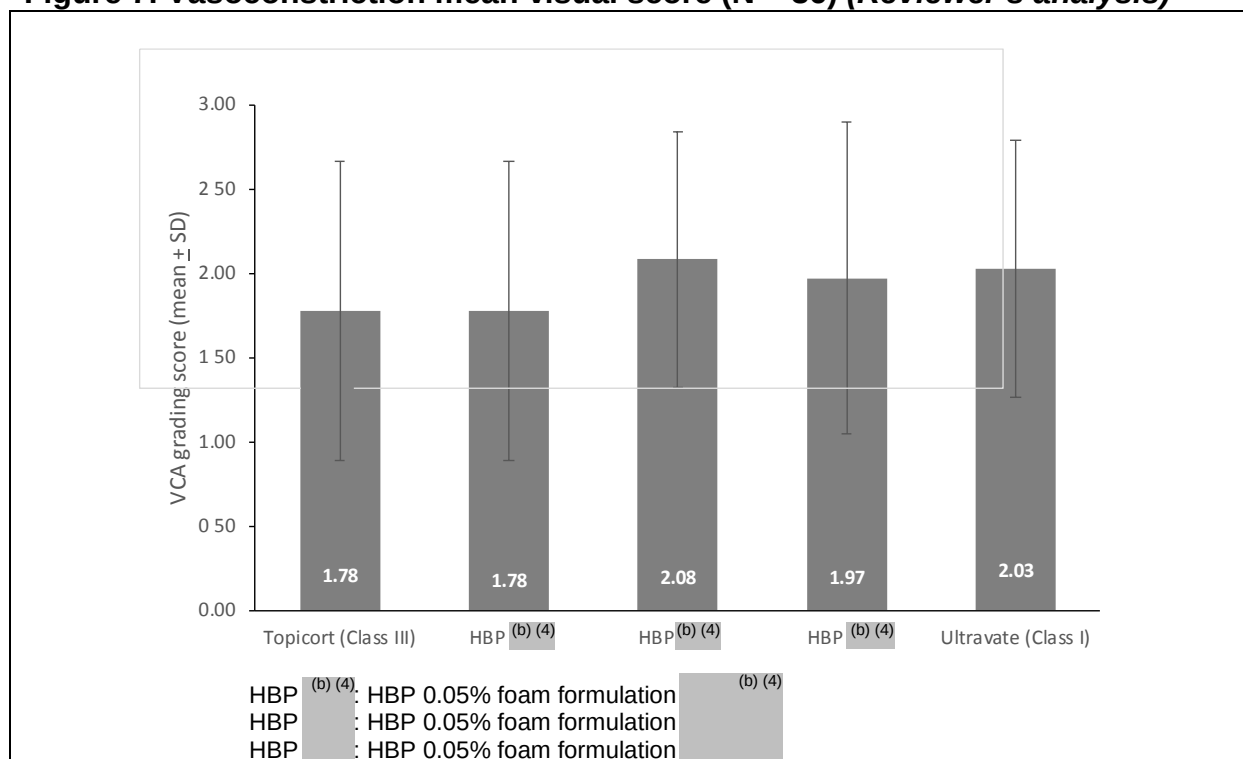
1. Halobetasol propionate foam 0.05% (Formulation# (b) (4))
2. Halobetasol propionate foam 0.05% (Formulation# (b) (4))
3. Halobetasol propionate foam 0.05% (formulation# (b) (4))
4. Ultravate (halobetasol propionate) cream 0.05% (Class I)
5. Topicort LP (desoximetasone) emollient cream 0.05% (Class III)

Each subject received a single topical application of all five products on the forearms for 18 hours. The efficacy endpoint was the degree of skin blanching assessed visually on a four-point ordinal scale (Stoughton-McKenzie method) ranging 0 = none, 1 = mild, 2 = moderate, and 3 = marked blanching.

