CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209354Orig1s000

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

Application Type	NDA
Application Number(s)	209354
Priority or Standard	Standard (RS)
Submit Date(s)	August 15, 2018
Received Date(s)	August 15, 2018
PDUFA Goal Date	February 15, 2019
Division/Office	Division of Dermatology and Dental Products Office of Drug Evaluation III
Review Completion Date	April 24, 2019
Established/Proper Name	halobetasol and tazarotene lotion, 0.01%/0.045%
(Proposed) Trade Name	Duobrii
Pharmacologic Class	Corticosteroid/Retinoid
Code name	N/A
Applicant	Bausch Health Americas, Inc. formerly known as Dow Pharmaceuticals, Inc.
Doseage form	Lotion
Applicant proposed Dosing Regimen	Topical application once daily
Applicant Proposed Indication(s)/Population(s)	For the topical treatment of plaque psoriasis
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	9014002 |Psoriasis (disorder)|
Recommendation on Regulatory Action	Approve
Recommended Indication(s)/Population(s) (if applicable)	For the topical treatment of plaque psoriasis in adults
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	9014002 |Psoriasis (disorder)|
Recommended Dosing Regimen	Apply a thin lagyer once daily to cover only affected areas and rub gently

Table of Contents

Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Strother Dixon
Chief, Project Management Staff	Barbara Gould
Nonclinical Reviewer	Renqin Duan
Nonclinical Team Leader	Barbara Hill
Pharmacology Reviewer(s)	Yanhui Lu
Pharmacology Team Leader(s)	Chinmay Shukla
Clinical Reviewer	Hamid Tabatabai
Clinical Team Leader	David Kettl
Statistical Reviewer	Matthew Guerra
Statistical Team Leader	Mohamed Alosh
Cross-Disciplinary Team Leader	David Kettl
Deputy Director (Signatory)	Jill Lindstrom

Additional Reviewers of Application

DDDP	
– **Associate Director for Labeling**	Nancy Xu
– **Deputy Director for Safety**	Tatiana Oussova
DPMH	
– **Maternal Health Reviewer**	Jane Liedtka
– **Maternal Health Team Leader**	Miriam Dinatale
– **Regulatory Project Manager**	Lori Gorski
OMP/DMPP	
– **Patient Labeling Reviewer**	Susan Redwood
– **Senior Patient Labeling Reviewer**	Shawna Hutchins
– **Associate Director for Patient Labeling**	LaShawn Griffiths
OPDP	
– **Regulatory Review Officer**	Laurie Buonaccorsi
– **Regualtory Review Team Leader**	Matthew Falter
OPQ	
• **Drug Product Reviewer**	Caroline Strasinger
• **Drug Product Team Leader(s)**	Jean (Zhe) Tang/Hamid Shafiei
• **Drug Substance Reviewer**	Ramsharan Mittal
• **Drug Substance Team Leader**	Donna Christener
• **Biopharmaceutics Reviewer**	An-Chi Lu
• **Biopharmaceutics Team Leader**	Vidula Kolhatkar
• **Microbiology Reviewer**	Vinayak Pawar
• **Facilities**	Lauren Nelson
• **Regulatory Business Project Manager**	Bamidele (Florence) Aisida
OSE/DMEPA	
• **DMEPA Safety Evaluator**	Madhuri R. Patel
• **DMEPA Team Leader**	Sevan Kolejian

DDDP=Division of Dermatology and Dental Products
DPMH=Division of Pediatric and Maternal Health
OB=Office of Biostatistics
OCP=Office of Clinical Pharmacology
OPDP=Office of Prescription Drug Promotion

OPQ=Office of Pharmaceutical Quality
OSE= Office of Surveillance and Epidemiology
- DMEPA=Division of Medication Error Prevention and Analysis
- DRISK=Division of Risk Management

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Renqin Duan, PhD	ODE III/DDDP	Section: 5	Select one: ✓ Authored ___ Approved
	Signature: *{See appended electronic signature page}*			
Nonclinical Supervisor	Barbara Hill, PhD	ODE III/DDDP	Section: 5	Select one: ___ Authored ✓ Approved
	Signature: *{See appended electronic signature page}*			
Clinical Pharmacology Reviewer	Yanhui Lu, PhD	OCP/DCPIII	Sections: 6	Select one: ✓ Authored ___ Approved
	Signature: *{See appended electronic signature page}*			
Clinical Pharmacology Team Leader	Chinmay Shukla, PhD	OCP/DCPIII	Section: 6	Select one: ___ Authored ✓ Approved
	Signature: *{See appended electronic signature page}*			
Clinical Reviewer	Hamid Tabatabai, MD	ODE III/DDDP	Section: 1	Select one: ✓ Authored ___ Approved
	Signature: *{See appended electronic signature page}*			
Clinical Team Leader	David Kettl, MD	ODE III/DDDP	Section: 1	Select one: ___ Authored ✓ Approved
	Signature: *{See appended electronic signature page}*			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Deputy Division Director	Jill Lindstrom, MD		Sections: ALL	Select one: ___ Authored ✓ Approved
	Signature: *{See appended electronic signature page}*			

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
ECG	electrocardiogram
FDA	Food and Drug Administration
IND	Investigational New Drug
NDA	new drug application
NME	new molecular entity
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
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

This application is a Complete Response resubmission of NDA 209354 for Duobrii lotion (halobetasol propionate and tazarotene lotion, 0.01%/0.045%) for the treatment of plaque psoriasis, under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act. NDA 209354 was initially submitted under section 505 (b)(2) regulatory pathway. The applicant requested a change in regulatory pathway from section 505(b)(2) to section 505(b)(1) in response to the Agency's Complete Response (CR) letter dated 15-June-2018.

The Agency's first-cycle review of NDA 209354 concluded that the applicant did not establish an adequate clinical bridge to the listed drugs Ultravate (halobetasol propionate) Cream, 0.05% and Tazorac (tazarotene) Cream, 0.05%. Therefore, the applicant could not rely on the Agency's findings of safety (including nonclinical toxicology data) for the listed drugs to support NDA approval.

Since the Complete Response action, the applicant acquired right-of-reference to all the nonclinical studies conducted to support approval of Ultravate (halobetasol propionate) Cream, 0.05% and Tazorac (tazarotene) Cream/Gel, 0.05% and 0.1%. In addition, the applicant has conducted additional nonclinical studies to support the safety of their new combination drug product.

The Pharmacology/Toxicology reviewer for the nonclinical data in the resubmission package for NDA 209354 concluded that Duobrii lotion is approvable for the topical treatment of plaque psoriasis from a Pharmacology/Toxicology perspective.

The Clinical and Clinical Pharmacology review of the data submitted under the first-cycle review found NDA 209354 to be acceptable for approval, provided that the applicant adequately addressed the nonclinical deficiencies listed in section 5 Nonclinical Pharmacology/Toxicology, and in the Agency's CR letter dated 15-June-2018.

No new clinical data was included in the resubmission package for NDA 209354. Review of the Clinical data included under the initial submission of NDA 209354 led to the following conclusions regarding efficacy and safety of Duobrii lotion for topical treatment of plaque psoriasis:

To establish the effectiveness of Duobrii, the applicant submitted data from two identically-designed, randomized, multicenter, vehicle-controlled, parallel-group, pivotal Phase 3 trials (Trials 301 and 302). Efficacy data submitted by the applicant support approval of this NDA for Duobrii lotion, for the treatment of adults with plaque psoriasis.

To support the safety of DUOBRII lotion, the applicant pooled data from the two phase 3 trials (Trials 301 and 302). The applicant conducted sufficient assessment of the safety of DUOBRII lotion in the target population. The size of the safety database and the safety evaluations were adequate to identify treatment-emergent adverse reactions.

A maximal use PK/HPA suppression/clinical safety study in pediatric subjects (b) (4) to less than 17 years of age with moderate to severe plaque psoriasis was agreed to in an agreed iPSP on 6/16/2016 and will be included as a PREA PMR.

This reviewer concurs with the assessment from the review team that all of the issues in the Complete Response action letter have been adequately addressed and the application can be approved pending agreement with the applicant of final labeling.

Note: The reader is referred to 1st Cycle Unireview of NDA 209354 for other discipline reviews.

2 Therapeutic Context

See 1st Cycle Unireview of NDA 209354

3 Regulatory Background

See 1st Cycle Unireview of NDA 209354

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

See 1st Cycle Unireview of NDA 209354

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The applicant has developed a combination drug product, DUOBRII (halobetasol propionate and tazarotene) lotion, 0.01%/0.045%, for the treatment of plaque psoriasis. The two drug substances contained in the drug product, halobetasol propionate and tazarotene, have been marketed for the treatment of plaque psoriasis for more than 20 and 10 years, respectively. All excipients used in DUOBRII (halobetasol propionate and tazarotene) lotion, 0.01%/0.045% are commonly used in topical products and are listed in the FDA's Inactive Ingredient Guide.

The applicant is seeking approval of DUOBRII (halobetasol propionate and tazarotene) lotion, 0.01%/0.045%, for the treatment of plaque psoriasis in patients 18 years of age and older via a 505(b)(1) regulatory pathway since the applicant has obtained right-of-reference to all the nonclinical studies conducted to support approval of Ultravate (halobetasol propionate) Cream, 0.05% and Tazorac (tazarotene) Cream/Gel, 0.05% and 0.1%. In addition, the applicant has conducted additional nonclinical studies to support the safety of their new combination drug product. The proposed dosing regimen is to topically apply the drug product to the affected area once daily. The total dosage should not exceed approximately 50 g per week because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis.

The applicant references the NDAs for Ultravate Cream, Tazorac Cream and Tazorac Gel for nonclinical pharmacology, pharmacokinetics (PK), and toxicology data including

fertility and reproduction, embryofetal development, genotoxicity and carcinogenicity (tazarotene only). The toxicities of both drugs are well characterized and typical for their respective drug classes.

The applicant submitted a pivotal 3-month repeat dose minipig dermal toxicity study. This study was conducted with five treatment groups included the IDP-118 Lotion at low (halobetasol propionate 0.002%/tazarotene 0.010%), mid (halobetasol propionate 0.01%/tazarotene 0.045%) and high doses (halobetasol propionate 0.02%/tazarotene 0.09%), as well as monad groups containing halobetasol propionate (0.02%) or tazarotene (0.090%) in lotion vehicle. The mid dose group was treated with the to-be-marketed formulation, which was later used in the Phase 3 clinical studies. Administration of IDP-118 Lotion as well as halobetasol propionate and tazarotene monads by once daily dermal application for 90 days was well tolerated in minipigs at low, clinical, and enhanced strengths up to 0.02% halobetasol propionate/0.090% tazarotene. IDP-118 Lotion was associated with body weight decreases, consistent with adverse effects of topical corticosteroids, and correlated to halobetasol propionate systemic exposure. Target organs included those previously reported for tazarotene and halobetasol propionate (i.e., skin dose site, adrenal glands, and thymus). The decreased organ weights and/or microscopic changes observed in target organs showed partial or full reversibility following a 1-month recovery period. No new toxicities or toxicological interactions arising from the combination were noted in the study. There were no test article-related ECG abnormalities in this study. Steady state exposures (AUC_{0-24}) at the mid dose (clinical strength) were 20 (males) and 14 ng•hr/mL (females) for tazarotenic acid (the active metabolite of tazarotene), and 2.6 (males) and 1.9 ng•hr/mL (females) for halobetasol propionate.

DUOBRII Lotion is approvable for the topical treatment of plaque psoriasis from a Pharmacology/Toxicology perspective. There are no recommended nonclinical PMCs/PMRs for this NDA.