#### **Results:**

Three HBP foam formulations (b) (4) had mean VCA scores of 1.78, 2.08, and 1.97, respectively (**Error! Reference source not found.**). Two reference products, Class I and Class III, demonstrated mean VCA scores of 2.03 and 1.78, respectively. Although the VCA score of Class I reference product was higher, there was no statistical difference between the mean VCA scores between two reference products. Two HBP formulations (b) (4) demonstrated comparable scores to the Class I reference product (Figure 1). However, the potency difference among all tested articles was not statistically different.

**Figure 7. Vasoconstriction mean visual score (N = 36) (Reviewer's analysis)**



**Reviewer's comments:** The study results were inconclusive due to lack of statistical difference in vasoconstriction between the reference products of Class I and Class III.

(b) (4)  
This reviewer recommended a post-marketing commitment to conduct a VCA study to identify the potency class of the commercial formulation of the product as potency class is used by the doctors to narrow down their treatment choice from the realm of topical corticosteroids that are available.

**Study 122-0551-202**

**Title:** An open level evaluation of the adrenal (HPA axis) suppression potential and pharmacokinetic properties of twice daily halobetasol propionate foam 0.05% in subjects with plaque psoriasis receiving two weeks of treatment

**Objective:** To determine the adrenal suppression potential and the PK properties of a new HBP foam applied twice daily in subjects with stable plaque psoriasis.

**Study design:** The study enrolled 25 subjects with plaque psoriasis. Two subjects were excluded in PK analysis; one subject missed two consecutive doses and the other subject did not have PK sampling at Visit 4. For HPA axis suppression, all 25 subjects were included. Subjects received twice daily for 14 days with the amount of 4.25g per application, for a total of approximately 60g per week. Cosyntropin Stimulation Test (CST) was performed for each subject at Visit 1 (Screening, which was at least 2 weeks before initiating dosing) and at the End of Study (EOS, Day 15) visit. The serum cortisol was assayed using a chemiluminescent immunoassay with a normal range of 3.1 and 22.4 mcg/dL. Subjects with an abnormal HPA axis response (defined as a post-stimulation serum cortisol level of  $\leq 18$  mcg/dL) at Screening were classified as a screen failure and not enrolled. An abnormal HPA axis response at EOS visit were considered as an adrenal suppression in the subject. For PK assessment, subjects had blood draws at pre-dose on Day 1, 8, and 9, and Day 14 and serial PK sampling post-dose on Day 14 at 1, 2, 4, 6, 8, 10, and 12 hours.

**Results:**

Demographic data of the study showed that there were 60% (15/25) male subjects and 40% (10/25) female subjects. Ethnicity of subjects was mainly non-Hispanic or Latino (76%, 19/25), and race was primarily White (84%; 21/25, Table 25).

**HPA axis suppression:** The HPA axis function was dichotomized to normal or abnormal based on the results of the CST which is an established surrogate measure of HPA axis suppression. Six of 25 subjects (24%) demonstrated an abnormal HPA axis response at Day 15, and all subjects returned to normal HPA axis function within 4 – 8 weeks after EOS: Mean cortisol level returned to  $24.55 \pm 3.33$  mcg/mL. The mean total dose (applied for 2 weeks) for the six subjects with suppressed HPA-axis was  $137.1 \pm 30.74$  g compared to the mean total dose of  $98.7 \pm 27.8$  g in subjects (N = 19) with normal HPA-axis function (Table 26). This justifies the dosing limitation of 50 g/week in the label. Subjects with HPA-axis suppression had a higher value of AUC than the subjects with normal HPA-axis function; mean AUC of HPA-axis suppressed was  $2779.0 \pm 2276.6$  pg·h/mL compared to mean AUC of  $1061.6 \pm 569.7$  pg·h/mL in normal HPA-axis function cohort (Table 26). However, there was high inter-subject variability in the systemic exposure to allow for any significant inference to be made.

**PK analysis:** PK data indicated that steady state exposure of HBP reached by Day 14 with the mean 12-hour post-dose HBP plasma concentrations differing by less than 9% between trough blood sampling times (i.e., Days 8, 14, and 15) and that the systemic exposure of topical HBP foam is low during the treatment period. At steady state, the

maximum plasma HBP concentration (mean  $\pm$  SD,  $C_{max}$ ) reached  $199.7 \pm 217.3$  pg/mL at median of 1 hour post-dose (Table 27). The  $C_{max}$  of 23 subjects ranged from 30.8 pg/mL to 945 pg/mL exhibiting a high inter-subject variability. The mean  $\pm$  SD AUC was  $1434.9 \pm 1310.6$  pg·h/mL.