5.2. Referenced NDAs, BLAs, DMFs

This NDA makes reference to the following DMFs.

DMF (b) (4)
DMF
DMF

The applicant has provided letters authorizing FDA to refer to the relevant nonclinical data for NDA 19967, NDA 20600 and NDA 21184 to support the current NDA.

NDA 19967: Ultravate (halobetasol propionate) Cream, 0.05%, approved on December 27, 1990.
NDA 20600: Tazorac (tazarotene) Gel, 0.05% and 0.1%, approved on June 13, 1997.

NDA 21184: Tazorac (tazarotene) Cream, 0.05% and 0.1%, approved on September 29, 2000.

The following nonclinical pharmacology and toxicology studies were reviewed under INDs 111218 or 126779. A summary of these studies is provided below. The code name for this drug product is IDP-118 lotion.

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 plaque psoriasis is unknown.

Tazarotene is a retinoid prodrug which is converted to its active form, the carboxylic acid of tazarotene, by deesterification. Tazarotenic acid binds to all three members of the retinoic acid receptor (RAR) family: RARα, RARβ, and RARγ, but shows relative selectivity for RARβ, and RARγ and may modify gene expression. The clinical significance of these findings for the treatment of plaque psoriasis 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

Study 1 Effects of Tazarotene, Tazarotenic Acid and Halobetasol Propionate and Mixtures on Cloned hERG Potassium Channels Expressed in Mammalian Cells (Study # V01-118A-608, Non-GLP)

The most common mechanism of drug-induced QT interval prolongation is inhibition of the delayed rectifier potassium channel. The potential of halobetasol propionate, tazarotene and tazarotenic acid (the active metabolite for tazarotene) to inhibit potassium channel currents was evaluated in the in vitro human ether-a-go-go-related gene (hERG) assay. Tazarotene inhibited hERG current with an IC_{50} of 5.7 µM; this level of inhibition is considered weak and not a concern because tazarotene is rapidly metabolized in vivo to tazarotenic acid and essentially not detected in human plasma following dermal administration. An IC_{50} >10 µM (the highest concentration tested) was established for halobetasol propionate and tazarotenic acid. Therefore, halobetasol

propionate and tazarotenic acid have negligible/no hERG inhibition potential based on the results from this in vitro study.

No standalone safety pharmacology studies with the individual drug substances or with the drug product have been conducted. The effects of IDP-118 on ECG measurements were evaluated in a 3-month repeat dose minipig dermal toxicity study. There were no test article-related ECG abnormalities in main study animals or in 1-month recovery animals.

The applicant also references safety pharmacology studies conducted with the individual drug substances previous submitted to support the approval of Ultravate (halobetasol propionate) Cream, 0.05%, Tazorac (tazarotene) Gel, 0.05% and 1%, and Tazorac (tazarotene) Cream, 0.05% and 1%.

5.4. ADME/PK

The applicant has not conducted nonclinical pharmacokinetic studies with the individual drug substances or with the combination drug product, IDP-118 Lotion. However, the toxicokinetics (TK) of halobetasol propionate, tazarotene and tazarotenic acid in plasma were determined in a 3-month repeat dose toxicity study in minipigs conducted with IDP-118 Lotion. A summary of these TK data is provided below. Refer to Section 5.5.1 (General Toxicology) for detailed information concerning the design of the 3-month repeat dose toxicity study in minipigs.

Type of Study	**Major Findings**
TK data from a repeat dose toxicology study A 3-month Study of IDP-118-A by Dermal Administration in Minipigs with a 1-month Recovery Period, Study # V01-118A-605	<u>Halobetasol propionate TK data for male minipigs</u> *T_{max}:* Low strength: 4 hrs Clinical strength: 4 hrs Enhanced strength: 4 hrs *AUC_{0-24}:* Low strength: 1.3 ng·hr/mL Clinical strength: 2.8 ng·hr/mL Enhanced strength: 4.0 ng·hr/mL *C_{max}:* Low strength: 0.14 ng/mL Clinical strength: 0.23 ng/mL Enhanced strength: 0.31 ng/mL *Accumulation:* No evidence of systemic accumulation from Day 28 to Day 90, indicating steady-state had been achieved by Day 28. *Dose proportionality:* Systemic exposure increased roughly dose-proportionally <u>Halobetasol propionate TK data for female minipigs</u> *T_{max}:* Low strength: 4 hrs Clinical strength: 3 hrs

Type of Study	Major Findings
	Enhanced strength: 4 hrs *AUC_{0-24}:* Low strength: 1.0 ng·hr/mL Clinical strength: 2.1 ng·hr/mL Enhanced strength: 4.9 ng·hr/mL *C_{max}:* Low strength: 0.10 ng/mL Clinical strength: 0.23 ng/mL Enhanced strength: 0.35 ng/mL *Accumulation:* No evidence of systemic accumulation from Day 28 to Day 90, indicating steady-state had been achieved by Day 28. *Dose proportionality:* Systemic exposure increased roughly dose-proportionally <u>Tazarotenic Acid TK data for male minipigs</u> *T_{max}:* Low strength: 2 hrs Clinical strength: 8 hrs Enhanced strength: 4 hrs *AUC_{0-24}:* Low strength: 6.1 ng·hr/mL Clinical strength: 32 ng·hr/mL Enhanced strength: 54 ng·hr/mL *C_{max}:* Low strength: 0.3 ng/mL Clinical strength: 2.1 ng/mL Enhanced strength: 3.0 ng/mL *Accumulation:* No evidence of systemic accumulation from Day 28 to Day 90, indicating steady-state had been achieved by Day 28. *Dose proportionality:* Systemic exposure increased roughly dose-proportionally <u>Tazarotenic Acid TK data for female minipigs</u> *T_{max}:* Low strength: 8 hrs Clinical strength: 4 hrs Enhanced strength: 3 hrs *AUC_{0-24}:* Low strength: 4.0 ng·hr/mL Clinical strength: 24 ng·hr/mL Enhanced strength: 42 ng·hr/mL *C_{max}:* Low strength: 0.23 ng/mL Clinical strength: 1.7 ng/mL Enhanced strength: 3.7 ng/mL *Accumulation:* No evidence of systemic accumulation from Day 28 to Day 90, indicating steady-state had been achieved by Day 28. *Dose proportionality:* Systemic exposure increased roughly dose-proportionally

The applicant also references the nonclinical pharmacokinetic studies conducted with the individual drug substances previous submitted to support the approval of Ultravate (halobetasol propionate) Cream, 0.05%, Tazorac (tazarotene) Gel, 0.05% and 1%, and Tazorac (tazarotene) Cream, 0.05% and 1%.

5.5. Toxicology

5.5.1. General Toxicology

Study 1 A Fourteen-Day Dermal Study of IDP-118 in Gottingen Minipigs (Study # 7001-U6HP-01-10, Non-GLP)

This study evaluated the dermal toxicity and systemic exposure to halobetasol propionate, tazarotene and tazarotenic acid following administration of IDP-118 prototypes W, Y and Z (0.09% tazarotene and 0.01% or 0.025% halobetasol propionate) and two comparators, Tazorac® Cream (0.1% tazarotene) and Ultravate® Cream (0.05% halobetasol propionate) in male Gottingen minipigs.

IDP-118 Formulas W, Y and Z, Ultravate Cream and Tazorac Cream were well-tolerated in minipigs when administered dermally for 14 days. All IDP- 118 formulas and Tazorac Cream produced slight and/or well-defined erythema at the application site, consistent with tazarotene-induced skin irritation. However, the IDP-118 Formulas were less irritating than Tazorac Cream, as indicated by delayed erythema onset, lower irritation grade and/or absence of mild eschar at the end of the study. Severity and occurrences of erythema was highest for Tazorac Cream followed by, in decreasing order, IDP-118 Formula Z, IDP-118 Formula W and IDP- 118 Formula Y. Reduced site of application skin irritation correlated with the presence of halobetasol propionate in the IDP-118 Formulas. Ultravate Cream did not produce erythema or signs of skin thinning or atrophy. HPA axis suppression was evident in the IDP-118 and Ultravate Cream groups based on Day 15 lower pre- and post-stimulation serum cortisol levels compared to Days -1 and 42. Animals treated with IDP-118 Formulas appeared to recover normal adrenal function by Day 42 while animals treated with Ultravate Cream showed slight signs of HPA suppression based on lower post-stimulation cortisol levels as compared to the rest of the groups. Animals treated with Tazorac Cream, which was used as the HPA axis suppression negative control, showed consistent cortisol levels across ACTH test days. IDP-118 Formula Z yielded consistently lower halobetasol propionate and tazarotenic acid maximum and total exposure parameter values compared to those following the administration of Tazorac Cream and Ultravate Cream, respectively, on Study Days 7 and 14. The highest mean halobetasol propionate plasma concentrations and systemic exposure were observed in animals administered IDP-118 Formula Y and correlated to the treatment group with least skin irritation.

Study 2 A 3-month Study of IDP-118-A by Dermal Administration in Minipigs with a 1-month Recovery Period (Study # V01-118A-605, GLP)

This study was appropriately conducted with five treatment groups included the IDP-118 Lotion at low (halobetasol propionate 0.002%/tazarotene 0.010%), mid (halobetasol propionate 0.01%/tazarotene 0.045%) and high doses (halobetasol propionate 0.02%/tazarotene 0.09%), as well as monad groups containing halobetasol propionate (0.02%) or tazarotene (0.090%) in lotion vehicle. The mid dose group was treated with the to-be-marketed formulation, which was later used in the Phase 3 clinical studies.

Administration of IDP-118 Lotion as well as halobetasol propionate and tazarotene monads by once daily dermal application for 90 days was well tolerated in minipigs at low, clinical, and enhanced strengths up to 0.02% halobetasol propionate/0.090% tazarotene.

IDP-118 Lotion was associated with body weight decreases, consistent with adverse effects of topical corticosteroids, and correlated to halobetasol propionate systemic exposure. Target organs included those previously reported for tazarotene and halobetasol propionate (i.e., skin dose site, adrenal glands, and thymus). The decreased organ weights and/or microscopic changes observed in target organs showed partial or full reversibility following a 1-month recovery period. No new toxicities or toxicological interactions arising from their combination were noted in the study.

ECG measurements were obtained prior to the first dose, during the last week of dosing (days 85/87), and during the last week of the recovery period (day 114). There were no test article-related ECG abnormalities in main study animals or in 1-month recovery animals.

Tazarotene is a prodrug of its active metabolite, tazarotenic acid. Halobetasol propionate and tazarotenic acid, but not tazarotene, were detected in plasma. Overall, drug systemic exposure was consistently achieved throughout the dosing interval, with C_{max} reached within a few hours after dosing. The highest exposures, based on C_{max}, were observed in the high dose group on Day 28 for halobetasol propionate and Day 90 for tazarotenic acid. There was no evidence of drug systemic accumulation between Days 28 and 90, and steady state appeared to be reached by Day 28. Drug absorption appeared to increase with the combination product as compared to the lotion monads. On Day 90, male and female C_{max} averaged 0.31 and 0.35 ng/mL for halobetasol propionate and 3.0 and 3.7 ng/mL for tazarotenic acid, respectively. Steady state exposures (AUC_{0-24}) at the mid dose (clinical strength) were 21 (males) and 14 ng•hr/mL (females) for tazarotenic acid, and 2.6 (males) and 1.9 ng•hr/mL (females) for halobetasol propionate.

5.5.2. Genetic Toxicology

The applicant has obtained the right of reference to the genetic toxicology studies conducted to support Ultravate (halobetasol propionate) Cream, 0.05%, Tazorac (tazarotene) Gel, 0.05% and 1%, and Tazorac (tazarotene) Cream, 0.05% and 1%. The following genetic toxicology information is included in the Ultravate (halobetasol propionate) Cream, 0.05% and Tazorac (tazarotene) Gel, 0.05% and 1% labels.

Ultravate (halobetasol propionate) Cream, 0.05%

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.

Tazorac (tazarotene) Gel, 0.05% and 1%

Tazarotene was non-mutagenic in the Ames assay and did not produce structural chromosomal aberrations in a human lymphocyte assay. Tazarotene was non-mutagenic in the CHO/HGPRT mammalian cell forward gene mutation assay and was non-clastogenic in the in vivo mouse micronucleus test.

5.5.3. Carcinogenicity

The applicant has obtained the right of reference to the carcinigenicity studies conducted to support Ultravate (halobetasol propionate) Cream, 0.05%, Tazorac (tazarotene) Gel, 0.05% and 1%, and Tazorac (tazarotene) Cream, 0.05% and 1%. The following carcinogenicity information is included in the Ultravate (halobetasol propionate) Cream, 0.05% and Tazorac (tazarotene) Gel, 0.05% and 1% labels.

Ultravate (halobetasol propionate) Cream, 0.05%

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

Tazorac (tazarotene) Gel, 0.05% and 1%

A long-term study of tazarotene following oral administration of 0.025, 0.050, and 0.125 mg/kg/day to rats showed no indications of increased carcinogenic risks. Based on pharmacokinetic data from a shorter-term study in rats, the highest dose of 0.125

mg/kg/day was anticipated to give systemic exposure in the rat 0.3 times that seen in subjects treated with the MRHD of tazarotene gel, 0.1%.

A long-term study with topical administration of up to 0.1% tazarotene in a gel formulation in mice terminated at 88 weeks showed that dose levels of 0.05, 0.125, 0.25, and 1 mg/kg/day (reduced to 0.5 mg/kg/day for males after 41 weeks due to severe dermal irritation) revealed no apparent carcinogenic effects when compared to vehicle control animals. Systemic exposure at the highest dose was 2 times that seen in subjects treated with the MRHD of tazarotene gel, 0.1%.

5.5.4. Reproductive and Developmental Toxicology

The applicant has obtained the right of reference to the fertility and embryofetal development studies conducted to support Ultravate (halobetasol propionate) Cream, 0.05%, Tazorac (tazarotene) Gel, 0.05% and 1%, and Tazorac (tazarotene) Cream, 0.05% and 1%. The following fertility and embryofetal development information is included in the Ultravate (halobetasol propionate) Cream, 0.05% and Tazorac (tazarotene) Gel, 0.05% and 1% labels.

Ultravate (halobetasol propionate) Cream, 0.05%

Fertility and Early Embryonic Development

Studies in the rat following oral administration at dose levels up to 50 mcg/kg/day indicated no impairment of fertility or general reproductive performance.

Embryo-Fetal Development

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 Ultravate. 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.

There are no adequate and well-controlled studies of the teratogenic potential of halobetasol propionate in pregnant women. Ultravate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Tazorac (tazarotene) Gel, 0.05% and 1%

Fertility and Early Embryonic Development

No impairment of fertility occurred in rats when male animals were treated for 70 days prior to mating and female animals were treated for 14 days prior to mating and continuing through gestation and lactation with topical doses of tazarotene gel up to 0.125 mg/kg/day. Based on data from another study, the systemic drug exposure in the rat at the highest dose was 0.3 times that observed in subjects treated with the MRHD of tazarotene gel, 0.1%.

No impairment of mating performance or fertility was observed in male rats treated for 70 days prior to mating with oral doses of up to 1 mg/kg/day tazarotene, which produced systemic exposure that was approximately equivalent to that observed in subjects treated with the MRHD of tazarotene gel, 0.1%.

No impairment of mating performance or fertility was observed in female rats treated for 15 days prior to mating and continuing through gestation day 7 with oral doses of tazarotene up to 2 mg/kg/day. However, there was a significant decrease in the number of estrous stages and an increase in developmental effects at that dose, which produced systemic exposure 2 times that observed in subjects treated with the MRHD of tazarotene gel, 0.1%.

Embryo-Fetal Development

In rats, a tazarotene gel, 0.05% formulation dosed topically during gestation days 6 through 17 at 0.25 mg/kg/day, which represented 0.5 times the maximum systemic exposure in subjects treated with the MRHD of tazarotene gel, 0.1% (i.e., 2 mg/cm2 over a 20% body surface area), resulted in reduced fetal body weights and reduced skeletal ossification. Rabbits dosed topically with 0.25 mg/kg/day tazarotene gel, which represented 7 times the maximum systemic exposure in subjects treated with the MRHD of tazarotene gel, 0.1%, during gestation days 6 through 18 were noted with single incidences of known retinoid malformations, including spina bifida, hydrocephaly, and heart anomalies.

When tazarotene was given orally to animals, developmental delays were seen in rats, and malformations and post-implantation loss were observed in rats and rabbits at doses producing 0.5 and 13 times, respectively, the maximum systemic exposure in subjects treated with the MRHD of tazarotene gel, 0.1%.

In female rats orally administered 2 mg/kg/day of tazarotene from 15 days before mating through gestation day 7, which represented 2 times the maximum systemic exposure in subjects treated with the MRHD of tazarotene gel, 0.1%, classic developmental effects of retinoids were observed including decreased number of implantation sites, decreased litter size, decreased numbers of live fetuses, and

decreased fetal body weights. A low incidence of retinoid-related malformations was observed at that dose.

In a pre- and postnatal development toxicity study, topical administration of tazarotene gel (0.125 mg/kg/day) to pregnant female rats from gestation day 16 through lactation day 20 reduced pup survival, but did not affect the reproductive capacity of the offspring. Based on data from another study, the maximum systemic exposure in the rat would be 0.3 times the maximum systemic exposure in subjects treated with the MRHD of tazarotene gel, 0.1%.

5.5.5. Other Toxicology Studies

Study 1 A Reduced Local Lymph Node Assay with IDP-118 Lotion (Study # 7001-U6HP-02-10, GLP)

This study was conducted to determine if two IDP-118 Lotion formulations, Formula A and Formula B, would induce a hypersensitivity response in mice as measured by the proliferation of lymphocytes in the draining auricular lymph nodes.

A 3-fold or greater increase in stimulation index (SI) was considered a positive response. The positive control, 35% hexylcinnamaldehyde (HCA) in acetone olive oil (AOO), resulted in a SI of 39.7 when compared to the AOO control. The 35% HCA in IDP-118 Formula A Vehicle and Formula B Vehicle, resulted in a SI of 9.8 and 29.6 when compared to the Formula A Vehicle and Formula B Vehicle controls, respectively.

Treatment with IDP-118 Lotion Formula A and IDP-118 Lotion Formula B did not result in a SI of greater than or equal to 3 relative to the Formula A or Formula B vehicles or the AOO control. Therefore, these findings suggest IDP-118 Lotion Formula A and IDP-118 Lotion Formula B are not sensitizers.

Study 2 IDP-118 Lotion: Topical Application Ocular Irritation Screening Assay Using the EpiOcular Human Cell Construct (Study # 7001-U6HP-04-10, GLP)

This study was conducted to evaluate the potential ocular irritation of the test articles by measuring 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) dye conversion by the EpiOcular™ tissue construct after topical exposure to the test articles, i.e., IDP-118 Lotion Formula A, IDP-118 Lotion Formula B, halobetasol propionate and tazarotene.

IDP-118 Lotion Formula A and B as well as the drug substances (halobetasol propionate and tazarotene) were predicted to be minimally-irritating to non-irritating to the eye based on the results from this study.

Study 3 Phototoxicity Assay Using the EpiDerm™ Skin Model (Study # V01-118A-607, GLP)

The phototoxicity potential of IDP-118 Lotion was evaluated in the EpiDerm™ in vitro skin model by treating tissues and subsequently exposing to ultraviolet-A (UVA)/visible light, and measuring tissue viability. According to the prediction model presented by (b) (4) IDP-118-A Lotion (lot # DP1615) and IDP-118-A Lotion Vehicle (lot # DP1612) did not show phototoxic potential; whereas Tazorac Cream 0.1% (lot # 81464) exhibited a phototoxic potential (i.e., test article induced ≥30% decrease in viability in the presence of UVA compared to the viability in the absence of UVA). The positive control, 0.02% chlorpromazine, met the acceptance criterion for a positive phototoxic response and validated the assay sensitivity.

5.5.6 Multiple of Human Exposure Calculations

The multiples of human exposure values based on AUC comparison between the NOAELs (or doses that generated treatment related effects) identified in pivotal toxicology studies and the maximum recommended human dose (MRHD) are shown in the table below. The human AUC_{0-t} mean value of 9.96 ng*hr/mL for tazarotenic acid obtained on Days 28 to 29 in the maximum use clinical PK study was used for the multiples of human exposure calculations.

The multiples of human exposure values (b) (4) provided by the sponsor are different than the mulitples of human exposure values provided in the table below. The applicant used an AUC_{0-t} geometric mean value of (b) (4) ng*hr/mL for tazarotenic acid from the maximum use clinical PK study for calculating the multiples of human exposure values. (b) (4)

Table: Multiples of Human Exposure Values for the Pivotal Toxicology Studies

Study	Route	NOAEL (mg/kg/day)	AUC (µg·hr/mL)	Multiples of human exposure[d] (based on AUC comparison)
Carcinogenicity study in rats	Oral (diet)	0.125	13.9[b]	1.4
Carcinogenicity study in mice	Dermal	1	344	35
Embryofetal development study in rats	Dermal	0.25[a]	107	11
Embryofetal development study in rabbits	Dermal	0.25 [a]	1160	116
Embryofetal development study in rats	Oral	0.5 [a]	94	9

Embryofetal development study in rabbits	Oral	0.2 [a]	2272[c]	228
Fertility and reproduction/ pre- and postnatal development study in rats	Demal	0.125	53.1	5
Fertility and reproduction in rats	Oral	1	164	16
Fertility and reproduction in rats	Oral	2	296	30

a The dose that produced the indicated effects.

b AUC vale was derived from a 3-month dietary study

c The AUC value was estimated from a dose range finding study.

d Comparison with the human AUC_{0-t} mean value of 9.96 ng*hr/mL for tazarotenic acid on Days 28 to 29 in the maximum use clinical PK study.

6 Clinical Pharmacology

6.1. Executive Summary

The applicant seeks approval of DUOBRII lotion, a combination drug product that contains halobetasol propionate, 0.01% and tazarotene, 0.045%, for topical treatment of adults with plaque psoriasis. This is a resubmission of an NDA that was initially submitted on August 18, 2017.

In the initial submission, the applicant proposed a 505(b)(2) regulatory pathway and identified Ultravate (halobetasol propionate) cream, 0.05% (NDA 019967) and Tazorac (tazarotene) cream, 0.05% (NDA 021184) as listed drugs for halobetasol propionate and tazarotene, respectively. A complete response letter was sent to the applicant on June 15, 2018 due to nonclinical deficiencies. Specifically, the applicant did not provide sufficient nonclinical toxicology data to support NDA approval as it was determined that an adequate clinical bridge to the listed drugs was not established. The bioavailability of the proposed product was higher than each of the listed drugs for the individual monads. Despite the higher bioavailability, the NDA was acceptable from a Clinical Pharmacology perspective because two Phase 3 studies and a long-term safety study supported the safety of the proposed product and the incidence of hypothalamic-pituitary-adrenal (HPA) axis suppression was considered low (i.e. 15%) under maximal use conditions.