**Safety:** There was a total of 8 out of 25 (32%) subjects with at least one adverse event (AE) with the overall total number of AEs is 12; one subject showed 5 of 12 AEs. Six (24%) subjects showed HPA axis suppression that was reversible on stopping the treatment. None of AEs required a change in treatment regimen. Only one AE (nasal congestion) required therapy. There were no local skin reactions reported related to topical steroid use in this study; telangiectasia, skin atrophy, and folliculitis were absent for all subjects (for further information on clinical safety, see Clinical review).

**Table 25. Demographic information (Source: Table 11.2-1 of Study report 122-0551-202)**

| CHARACTERISTIC         | N (%)<br>N=25 |
|------------------------|---------------|
| SEX AT BIRTH           |               |
| Male                   | 15 (60.0%)    |
| Female                 | 10 (40.0%)    |
| ETHNICITY              |               |
| Not Hispanic or Latino | 19 (76.0%)    |
| Hispanic or Latino     | 6 (24.0%)     |
| RACE                   |               |
| White                  | 21 (84.0%)    |
| Asian                  | 3 (12.0%)     |
| Islander               | 1 (4.0%)      |
| AGE (years)            |               |
| Mean                   | 50.7          |
| Median                 | 53.3          |
| Standard Deviation     | 11.64         |
| Minimum to Maximum     | 29.8 to 71.0  |

**Table 26. Summary of HPA axis response, dose and HBP AUC in Study #122-0551-202**

|                                                           | HPA-axis<br>Suppressed | HPA-axis<br>Non-suppressed | All                 |
|-----------------------------------------------------------|------------------------|----------------------------|---------------------|
| N                                                         | 6                      | 19                         | 25                  |
| Total dose<br>(mean $\pm$ SD, g)                          | $137.1 \pm 30.74$      | $98.7 \pm 27.83$           | $107.9 \pm 31.88$   |
| Cortisol level<br>(mean $\pm$ SD,<br>mcg/mL) at Day<br>15 | $11.13 \pm 4.13$       | $22.42 \pm 3.84$           | $19.71 \pm 6.21$    |
| *HBP AUC<br>(mean $\pm$ SD,<br>pg·h/mL)                   | $2779.0 \pm 2276.6$    | $1061.6 \pm 569.74$        | $1434.9 \pm 1281.8$ |

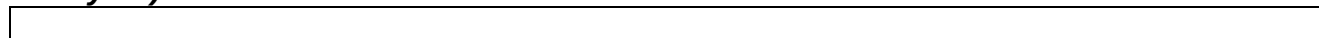
\* Two subjects are excluded (N = 5 and 18 for HPA-axis suppressed and non-suppressed, respectively) due to missed treatments and missed PK blood draws.

**Table 27. Systemic PK parameters of HBP foam 0.05% (Source: Table 11.5-2 of Study report 122-0551-202)**

| PK Population (n = 23) |                       |                 |
|------------------------|-----------------------|-----------------|
| Parameter              |                       |                 |
| $C_{max}$<br>(pg/mL)   | Mean (SD)             | 199.7 (217.3)   |
|                        | Geometric Mean (CV%)† | 137.1 (104%)    |
|                        | Median                | 150             |
|                        | Range: Min to Max     | 30.8 to 945     |
| $T_{max}$<br>(h)       | Mean (SD)             | 3 (3.96)        |
|                        | Median                | 1               |
|                        | Range: Min to Max     | 0 to 12         |
| $C_{min}$<br>(pg/mL)   | Mean                  | 80.7 (69.5)     |
|                        | Geometric Mean (CV%)† | 62.0 (82%)      |
|                        | Median                | 64.9            |
|                        | Range: Min to Max     | 21.4 to 287     |
| $T_{min}$<br>(h)       | Mean (SD)             | 6.6 (4.1)       |
|                        | Median                | 8               |
|                        | Range: Min to Max     | 0 to 10         |
| $C_{avg}$<br>(pg/mL)   | Mean (SD)             | 119.6 (109.2)   |
|                        | Geometric Mean (CV%)† | 89.5 (88.2%)    |
|                        | Median                | 101.1           |
|                        | Range: Min to Max     | 25.3 to 484.1   |
| AUC<br>(h*pg/mL)       | Mean (SD)             | 1434.9 (1310.6) |
|                        | Geometric Mean (CV%)† | 1073.8 (88.2%)  |
|                        | Median                | 1213.4          |
|                        | Range: Min to Max     | 304 to 5809.3   |