In this resubmission, the applicant seeks approval of the proposed product through a 505(b)(1) regulatory pathway and provided right of reference letters for the Agency to review nonclinical information contained in the NDA submissions of the following approved products:

- Ultravate (halobetasol propionate) Cream, 0.05% (NDA 019967)
- Tazorac (tazarotene) Cream, 0.05% (NDA 021184)

- Tazorac (tazarotene) Gel, 0.05%, 0.1% (NDA 020600)

No additional Clinical Pharmacology information was included in this resubmission. This review summarized key findings of the Clinical Pharmacology from the first review cycle (for more details, refer to Section 6 of Multi-Disciplinary Review and Evaluation for NDA 209354 dated 06/15/2018 in DARRTS) and focuses on potency classification and labelling recommendation.

An agreed initial pediatric study plan (iPSP) was issued on 6/16/2016. The agreed iPSP included a deferral of a pharmacokinetics (PK)/HPA axis suppression/safety study in pediatric population (b) (4) to 16 years 11 months. This study will be included as a PREA post-marketing requirement (PMR) and the lower limit of the study subjects' age is recommended to be 4 years.

6.1.1. Recommendations

The Office of Clinical Pharmacology, Division of Clinical Pharmacology 3 found the Clinical Pharmacology information contained in the resubmission of this NDA acceptable.

6.1.2. Post-Marketing Requirements

PK/HPA axis suppression/safety open-label study of halobetasol propionate and tazarotene lotion, 0.01%/0.045% in 45 pediatric subjects age 4 to less than 17 years with moderate to severe plaque psoriasis. PK and HPA axis suppression assessments should be done in at least 20 evaluable subjects under maximal use conditions.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

6.2.1.1. Bioavailability and HPA axis suppression

The applicant conducted a maximal use PK/HPA axis suppression study (V01-118A-501) for the proposed product, halobetasol propionate and tazarotene lotion, 0.01%/0.045%, following once daily (QD) application for 8 weeks in subjects with moderate to severe plaque psoriasis affecting at least 20% body surface area (BSA). The study also evaluated the PK and HPA axis suppression potential of Ultravate (halobetasol propionate) Cream, 0.05% following a 2-week QD treatment, and the PK of Tazorac (tazarotene) Cream, 0.05% following a 4-week QD treatment. Study results showed that systemic exposure of halobetasol propionate and tazarotene lotion, 0.01%/0.045% was at or near steady state by Day 28. In this treatment group, on Day 28, plasma concentrations of halobetasol propionate [lower limit of quantification (LLOQ) = 50 pg/mL] and tazarotene (LLOQ = 5 pg/mL) were quantifiable in 13 and 18 out of a total number of 22 subjects, respectively, and tazarotenic acid (LLOQ = 5 pg/mL) was quantifiable in all subjects. The systemic exposure (both C_{max} and AUC) of

halobetasol propionate and tazarotenic acid resulting from the proposed combination product was higher than that from Ultravate (halobetasol propionate) Cream, 0.05% and Tazorac (tazarotene) Cream, 0.05%, respectively (*for more details, refer to Section 6 of Multi-Disciplinary Review and Evaluation for NDA 209354 dated 06/15/2018 in DARRTS*).

Reviewer comments: *The applicant has obtained a right of reference to the listed drugs previously proposed in the original submission and seeks approval through the regulatory pathway of 505(b)(1) in this resubmission. The fact that the systemic exposure of the combination product, halobetasol propionate and tazarotene lotion, 0.01%/0.045%, was higher than Ultravate (halobetasol propionate) Cream, 0.05% and Tazorac (tazarotene) Cream, 0.05% for each of the corresponding active moiety will not impact the approvability of this product from a Clinical Pharmacology perspective as with the change in the regulatory pathway, a clinical bridge will not be needed.*
In the proposed drug product treatment group, HPA axis suppression rate was 15% (3 out of 20 subjects) on Day 29 but no subjects (0%) had suppression on Day 57. In the Ultravate (halobetasol propionate) Cream, 0.05% treatment group, 5% (1 of 20) subjects had HPA axis suppression on Day 15. The incidence of HPA axis suppression in the proposed combination product treatment group was sufficiently low to allow for further assessment in pediatric subjects which will be requested as a PMR.

6.2.2. Potency Classification

The applicant conducted a single point vasoconstrictor (VCA) study to compare the potency of the proposed product to four currently marketed topical corticosteroid formulations of known potency and a vehicle lotion formulation. The potency classification of the proposed product will be further discussed in this review cycle.

VCA test results using visual assessment (primary endpoint) data suggested that the proposed product, Betamethasone Dipropionate Cream, 0.05% (Class 3, upper mid-strength potency), and Ultravate Cream, 0.05% (Class 1, super-high potency) were in the same group and had a higher rank than that of Fluocinonide Cream, 0.05% (Class 2, high strength potency).

The chromameter assessment (secondary endpoint) data ranked the proposed product to be lower than that of Ultravate Cream, 0.05% (Class 1, supper-high potency) and similar to that of Fluocinonide Cream, 0.05% (Class 2, high strength potency) and Betamethasone Dipropionate Cream, 0.05% (Class 3, upper mid-strength potency).

Reviewer's comment: *The skin blanching results using visual assessment ranked the potency of Fluocinonide Cream, 0.05% (high strength or Class 2) lower than that of Betamethasone dipropionate cream, 0.05% (upper mid-strength or Class 3) and the overlapping skin blanching effects among reference products with different known potency make it difficult to classify the proposed product into a definitive class. Data*

from both visual and chromameter assessments suggested that the potency of the proposed product is within the range of upper mid-strength to super-high strength.

Considering that the proposed product had higher systemic exposure of halobetasol propionate than Ultravate Cream, 0.05%, a super-high strength corticosteroid, under maximal use conditions, the totality of the evidences suggested that this product should be classified into the range of high to super-high potency, despite the fact that the VCA study results were not fully conclusive. The need for additional assessment for potency classification of the proposed product was deemed not necessary.

6.3. Summary of Labeling Recommendations

The Office of Clinical Pharmacology has the following labeling recommendation and comments:

Section 5.4 Hypothalamic-Pituitary-Adrenal (HPA) Axis Suppression and Other Unwanted Systemic Glucocorticoid Effects: Change the numbering and the title of this subsection from the originally proposed (b) (4). Rearrange the language of describing the HPA axis suppression results. Add "Use of more than one corticosteroid-containing product at the same time may increase the total systemic exposure to topical corticosteroids. Pediatric patients may be more susceptible than adults to systemic toxicity from the use of topical corticosteroids because of their larger surface-to-body mass ratio [see Use in Specific Populations (8.4)]".

Section 7 Drug Interactions: Remove this section because no drug-drug interaction studies have been conducted for the proposed product.

Section 12.2 Pharmacodynamics: Rearrange the language of describing the potency of the product and the results of HPA axis suppression. For completeness, add "The pharmacodynamics of tazarotene is unknown".

Section 12.3 Pharmacokinetics: Rearrange the format and language of describing the PK results of the product. Remove unnecessary details.

7 Sources of Clinical Data and Review Strategy

See 1st Cycle Unireview of NDA 209354

8 Statistical and Clinical and Evaluation

See 1st Cycle Unireview of NDA 209354

9 Advisory Committee Meeting and Other External Consultations

See 1st Cycle Unireview of NDA 209354

10 Pediatrics

Clinical studies were conducted only in adults. Because DUOBRII is a new fixed combinations product, This NDA is required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients, under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c).

On 6/16/2016, the Division agreed to the Agreed initial pediatric study plan (Agreed iPSP) submitted by the sponsor, following a Pediatrics Review Committee (PeRC) meeting held on 6/8/2016. The Agreed iPSP included the following:

- Partial waiver to conduct PK and clinical safety studies for children from 0 to less than (b) (4) years of age. The prevalence of moderate to severe psoriasis in pediatric population in this age group is low. Therefore, studies in psoriasis patients less than (b) (4) years of age would be impossible or highly impracticable (Section 505B (a)(4)(B)(i) of the Act).
- Deferral to conduct a PK/HPA axis suppression/safety study for children fro (b) (4) to less than 17 years of age.

On 4/24/2019, the PeRC reassessed the applicant's pediatric study plan and recommended the pediatric PK/HPA axis suppression/safety study be conducted in children from 4 to less than 17 years of age and the Division agreed.

11 Risk Evaluation and Mitigation Strategies (REMS)

See 1st Cycle Unireview of NDA 209354

12 Postmarketing Requirements and Commitment

A PREA PMR will be issued: PK/HPA axis suppression/safety open-label study of halobetasol propionate and tazarotene lotion, 0.01%/0.045% in 45 pediatric subjects age 4 to less than 17 years with moderate to severe plaque psoriasis. PK and HPA axis suppression assessments should be done in at least 20 evaluable subjects under maximal use conditions.

The milestones of the PMR will be:
Final Protocol Submission: 06/2019
Study/Trial Completion: 06/2022
Final Report Submission: 12/2022

20 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

BARBARA J GOULD
04/24/2019 06:19:30 PM

Renqin DUAN
04/24/2019 06:23:02 PM

BARBARA A HILL
04/25/2019 06:48:55 AM

YANHUI LU
04/25/2019 08:07:36 AM

CHINMAY SHUKLA
04/25/2019 09:40:05 AM

HAMID N TABATABAI
04/25/2019 10:16:19 AM

GARY T CHIANG
04/25/2019 10:30:39 AM
I am acting TL for Dr. Kettl

JILL A LINDSTROM
04/25/2019 11:47:11 AM

NDA/BLA Multi-disciplinary Review and Evaluation

Application Type	NDA 505 (b)(2)
Application Number(s)	209354
Priority or Standard	Standard
Submit Date(s)	August 18, 2017
Received Date(s)	August 18, 2017
PDUFA Goal Date	June 18, 2017
Division/Office	Division of Dermatology and Dental Products/ Office of Drug Evaluation III
Review Completion Date	See DARRTS electronic signature page
Established Name	halobetasol propionate and tazarotene lotion, 0.01%/0.045%
(Proposed) Trade Name	DUOBRII
Pharmacologic Class	Corticosteroid/Retinoid
Code name	NA
Applicant	Dow Pharmaceutical Sciences, Inc.
Formulation(s)	Each gram of DUOBRII Lotion contains 0.1 mg (0.01%) halobetasol propionate and 0.45 mg (0.045%) tazarotene in a white to off-white lotion
Dosing Regimen	Topical application once daily
Applicant Proposed Indication(s)/Population(s)	topical treatment of plaque psoriasis
Recommendation on Regulatory Action	Complete Response
Recommended Indication(s)/Population(s) (if applicable)	NA

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Reviewers Team and Signature Approval Section

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ ACKNOWLEDGED/ APPROVED	AUTHORED/ ACKNOWLEDGED/ APPROVED
Product Quality Team Lead	Yichun Sun, PhD	OPQ/ONDP/ Division of New Drug Products II	Sections 1.1 and 4.2	**Select one:** ____ Authored ____ Acknowledged ____ Approved
	Signature:			
Nonclinical Reviewer	Renqin Duan, PhD	ODE III/DDDP	Sections 5 and 13.4	**Select one:** ____ Authored ____ Acknowledged ____ Approved
	Signature:			
Nonclinical Supervisor	Barbara Hill, PhD	ODE III/DDDP	Sections 5 and 13.4	**Select one:** ____ Authored ____ Acknowledged ____ Approved
	Signature:			
Clinical Pharmacology Reviewer	Yanhui Lu, PhD	OTS/OCP/DCPIII	Sections 6 and 13.5	**Select one:** ____ Authored ____ Acknowledged ____ Approved