**Reviewer's comments:** The analysis to evaluate the relation of HPA-axis function and total dose after 2-week application or AUC of HBP indicated that there is a trend that higher AUC or higher total dose may be correlated to a decrease of systemic cortisol level, an indicative of HPA-axis function, on Day 15 (Figure 8 **Error! Reference source not found.**).

**Figure 8. Comparison of systemic cortisol level vs AUC or Total dose (Reviewer's analysis)**



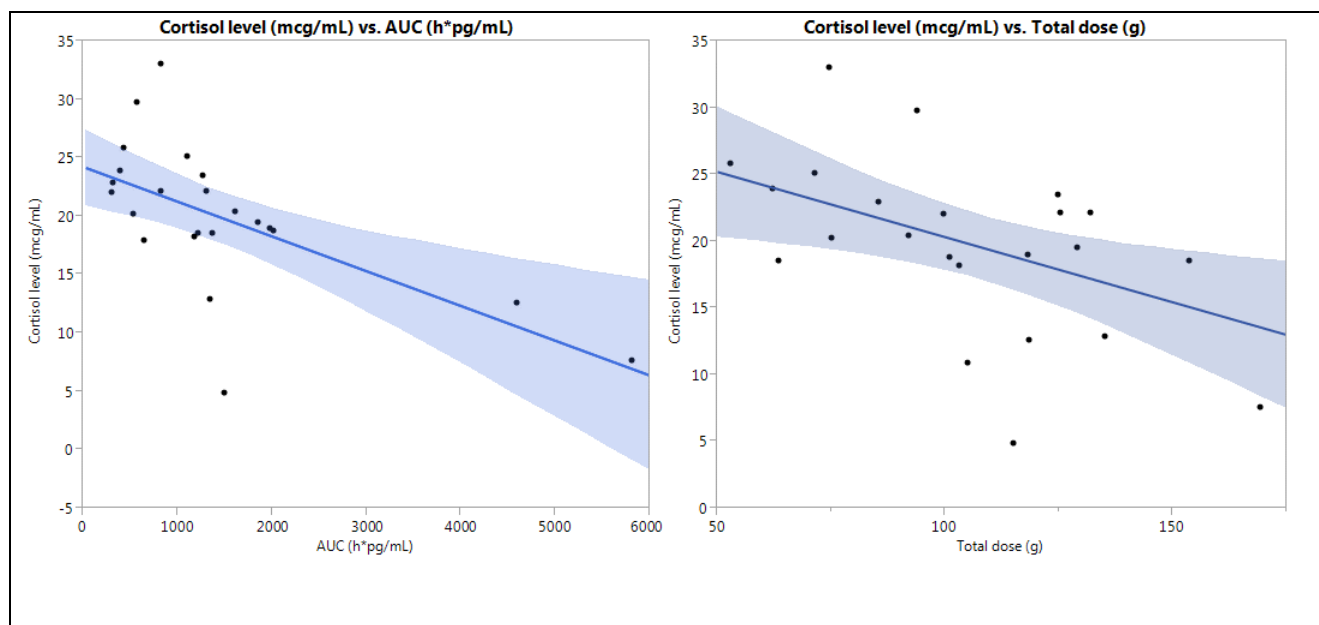
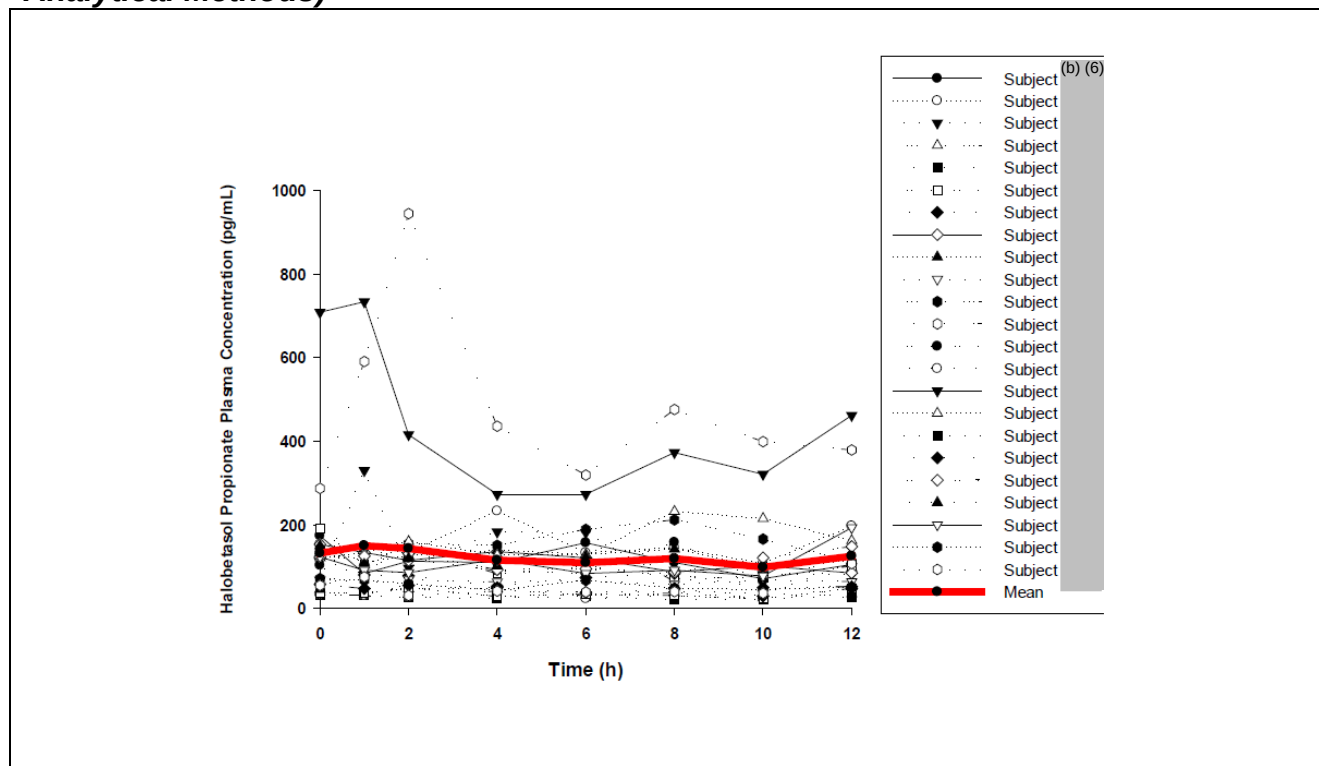


**Figure 9. Mean plasma HBP concentration-time profile on Day 14 in Study #122-0551-202 (Source: Figure 1 of 2.7.1 Summary of Biopharm Studies & Associated Analytical Methods)**



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/s/  
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CRISTINA Petruccelli Attinello  
05/24/2018

JILL A LINDSTROM  
05/24/2018  
Concur.