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ ACKNOWLEDGED/ APPROVED	AUTHORED/ ACKNOWLEDGED/ APPROVED
	Signature:			
Clinical Pharmacology Team Leader	Chinmay Shukla, PhD	OTS/OCP/DCPIII	Sections 6 and 13.5	**Select one:** ____ Authored ____ Acknowledged ____ Approved
	Signature:			
Clinical Pharmacology Division Acting Director	Chandrahas G. Sahajwalla, PhD	OTS/OCP/DCPIII	Sections 6 and 13.5	**Select one:** ____ Authored ____ Acknowledged ____ Approved
	Signature:			
Biostatistics Reviewer	Matthew Guerra, PhD	OTS/OB/DBIII	Sections 7.1, 7.2, 7.4, and 13.3	**Select one:** ____ Authored ____ Acknowledged ____ Approved
	Signature:			
Biostatistics Team Leader	Mohamed Alosh, PhD	OTS/OB/DBIII	Sections 7.1, 7.2, 7.4, and 13.3	**Select one:** ____ Authored ____ Acknowledged ____ Approved
	Signature:			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ ACKNOWLEDGED/ APPROVED	AUTHORED/ ACKNOWLEDGED/ APPROVED
Acting Division Director (DB III)	Laura Lee Johnson, PhD	OTS/OB/DBIII	Sections 7.1, 7.2, 7.4, and 13.3	**Select one:** ____ Authored ____ Acknowledged ____ Approved
	Signature:			
Clinical Reviewer	Hamid Tabatabai, MD	ODE III/DDDP	Sections 1.1, 1.2, 1.3,1.4, 2.1, 2.2, 3.1, 3.2, 4.1, 7.1, 7.3, part of 7.4.2, 8, 9, 10, 11, 12, 13.1, 13.2	**Select one:** __ _ Authored ____ Acknowledged ____ Approved
	Signature:			
Clinical Team Leader	Snezana Trajkovic, MD	ODE III/DDDP	Sections 1.1, 1.2, 1.3,1.4, 2.1, 2.2, 3.1, 3.2, 4.1, 7.1, 7.3, part of 7.4.2, 8, 9, 10, 11, 12, 13.1, 13.2	**Select one:** ____ Authored ____ Acknowledged ____ Approved
	Signature:			
Deputy Director	Jill A. Lindstrom, MD	ODE III/DDDP		**Select one:** ____ Authored ____ Acknowledged ____ Approved
	Signature:			

Additional Reviewers of Application

OPQ	Drug Product- Caroline Strasinger, PhD Drug Substance-Ramsharan Mittal, PhD Drug Process-Jingbo Xiao, Yubing Tang, PhD BioPharm- An-Chi Lu, Vidula Kolhatkar, PhD Micro- Vinayak Pawar, PhD Facilities-Laurie Nelson, PhD
OSI	Bei Yu, PhD
OSE/DMEPA	Carlos Mena-Grillasca, BSPharm

OPQ=Office of Pharmaceutical Quality
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

Glossary

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
BSA	body surface area
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
CMH	CMH Cochran-Mantel-Haenszel
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
EOT	end of treatment
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
GEE	Generalized Estimating Equations
GRMP	good review management practice
ICH	International Conference on Harmonization
IGA	Investigator Global Assessment
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application

NME	new molecular entity
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
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

The applicant proposes marketing of DUOBRII lotion, a combination drug product that contains halobetasol propionate, 0.01%; and tazarotene, 0.045%, for topical treatment of adults with plaque psoriasis. The proposed dose is once daily application to affected areas (b) (4).

Halobetasol propionate, a synthetic super-high potency corticosteroid, is currently marketed in the U.S. at concentration of 0.05% in several dosage forms: ointment, cream, and lotion. Halobetasol propionate, like other corticosteroids, has anti-inflammatory, anti-pruritic, and vasoconstrictive properties.

Tazarotene, a retinoid, is currently marketed in the U.S. in several dosage forms and concentrations: cream (0.05% and 0.1%), gel (0.05% and 0.1%), and aerosol foam (0.1%).

The drug product, DUOBRII™, is a topical lotion which contains 0.01% (w/w) halobetasol propionate and 0.045% (w/w) tazarotene. Halobetasol propionate is a synthetic corticosteroid. Tazarotene is a member of the acetylenic class of retinoids. The lotion is indicated for the topical treatment of plaque psoriasis in patients of 18 years and older. The inactive ingredients used in the drug product include: carbomer copolymer type B, carbomer homopolymer type A, diethyl sebacate, edetate disodium dihydrate, light mineral oil, methylparaben, propylparaben, purified water, sodium hydroxide, sorbitan monooleate and sorbitol solution, 70%. The drug product is packaged as a nominal 3, 45, 60 or 100 g fill size in a (b) (4) aluminum tube with (b) (4) cap.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The applicant submitted data from two adequate and well controlled trials (Trials -301 and -302), which provided evidence of the effectiveness of DUOBRII lotion for the treatment of moderate to severe plaque psoriasis in adult subjects. Both trials assessed changes from baseline to Week 8, compared to placebo, in the primary efficacy endpoint of proportion of subjects with treatment success, defined as an Investigator Global Assessment (IGA) score of 0 (clear) or 1 (almost clear), with at least 2-grade improvement from baseline.

DUOBRII lotion was statistically superior to placebo (p-values < 0.001) on the primary efficacy endpoint in Trials -301 and -302. The applicant has demonstrated that DUOBRII lotion 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 Summary and Assessment

Psoriasis is a chronic, inflammatory disease that primarily affects the skin and is characterized by erythematous, scaly plaques and substantial impairment of quality of life. DUOBRII lotion is proposed for the topical treatment of adults with (b) (4) plaque psoriasis. Halobetasol propionate and tazarotene are the active ingredients in DUOBRII lotion, a new combination product. Halobetasol propionate, a synthetic super-high potency corticosteroid, like other corticosteroids, has anti-inflammatory, anti-pruritic, and vasoconstrictive properties. Tazarotene, a retinoid that binds to retinoic acid receptors and may modify gene expression, is indicated for topical treatment of plaque psoriasis and acne vulgaris.

For the treatment of moderate to severe plaque psoriasis, current therapeutic options include phototherapy and photochemotherapy with methoxsalen, systemic small molecule drugs (acitretin, apremilast, cyclosporine, methotrexate), and biologic products (adalimumab, etanercept, infliximab, ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab, and tildrakizumab). Although the efficacy varies, no product produces a response in all patients or provides a permanent cure. Phototherapy and photochemotherapy may be impractical due to office based administration requirements. All the systemic products may have one or more serious adverse reactions, including malignancy, serious infections, teratogenicity, depression, nephrotoxicity, hepatotoxicity, and bone marrow suppression[1].

The applicant is seeking approval of this product via a 505(b)(2) regulatory pathway, and has identified Ultravate (halobetasol propionate) cream, 0.05% (NDA 019967) and Tazorac (tazarotene) cream, 0.05% (NDA 021184) as listed drugs for halobetasol propionate and tazarotene respectively. The applicant intended to rely on the Agency's finding of safety for the listed drugs that include non-clinical data from the approved labels for the listed drugs, including fertility and reproduction, embryofetal development, genotoxicity and carcinogenicity (tazarotene only). For systemic products, an adequate clinical bridge is usually established by demonstrating comparative bioavailability. For topical products, this is usually accomplished through conduct of well-controlled trials with clinical endpoints, assessment of comparative bioavailability, and for topical corticosteroids, an assessment of the effect of the product on the HPA axis suppression. To be able to rely on the Agency's finding of safety for the listed drugs, the applicant conducted a total of three clinical studies to establish clinical bridges to the two listed drug. The applicant conducted study (V01-118A-501), a comparative bioavailability and HPA axis suppression study conducted under maximal use conditions to provide part of the support for a clinical bridge to each RLD. In addition, the applicant conducted two Phase 2, multi-center, double-blind, randomized, vehicle-controlled clinical trials to compare safety and efficacy of DUOBRII, compared to each of its RLDs: Trial V01-118A-202 (DUOBRII compared to Tazorac cream, 0.05%), and Trial V01-118A-203 (DUOBRII compared to Ultravate cream, 0.05%).

To establish efficacy and safety of their combination drug product, the applicant conducted two Phase 3 clinical trials (-301 and -302).

A total of 418 adult subjects with moderate to severe plaque psoriasis were randomized to treatment with DUOBRII lotion (N=276) or vehicle lotion (N=142) (the Intent to Treat (ITT) population). Subjects had a baseline Investigator's Global Assessment (IGA) scores of 3 ("moderate") or 4 ("severe") on a 5-point scale of overall disease severity, and an affected body surface area (BSA) involvement of between 3% to 12%.

For both trials, DUOBRII lotion was superior to placebo on the primary efficacy endpoint (in Trial -301: 35.8% vs 7.0% and in Trial -302: 45.3% vs 12.5%; p-values < 0.001). Secondary efficacy endpoints included the proportion of subjects at Weeks 2, 4, 6, and 12 who achieved IGA success. DUOBRII lotion was statistically superior to placebo at weeks 4, 6, and 12 in both trials. At Week 2, DUOBRII lotion was statistically superior to the vehicle lotion in Trial -302 (p-value = 0.004), it was not statistically superior to the vehicle lotion in Trial -301 (p-value =0.098).

The primary clinical safety database, which consisted of data from the pooled Phase 3 Trials (-301 and -302), was adequate to characterize the safety profile of DUOBRII lotion. Three subjects experienced 4 Serious Adverse Events (SAE)s: anemia in 1 subject, facial cellulitis in 1 subject, and asthma and pneumonia in 1 subject. None of the SAEs were related to the study drug. Overall, the frequency of SAEs experienced by subjects treated with DUOBRII lotion (1.1%) was slightly higher than the placebo group (0).

Adverse Reactions (AR)s occurring in ≥ 1% of subjects treated with DUOBRII lotion through Week 8, and observed more frequently than in the placebo group, included contact dermatitis (6.3%), application site pain (2.6%), skin atrophy (1.9%), folliculitis (1.9%), rash (1.5%), and excoriation (1.1%).

HPA axis suppression under maximal use conditions was evaluated in study (-501). The incidence of HPA axis suppression with DUOBRII lotion was 15% on Day 29, and 0 on Day 57.

Relative bioavailability to the listed drugs was assessed in a maximal use PK study (-501) to support establishing a clinical bridge to each listed drug.

For halobetasol propionate, following once daily application of DUOBRII lotion, the mean(SD) C_{max} and AUC_{last} values were 87.2

(96.6) pg/mL and 1145 (1501) pg*hr/mL on Day 14 and 101.9 (135.4) pg/mL and 1300 (1959) pg*hr/mL on Day 28, respectively. The mean (SD) C_{max} and AUC_{last} values of halobetasol propionate on Day 14 following once daily application of Ultravate Cream, 0.05% for 2 weeks were 58.8 (72.8) pg/mL and 708 (1099) pg*hr/mL, respectively.

For tazarotenic acid, following once daily application of DUOBRII lotion, the mean(SD) C_{max} and AUC_{last} values were 466.1 (390.0) pg/mL and 8513 (7096) pg*hr/mL on Day 14 and 523.4 (523.3) pg/mL and 9954 (10091) pg*hr/mL on Day 28, respectively. Following once daily application of Tazorac Cream, 0.05% for 4 weeks, the mean (SD) C_{max} and AUC_{last} values of tazarotenic acid were 288.8 (327.5) pg/mL and 5331 (5932) pg*hr/mL on Day 14 and 340.3 (351.8) pg/mL and 6419 (6842) pg*hr/mL on Day 28, respectively.