**OFFICE OF CLINICAL PHARMACOLOGY  
MEMORANDUM**

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|                           |                                                        |                         |            |
|---------------------------|--------------------------------------------------------|-------------------------|------------|
| <b>NDA:</b>               | 210566                                                 | <b>Submission Date:</b> | 07/28/2017 |
| <b>Brand Name</b>         | N/A                                                    |                         |            |
| <b>Generic Name</b>       | Halobetasol propionate foam, 0.05%                     |                         |            |
| <b>Primary Reviewer</b>   | Luke Oh, Ph.D.                                         |                         |            |
| <b>Secondary Reviewer</b> | Chinmay Shukla, Ph.D.                                  |                         |            |
| <b>Tertiary Reviewer</b>  | Chandra Sahajwalla, Ph.D.                              |                         |            |
| <b>OCP Division</b>       | Division of Clinical Pharmacology 3                    |                         |            |
| <b>OND Division</b>       | Division of Dermatology and Dental Products            |                         |            |
| <b>Submission Type</b>    | Original NDA                                           |                         |            |
| <b>Applicant</b>          | Therapeutics, Inc.                                     |                         |            |
| <b>Indication</b>         | Plaque psoriasis in patients 18 years of age and older |                         |            |

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**Summary:** The Applicant is seeking approval of an alternative dosage form of halobetasol propionate (HBP) to treat plaque psoriasis. Halobetasol propionate, a super-potent corticosteroid, is currently being marketed as 0.05% HBP Cream, ointment, and lotion. The applicant has obtained a right of reference for Ultravate<sup>®</sup> cream and ointment and hence they have followed a 505(b)(1) regulatory pathway. This submission includes study reports from seven clinical studies including one Phase 1 vasoconstrictor assay (VCA) study and one Phase 2 Pharmacokinetic (PK)/ Hypothalamic-pituitary-adrenal (HPA) study. The Phase 2 HPA/PK study was conducted under maximal use conditions in subjects with plaque psoriasis with at least 15% body surface area (BSA) involved. The proposed dosing regimen is similar to other HBP products, which is twice daily for 14 days, and the total dose is limited to (b) (4) 50g per week.

In the Phase 2 PK/HPA Study the systemic exposure of HBP was quantifiable in 23 out of 25 subjects, and systemic concentration were at steady state by Day 14. The mean  $\pm$  SD  $C_{max}$  and AUC on Day 14 were  $199.7 \pm 217.3$  pg/mL and  $1434.9 \pm 1310.6$  pg·h/mL, respectively, and 6 out of 25 subjects (24%) with plaque psoriasis developed a HPA axis suppression by the end of treatment (i.e., Day 14). All HPA axis suppression returned to normal after discontinuing the drug product. The incident of HPA axis suppression in adults was sufficiently low to allow for further assessment in pediatric subjects, which will be requested as a post marketing requirement (PMR).

The outstanding issue from a clinical pharmacology's perspective is that VCA Study # 122-0551-101 did not include the to-be-marketed formulation and failed to demonstrate the potency classification of tested drug products. The VCA study included three HBP foam formulations and two reference products of Class I and Class III. No statistical difference of potency was

observed between Class I and Class III reference products. Potency of the topical corticosteroid product is included in the label as this information helps medical practitioners narrow down their treatment choice from the realm of topical corticosteroids that are available. However, since potency classification impacts the labeling, VCA study to identify the potency class is being requested as a post marketing commitment (PMC).

The clinical pharmacology review is complete and will be added to a NDA Multi-disciplinary Review and Evaluation which will be uploaded to DARRTS when it is finalized. Refer to the Multi-disciplinary Review and Evaluation for details.

**Recommendation:** From a Clinical Pharmacology standpoint, NDA 210566 is acceptable provide the applicant adequately addresses the labeling comments.

**Post Marketing Commitment (PMC):** Conduct a VCA study with the final commercial formulation to identify the potency class of the HBP foam product using visual assessment as a primary end-point.

**Reviewer comments:** *As described in Summary, the potency classification is an initial guide of topical corticosteroid selection for medical practitioners, and this information can be submitted as PMC.*

**Post-Marketing Requirement (PMR):** Conduct a maximal use PK and HPA axis suppression study in subjects 12 to < 17 years of age with psoriasis.

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/s/  
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LUKE Y OH  
04/11/2018

CHINMAY SHUKLA  
04/11/2018

CHANDRAHAS G SAHAJWALLA  
04/11/2018