The relative bioavailability assessments showed that the bioavailability of DUOBRII lotion was higher than each of the listed drugs for the individual monads. The 90% confidence interval on the ratio of geometric means of C_{max} and AUC for both halobetasol propionate and tazarotenic acid (an active metabolite of tazarotene) were higher than the no effect boundary of 80% to 125%. The results indicated that the clinical bridges to listed drugs were not established. Therefore, the applicant cannot rely on the FDA's findings of safety for the listed drugs.

Based on 21 CFR §314.125(b)(4), i.e., there is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling. Therefore, this reviewer recommends a Complete Response for this NDA.

The following nonclinical information is needed to resolve the **Complete Response** deficiencies:

1. Adequate data from a complete battery of genetic toxicology studies for both monads.

2. Adequate data from systemic embryofetal development studies in a rodent and a nonrodent species for both monads. It is recommended that embryofetal development studies involve systemic dosing to ensure adequate exposure to the drug substances.

3. Adequate data from a study or studies in male and female rodents for effects upon fertility, reproductive function, or early embryonic development for both monads.

4. Adequate data from a study in rodents for effects on pre- and postnatal development for both monads.

Potential of the drug product or drug substances to induce carcinogenicity should be evaluated in two species for both monads. One study should be conducted using a systemic route of administration and the other by the dermal route of administration. It is recommended that protocols for carcinogenicity studies be submitted to the Division for evaluation by the Executive Carcinogenicity Assessment Committee of CDER.		
Dimension	**Evidence and Uncertainties**	**Conclusions and Reasons**
Analysis of Condition	• 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 U.S. is approximately 2-3 %, of which an estimated 20% have moderate to severe disease. One third of patients have concomitant arthritis. Other comorbidities include depression/suicide, autoimmune disease, cardiovascular disease, and metabolic syndrome[1].	Moderate to severe plaque Psoriasis is a serious disease because of its chronicity, impact on quality of life, and co-morbidities.
Current Treatment Options	• Approved products for the treatment of moderate to severe psoriasis include anti-metabolites (methotrexate), tumor necrosis factor (TNF) inhibitors (etanercept, adalimumab and infliximab), IL-12/23 blockers (ustekinumab), IL-17A blockers (secukinumab and ixekizumab), an IL-17A receptor antagonist (brodalumab), IL-23 blockers (guselkumab and tildrakizumab), a T cell inhibitor (cyclosporine), retinoids (acitretin) and phosphodiesterase 4 inhibitors (apremilast). Other treatment options include phototherapy with either PUVA (UVA light combined with methoxsalen) or UVB light (narrow or broadband). • All approved therapeutic options may be associated with the risk of serious adverse reactions or administration challenges. The use of phototherapy and photochemotherapy are limited by the need for office administration and additional photoprotection. Teratogenicity and hyperlipidemia are labeled risks with acitretin. Depression and weight loss are safety concerns with apremilast. The primary risks of cyclosporine use are nephrotoxicity and hypertension. Methotrexate has teratogenic,	There are several FDA-approved products with an acceptable benefit-risk profile for the treatment of moderate-to-severe plaque psoriasis in adults. None of these treatments provides a permanent cure or universal response and all these products are associated with one or more serious risks. Because treatment may be complicated by inadequate response, loss of response, adverse reactions, and the presence of comorbidities or concomitant illnesses, there is a need for additional therapeutic options.

	hepatotoxic, and nephrotoxic effects and may cause bone marrow toxicity and pulmonary fibrosis. Other systemic products may cause immunosuppression, serious infections and malignancy. All biologic products may be associated with loss of effect and serious hypersensitivity reactions. See the summary tables of topical and systemic treatments for moderate to severe plaque psoriasis for the specific labeled safety issues for each product.	
Benefit	• For Phase 3 trials (-301 and -302), results for the primary efficacy endpoint for the ITT and PP populations showed that DUOBRII lotion was statistically superior to vehicle lotion at Week 8 (in Trial -301: 35.8% vs 7.0% and in Trial -302: 45.3% vs 12.5%; p-values < 0.001).	
Risk	• The primary safety database consisted of 270 subjects from the Phase 3 trials (-301 and -302), treated once daily for 8 weeks. In addition, the long-term safety trial (-303) included 550 subjects: 391 subjects completed 6 months, and 138 subjects completed 12 months of treatment with DUOBRII lotion. The safety database is adequate to characterize the safety profile of DUOBRII lotion. • During the Phase 3 trials (-301 and -302), SAEs occurred in 1.1% of subjects treated with DUOBRII lotion, compared to no subjects in the vehicle group. The SAEs were unrelated to the study drug. • During the Phase 3 trials (-301 and -302), adverse reactions (AR)s occurred in 20.4% of subjects in the DUOBRII lotion group, compared to 7.9% of subjects in the vehicle lotion group. The most common ARs in subjects treated with DUOBRII lotion were contact dermatitis (6.3%), application site pain (2.6%), skin atrophy (1.9%), folliculitis (1.9%), rash (1.5%), and excoriation (1.1%).	

	• The effects of DUOBRII on pregnant or lactating women are unknown.	
Risk Management	• Not applicable.	

1.4. Patient Experience Data

Table 1: Patient Experience Data Relevant to this Application

□	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	□	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	DLQI, Section 9.7.1.7.6, CSR -301, Other endpoints
		□	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	IGA, Section 9.7.1.7.2, CSR-301, primary efficacy Change from baseline in psoriasis signs (erythema, plaque elevation, scaling), Section 11.4.1.3, CSR -301, tertiary efficacy endpoints
		□	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		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify)		
□	Patient experience data that were not submitted in the application, but were considered in this review:			
		□	Input informed from participation in meetings with patient stakeholders	
		□	Patient-focused drug development or other stakeholder meeting summary reports	
		□	Observational survey studies designed to capture patient experience data	
		□	Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.			

2 Therapeutic Context

2.1. Analysis of Condition

Psoriasis is a common, chronic, immune-mediated skin disorder. The characteristic lesion is a sharply demarcated erythematous plaque with micaceous scale, and the plaques may be localized or widespread in distribution[2]. Psoriasis is a complex autoimmune inflammatory disease that occurs in genetically susceptible individuals. The pathophysiology of psoriasis involves the activation of innate immune cells in the skin, which produce proinflammatory cytokines which trigger and perpetuate the inflammatory cascade[3].

In the U.S. and Canada, prevalence as high as 4.6% and 4.7% have been reported, respectively[2]. It is estimated that approximately 7.5 million people in the United States have psoriasis. Approximately 80 percent of those affected with psoriasis have mild to moderate disease, while 20 percent have moderate to severe psoriasis affecting more than 5 percent of the body surface area. The most common form of psoriasis is plaque psoriasis, affecting about 80 to 90 percent of patients with psoriasis[4].

Psoriasis can first appear at any age, from infancy to the eighth decade of life. Two peaks in age of onset have been reported: one at 20–30 years of age and a second peak at 50–60 years. In approximately 75% of patients, the onset is before the age of 40 years, and in 35–50%, it is before the age of 20 years. The average age of onset is earlier in women than in men[2].

The natural history of psoriasis is chronic with intermittent remissions. Although plaque psoriasis is the most common presentation, other forms of psoriasis include guttate, pustular, erythrodermic, and inverse psoriasis. Psoriasis may affect fingernails and toenails, most frequently in association with psoriatic arthritis. A diagnosis of psoriasis can be made by history and physical examination in most cases. The differential diagnosis of psoriasis may include seborrheic dermatitis, lichen simplex chronicus, atopic dermatitis, and nummular eczema. Occasionally, a skin biopsy is performed to rule out other conditions[2].

The presentation of psoriasis in the pediatric population can be different from that in adults. Psoriasis in infants often presents with involvement of the diaper area. Infants with diaper-area involvement typically develop symmetrical, well-demarcated erythematous patches with little scale. Maceration may be present. Unlike irritant diaper dermatitis, the inguinal folds are usually involved. Affected infants may also have psoriatic plaques in other body areas. These plaques are often smaller and thinner than the psoriatic plaques in adult patients. In children, scalp involvement is a common and often initial presentation of chronic plaque psoriasis. In addition, children with chronic plaque psoriasis are more likely to have facial involvement than adults[2].

A number of comorbid systemic conditions occur more frequently in patients with psoriasis. Examples of these conditions include cardiovascular disease, malignancy, diabetes, hypertension, metabolic syndrome, inflammatory bowel disease, serious infections, and autoimmune disorders. Psychiatric comorbidities associated with psoriasis include depression and suicidal ideation; neurotic, stress-related, or somatoform disorders; and personality and behavioral disorders[5].

The impact of psoriasis on the daily lives of patients was among the topics discussed at a Patient-Focused Drug Development Meeting for psoriasis held by the Agency on March 17, 2016. Patients who attended the meeting described severe physical, social and emotional impact including: depression, anxiety, limitations on activities, embarrassment, stigma, and social discrimination. Patients shared their experiences with currently available therapies, and they described varying degrees of success in managing symptoms with these therapies. Patients stressed need to enlarge the treatment armamentarium, given current challenges with variability in effectiveness, tolerability, access to available treatments, and uncertainty regarding long-term effects of available treatments.

Psoriasis is a chronic, debilitating disease with significant impacts on the lives of affected patients. At the Patient Focused Drug Development meeting, patients discussed current challenges with variability in effectiveness, tolerability, access to available treatments, and uncertainty regarding long-term effects of available treatments. Therefore, development of additional safe and effective therapies continues to be an important goal. This is especially true for certain subgroups of patients with psoriasis, such as women during pregnancy and pediatric
patients.

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[1]Menter A et al. Guidelines of care for the management of psoriasis and psoriatic arthritis Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. J Am Acad Dermatol 2008; 58:826-50.
[2] Feldman, Steven R., MD. PhD; Epidemiology, Clinical Manifestations, and Diagnosis of Psoriasis; UpToDate.com; updated December 9, 2015
[3] Blauvelt, Andrew and Ehst, Benjamin D, Pathophysiology of Psoriasis; UpToDate.com; updated July 8,[1] 2015
[4] Menter A, Gottlieb A, Feldman SR, Van Voorhees AS et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. J Am Acad Dermatol 2008 May; 58(5):826-50.
[5] Korman, Neil; Comorbid Disease in Psoriasis; UpToDate.com; updated March 24, 2017.

2.2. Analysis of Current Treatment Options

The proposed indication for DUOBRII lotion is topical treatment of plaque psoriasis in adults 18 years of age or older. There are multiple treatments available for moderate to severe plaque psoriasis, as summarized in the following tables:

Table 2 : Topical Treatments for Moderate to Severe Plaque Psoriasis

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

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

Table 3: Approved Systemic Treatments for Moderate to Severe Plaque Psoriasis

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

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Because DUOBRII lotion is not currently marketed in the United States, this section is not applicable.

3.2. Summary of Presubmission/Submission Regulatory Activity

3.2.1. Regulatory Pathway

The applicant submitted the current original NDA under Section 505(b)(2) of the Federal Food, Drugs and Cosmetic Act and 21 CFR 314.50. The applicant conducted clinical studies to evaluate efficacy and safety of DUOBRII lotion in their clinical development program, but planned to use some of the information required for approval from the studies not conducted by or for the applicant and for which the applicant had not obtained a right of reference. The nonclinical pharmacology/toxicology information the applicant planned to use for the basis of this 505(b)(2) submission are from the following listed drugs:

- Ultravate (halobetasol propionate) cream, 0.05% for the treatment of corticosteroid responsive dermatosis (NDA 019967) approved on 12/27/1990.
- Tazorac (tazarotene) cream, 0.05% for the treatment of plaque psoriasis (NDA 021184) approved on 9/29/2000.

3.2.2. Presubmission Regulatory Activity

This product was developed under IND 111218, submitted on 10/24/2011.
Milestone interactions with the applicant are described below:

Pre-IND:
A Teleconference was held with the sponsor on 6/15/2011. The following topics were discussed during this meeting:

- Requirements to establish clinical bridges to reference products under a 505 (b)(2) pathway
- Non-clinical studies to be conducted prior to IND clinical studies
- Outline of clinical studies to be conducted under IND 111218
- Discussion of criteria for maximal use study and efficacy endpoints / IGA scale

EOP2 Meeting:
A meeting was held with the sponsor on 2/25/2015. The following topics were discussed during this meeting:

- CMC issues related to specifications and stability requirements
- Non-clinical development program
- Clinical pharmacology / maximal use study design
- IGA scale for clinical endpoints assessments
- Subject population / number of subjects / clinical bridge study requirements / long-term safety, dermal safety and photosafety studies / combination drug policy / statistical testing

iPSP:
The FDA agreed with the sponsor's iPSP on 6/16/2016. Refer to section 7.3.8 of this review for additional details.

Pre-NDA:
A teleconference was held with the sponsor on 2/15/2017. The content and format of the NDA was discussed during this meeting, including the following topics:

- CMC: drug substance specifications / stability studies / impurities / antimicrobial effectiveness testing (AET) / USP <3> uniformity
- Pharmacology / toxicology: clinical bridge / adequacy of nonclinical program
- Clinical pharmacology: TQT waiver discussion / additional comments for sponsor
- Clinical / Biostatistics: number of subjects exposed to the to-be-marketed formulation per ICH E1A guidance / statistical analysis plan for pooling of trials -301 and -302 in ISS and ISE

Good Clinical Practice and Financial Disclosure:

The applicant stated that all clinical trials in their DUOBRII development program were conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, and with Good Clinical Practice (GCP), as required by the US Code of Federal Regulations applicable to clinical studies (21 CFR Parts 11, 50, 54, 56 and 312, 42 USC 282(j), International Conference on Harmonisation, Harmonised Tripartite Guideline E6(R1): GCP and E2A: Safety Data Management, and applicable local or national regulations.

For financial disclosure information, refer to Section 13.2 of this review.

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

4.1. Office of Scientific Investigations (OSI)

The overall quality of the clinical information contained in this submission is adequate. The division requested that the office of scientific investigations (OSI) conduct clinical site inspections. All Phase 3 trials were conducted at sites in the U.S.

Three sites were selected for inspection mainly due to high site efficacy effect and the fact that these clinical investigators had no prior history of good clinical practice (GCP) inspections.

The clinical inspection summary included the following results (Review by Bei Yu, Ph.D., dated 3/16/2018):

Table 4: Site Inspection Results

Site #/ Name of CI/ Address	Protocol # / # of Subjects Enrolled	Inspection Dates	Classification
Site #201 **Jerry Bagel, M.D.** 59 One Mile Road, Suite B East Windsor, NJ 08520	V01-118A-302 Subjects: 18	3, 5, 8 - 11 Jan 2018	NAI
Site #104 **Janet DuBois, M.D.** 8140 N. Mopac, Bldg 3, Suite 120 Austin, TX 78759	V01-118A-301 Subjects: 21	16 - 19 Jan 2018	NAI
Site #101 **Reginold Simmons, M.D.** 4257 West Kennedy Blvd. Tampa, FL 33609	V01-118A-301 Subjects: 21	2 - 4 Jan 2018	NAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.

Dr. Yu concluded that based on the results of these inspections, the studies appear to have been conducted adequately, and the data generated by these sites and as reported by the sponsor to the NDA appear acceptable in support of the respective

indication.
The final classification of the inspections of these clinical investigators was No Action Indicated (NAI).

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.

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

4.3. Clinical Microbiology

Not applicable to this review.

4.4. Devices and Companion Diagnostic Issues

Not applicable to this review.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The applicant has developed a combination drug product, DUOBRII (halobetasol propionate and tazarotene) lotion, 0.01%/0.045%, for the treatment of plaque psoriasis. The two drug substances contained in the drug product, halobetasol propionate and tazarotene, have been marketed for the treatment of plaque psoriasis for more than 20 and 10 years, respectively. All excipients used in DUOBRII (halobetasol propionate and tazarotene) lotion, 0.01%/0.045% are commonly used in topical products and are listed in the FDA's Inactive Ingredient Guide.

The applicant is seeking approval of DUOBRII (halobetasol propionate and tazarotene) lotion, 0.01%/0.045%, for the treatment of plaque psoriasis in patients 18 years of age and older via a 505(b)(2) regulatory pathway. The proposed dosing regimen is to topically apply the drug product to the affected area once daily. The total dosage should not exceed approximately 50 g per week because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis.

The applicant intended to establish an adequate clinical bridge to the Listed Drugs, Ultravate (halobetasol propionate) Cream, 0.05% and Tazorac (tazarotene) Cream, 0.05%, and rely on the Agency's finding of safety for the Listed Drugs. The nonclinical data from the approved labels for the Listed Drugs that the sponsor intended to rely on included fertility and reproduction, embryofetal development, genotoxicity and carcinogenicity (tazarotene only). The toxicities of both drugs are well characterized and typical for their respective drug classes.

The applicant submitted a pivotal 3-month repeat dose minipig dermal toxicity study. This study was conducted with five treatment groups included the IDP-118 Lotion at low (halobetasol propionate 0.002%/tazarotene 0.010%), mid (halobetasol propionate 0.01%/tazarotene 0.045%) and high doses (halobetasol propionate 0.02%/tazarotene 0.09%), as well as monad groups containing halobetasol propionate (0.02%) or tazarotene (0.090%) in lotion vehicle. The mid dose group was treated with the to-be-marketed formulation, which was later used in the Phase 3 clinical studies. Administration of IDP-118 Lotion as well as halobetasol propionate and tazarotene monads by once daily dermal application for 90 days was well tolerated in minipigs at low, clinical, and enhanced strengths up to 0.02% halobetasol propionate/0.090% tazarotene. IDP-118 Lotion was associated with body weight decreases, consistent with adverse effects of topical corticosteroids, and correlated to halobetasol propionate systemic exposure. Target organs included those previously reported for tazarotene and halobetasol propionate (i.e., skin dose site, adrenal glands, and thymus). The decreased organ weights and/or microscopic changes observed in target organs showed partial or full reversibility following a 1-month recovery period. No new toxicities or toxicological interactions arising from the combination were noted in the study. There were no test article-related ECG abnormalities in this study. Steady state exposures

(AUC_{0-24}) at the mid dose (clinical strength) were 20 (males) and 14 ng•hr/mL (females) for tazarotenic acid (the active metabolite of tazarotene), and 2.6 (males) and 1.9 ng•hr/mL (females) for halobetasol propionate.

The applicant conducted a maximal use clinical pharmacokinetic (PK)/hypothalamic-pituitary-adrenal (HPA) axis suppression study and other clinical studies to establish an adequate clinical bridge to the listed drugs. However, it was determined that an adequate clinical bridge to the Listed Drugs, Ultravate (halobetasol propionate) Cream, 0.05% and Tazorac (tazarotene) Cream, 0.05%, was not established based on the clinical studies the applicant submitted in the NDA. Refer to Clinical Pharmacology section of this review for the details. The applicant did not submit adequate published literature that provides nonclinical data required for labeling for each monad including fertility and reproduction, embryofetal development, genotoxicity and carcinogenicity.

Therefore, a Complete Response is recommended for this NDA from a Pharmacology/ Toxicology perspective based on 21 CFR §314.125(b)(4), i.e., there is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling. Specifically, the applicant has not provided sufficient nonclinical toxicology data to address the fertility and reproduction, embryofetal development, genotoxicity and carcinogenicity of each monad.

5.2. Referenced NDAs, BLAs, DMFs

This NDA makes reference to the following DMFs.

(b) (4)

DMF
DMF
DMF

The applicant intended to rely on the Agency's findings of safety for the following NDAs. However, it was determined that an adequate clinical bridge to the Listed Drugs Ultravate (halobetasol propionate) Cream, 0.05% and Tazorac (tazarotene) Cream, 0.05%. was not established.

NDA 21184: Tazorac (tazarotene) Cream, 0.1%, approved on September 29, 2000.
NDA 19967: Ultravate (halobetasol propionate) Cream, 0.05%, approved on December 27, 1990.

The following nonclinical pharmacology and toxicology studies were reviewed under INDs 111218 or 126779. A summary of these studies is provided below. The code name for this drug product is IDP-118 lotion.

5.3. Pharmacology

Primary pharmacology

No primary pharmacology studies with the individual drug substances or with the drug product have been conducted. The applicant intended to rely on scientific pharmacology literature references for the drug substances and their respective drug classes, tazarotene-steroid combination psoriasis clinical experience and the Agency's previous finding of safety and efficacy for the listed drugs Ultravate (halobetasol propionate) Cream, 0.05% and Tazorac (tazarotene) Cream, 0.05%.

It was determined that an adequate clinical bridge to the Listed Drugs, Ultravate (halobetasol propionate) Cream, 0.05% and Tazorac (tazarotene) Cream, 0.05%, was not established based on the clinical studies the applicant submitted in the NDA. Refer to Clinical Pharmacology section of this review for the details.

The applicant submitted a number of published primary pharmacology literature references (1, 2, 3, 4, 5, and 6, see Section 13.3 Appendices). The information from these published primary pharmacology literature references are sufficient to support Section 12.1 "Mechanisms of Action" in the label for this product with appropriate edits. The labeling for this drug product will be addressed when the NDA is resubmitted to address the nonclinical deficiencies identified below.

Secondary Pharmacology

No studies have been conducted to characterize secondary pharmacodynamic properties of tazarotene, halobetasol propionate or their combination.

Safety Pharmacology

Study 1 Effects of Tazarotene, Tazarotenic Acid and Halobetasol Propionate and Mixtures on Cloned hERG Potassium Channels Expressed in Mammalian Cells (Study # V01-118A-608, Non-GLP)

The most common mechanism of drug-induced QT interval prolongation is inhibition of the delayed rectifier potassium channel. The potential of halobetasol propionate, tazarotene and tazarotenic acid (the active metabolite for tazarotene) to inhibit potassium channel currents was evaluated in the in vitro human ether-a-go-go-related gene (hERG) assay. Tazarotene inhibited hERG current with an IC_{50} of 5.7 μM; this level of inhibition is considered weak and not a concern because tazarotene is rapidly metabolized in vivo to tazarotenic acid and essentially not detected in human plasma following dermal administration. An IC_{50} >10 μM (the highest concentration tested) was established for halobetasol propionate and tazarotenic acid. Therefore, halobetasol propionate and tazarotenic acid have negligible/no hERG inhibition potential based on the results from this in vitro study.

No standalone safety pharmacology studies with the individual drug substances or with the drug product have been conducted. The effects of IDP-118 on ECG measurements were evaluated in a 3-month repeat dose minipig dermal toxicity study. There were no test article-related ECG abnormalities in main study animals or in 1-month recovery animals.

The applicant also intended to rely on the safety pharmacology data in the literature for the drug substances and their respective drug classes and the Agency's previous finding of safety for the Listed Drugs, Ultravate (halobetasol propionate) Cream, 0.05% and Tazorac (tazarotene) Cream, 0.05%. However, it was determined that an adequate clinical bridge to the Listed Drugs was not established based on the clinical studies the applicant submitted in the NDA. Refer to Clinical Pharmacology section of this review for the details. The applicant did not submit any safety pharmacology published literature data for halobetasol propionate or tazarotene.

5.4. ADME/PK

The applicant has not conducted nonclinical pharmacokinetic studies with the individual drug substances or with the combination drug product, IDP-118 Lotion. However, the toxicokinetics (TK) of halobetasol propionate, tazarotene and tazarotenic acid in plasma were determined in a 3-month repeat dose toxicity study in minipigs conducted with IDP-118 Lotion. A summary of these TK data is provided below. Refer to Section 5.5.1 (General Toxicology) for detailed information concerning the design of the 3-month repeat dose toxicity study in minipigs.

Type of Study	**Major Findings**
TK data from a repeat dose toxicology study A 3-month Study of IDP-118-A by Dermal Administration in Minipigs with a 1-month Recovery Period, Study # V01-118A-605	<u>Halobetasol propionate TK data for male minipigs</u> *T_{max}:* Low strength: 4 hrs Clinical strength: 4 hrs Enhanced strength: 4 hrs *AUC_{0-24}:* Low strength: 1.3 ng·hr/mL Clinical strength: 2.8 ng·hr/mL Enhanced strength: 4.0 ng·hr/mL *C_{max}:* Low strength: 0.14 ng/mL Clinical strength: 0.23 ng/mL Enhanced strength: 0.31 ng/mL *Accumulation:* No evidence of systemic accumulation from Day 28 to Day 90, indicating steady-state had been achieved by Day 28. *Dose proportionality:* Systemic exposure increased roughly dose-

Type of Study	Major Findings
	proportionally <u>Halobetasol propionate TK data for female minipigs</u> *T_{max}:* Low strength: 4 hrs Clinical strength: 3 hrs Enhanced strength: 4 hrs *AUC_{0-24}:* Low strength: 1.0 ng·hr/mL Clinical strength: 2.1 ng·hr/mL Enhanced strength: 4.9 ng·hr/mL *C_{max}:* Low strength: 0.10 ng/mL Clinical strength: 0.23 ng/mL Enhanced strength: 0.35 ng/mL *Accumulation:* No evidence of systemic accumulation from Day 28 to Day 90, indicating steady-state had been achieved by Day 28. *Dose proportionality:* Systemic exposure increased roughly dose-proportionally <u>Tazarotenic Acid TK data for male minipigs</u> *T_{max}:* Low strength: 2 hrs Clinical strength: 8 hrs Enhanced strength: 4 hrs *AUC_{0-24}:* Low strength: 6.1 ng·hr/mL Clinical strength: 32 ng·hr/mL Enhanced strength: 54 ng·hr/mL *C_{max}:* Low strength: 0.3 ng/mL Clinical strength: 2.1 ng/mL Enhanced strength: 3.0 ng/mL *Accumulation:* No evidence of systemic accumulation from Day 28 to Day 90, indicating steady-state had been achieved by Day 28. *Dose proportionality:* Systemic exposure increased roughly dose-proportionally

Type of Study	Major Findings
	Tazarotenic Acid TK data for female minipigs *T_{max}:* Low strength: 8 hrs Clinical strength: 4 hrs Enhanced strength: 3 hrs *AUC_{0-24}:* Low strength: 4.0 ng·hr/mL Clinical strength: 24 ng·hr/mL Enhanced strength: 42 ng·hr/mL *C_{max}:* Low strength: 0.23 ng/mL Clinical strength: 1.7 ng/mL Enhanced strength: 3.7 ng/mL *Accumulation:* No evidence of systemic accumulation from Day 28 to Day 90, indicating steady-state had been achieved by Day 28. *Dose proportionality:* Systemic exposure increased roughly dose-proportionally

The applicant conducted a human maximal use pharmacokinetic/hypothalamic-pituitary-adrenal (HPA) axis suppression study and other clinical studies to establish an adequate clinical bridge to the listed drugs. However, it was determined that an adequate clinical bridge to the Listed Drugs, Ultravate (halobetasol propionate) Cream, 0.05% and Tazorac (tazarotene) Cream, 0.05%, was not established based on the clinical studies the applicant submitted in the NDA. Refer to Clinical Pharmacology section of this review for the details.

5.5. Toxicology

5.5.1. General Toxicology

Study 1 A Fourteen-Day Dermal Study of IDP-118 in Gottingen Minipigs (Study # 7001-U6HP-01-10, Non-GLP)

This study evaluated the dermal toxicity and systemic exposure to halobetasol propionate, tazarotene and tazarotenic acid following administration of IDP-118 prototypes W, Y and Z (0.09% tazarotene and 0.01% or 0.025% halobetasol propionate) and two comparators, Tazorac® Cream (0.1% tazarotene) and Ultravate® Cream (0.05% halobetasol propionate) in male Gottingen minipigs.

IDP-118 Formulas W, Y and Z, Ultravate Cream and Tazorac Cream were well-tolerated in minipigs when administered dermally for 14 days. All IDP- 118 formulas and Tazorac Cream produced slight and/or well-defined erythema at the application site, consistent with tazarotene-induced skin irritation. However, the IDP-118 Formulas were less irritating than Tazorac Cream, as indicated by delayed erythema onset, lower irritation grade and/or absence of mild eschar at the end of the study. Severity and occurrences of erythema was highest for Tazorac Cream followed by, in decreasing order, IDP-118 Formula Z, IDP-118 Formula W and IDP- 118 Formula Y. Reduced site of application skin irritation correlated with the presence of halobetasol propionate in the IDP-118 Formulas. Ultravate Cream did not produce erythema or signs of skin thinning or atrophy. HPA axis suppression was evident in the IDP-118 and Ultravate Cream groups based on Day 15 lower pre- and post-stimulation serum cortisol levels compared to Days -1 and 42. Animals treated with IDP-118 Formulas appeared to recover normal adrenal function by Day 42 while animals treated with Ultravate Cream showed slight signs of HPA suppression based on lower post-stimulation cortisol levels as compared to the rest of the groups. Animals treated with Tazorac Cream, which was used as the HPA axis suppression negative control, showed consistent cortisol levels across ACTH test days. IDP-118 Formula Z yielded consistently lower halobetasol propionate and tazarotenic acid maximum and total exposure parameter values compared to those following the administration of Tazorac Cream and Ultravate Cream, respectively, on Study Days 7 and 14. The highest mean halobetasol propionate plasma concentrations and systemic exposure were observed in animals administered IDP-118 Formula Y and correlated to the treatment group with least skin irritation.

Study 2 A 3-month Study of IDP-118-A by Dermal Administration in Minipigs with a 1-month Recovery Period (Study # V01-118A-605, GLP)

This study was appropriately conducted with five treatment groups included the IDP-118 Lotion at low (halobetasol propionate 0.002%/tazarotene 0.010%), mid (halobetasol propionate 0.01%/tazarotene 0.045%) and high doses (halobetasol propionate 0.02%/tazarotene 0.09%), as well as monad groups containing halobetasol propionate (0.02%) or tazarotene (0.090%) in lotion vehicle. The mid dose group was treated with the to-be-marketed formulation, which was later used in the Phase 3 clinical studies.

Administration of IDP-118 Lotion as well as halobetasol propionate and tazarotene monads by once daily dermal application for 90 days was well tolerated in minipigs at low, clinical, and enhanced strengths up to 0.02% halobetasol propionate/0.090% tazarotene.

IDP-118 Lotion was associated with body weight decreases, consistent with adverse effects of topical corticosteroids, and correlated to halobetasol propionate systemic exposure. Target organs included those previously reported for tazarotene and halobetasol propionate (i.e., skin dose site, adrenal glands, and thymus). The decreased organ weights and/or microscopic changes observed in target organs showed partial or full reversibility following a 1-month recovery period. No new toxicities or toxicological interactions arising from their combination were noted in the study.

ECG measurements were obtained prior to the first dose, during the last week of dosing (days 85/87), and during the last week of the recovery period (day 114). There were no test article-related ECG abnormalities in main study animals or in 1-month recovery animals.

Tazarotene is a prodrug of its active metabolite, tazarotenic acid. Halobetasol propionate and tazarotenic acid, but not tazarotene, were detected in plasma. Overall, drug systemic exposure was consistently achieved throughout the dosing interval, with C_{max} reached within a few hours after dosing. The highest exposures, based on C_{max}, were observed in the high dose group on Day 28 for halobetasol propionate and Day 90 for tazarotenic acid. There was no evidence of drug systemic accumulation between Days 28 and 90, and steady state appeared to be reached by Day 28. Drug absorption appeared to increase with the combination product as compared to the lotion monads. On Day 90, male and female C_{max} averaged 0.31 and 0.35 ng/mL for halobetasol propionate and 3.0 and 3.7 ng/mL for tazarotenic acid, respectively. Steady state exposures (AUC_{0-24}) at the mid dose (clinical strength) were 21 (males) and 14 ng•hr/mL (females) for tazarotenic acid, and 2.6 (males) and 1.9 ng•hr/mL (females) for halobetasol propionate.

5.5.2. Genetic Toxicology

No genetic toxicity studies were conducted with the combination of halobetasol propionate and tazarotene.

The applicant intended to establish an adequate clinical bridge to the Listed Drugs, Ultravate (halobetasol propionate) Cream, 0.05% and Tazorac (tazarotene) Cream, 0.05%, and rely on the Agency's finding of safety for the Listed Drugs and reference their labels for genetic toxicology information to support NDA approval. However, it was determined that an adequate clinical bridge to the Listed Drugs was not established. Therefore, the sponsor cannot rely on the genetic toxicology information contained in the Listed Drug labels to support the safety of their combination drug product.

The applicant also submitted a scientific article titled (b) (4) his published literature article contains summary information for the genetic toxicity (b) (4). However, no study reports for those genetic toxicity studies were provided by the applicant. The summary information for genetic toxicity of (b) (4) included in the article is not adequate to support NDA approval.

Therefore, the applicant needs to provide adequate data from a complete ICH battery of genetic toxicology studies for both monads to support NDA approval.

5.5.3. Carcinogenicity

No carcinogenicity studies were conducted with IDP-118 lotion.

The applicant intended to establish an adequate clinical bridge to the Listed Drugs, Ultravate (halobetasol propionate) Cream, 0.05% and Tazorac (tazarotene) Cream, 0.05%, and rely on the Agency's finding of safety for the Listed Drugs and reference their labels for carcinogenicity information to support NDA approval. However, it was determined that an adequate clinical bridge to the Listed Drugs was not established. Therefore, the sponsor cannot rely on the carcinogenicity information contained in the Listed Drug labels to support the safety of their combination drug product.

The applicant did not submit any published literature data to address the carcinogenetic potential of halobetasol propionate or tazarotene.

Therefore, the applicant needs to provide adequate carcinogenicity data for both monads to support NDA approval.

5.5.4. Reproductive and Developmental Toxicology

No reproductive and developmental toxicity studies were conducted with IDP-118 lotion.

The applicant intended to establish an adequate clinical bridge to the Listed Drugs, Ultravate (halobetasol propionate) Cream, 0.05% and Tazorac (tazarotene) Cream, 0.05%, and rely on the Agency's finding of safety for the Listed Drugs and reference their labels for reproductive and developmental toxicology information to support NDA approval. However, it was determined that an adequate clinical bridge to the Listed Drugs was not established. Therefore, the sponsor cannot rely on the reproductive and developmental toxicology information contained in the Listed Drug labels to support the safety of their combination drug product.

The applicant has not submitted any published literature data for reproductive and developmental toxicity of halobetasol propionate or tazarotene.

Therefore, the applicant needs to provide adequate reproductive and developmental toxicity data from systemic embryofetal development studies in a rodent and a nonrodent species, a study or studies in male and female rodents for effects upon fertility, reproductive function, or early embryonic development, and a study in rodents for effects on pre- and postnatal development for both monads to support NDA approval.

5.5.5. Other Toxicology Studies

Study 1 A Reduced Local Lymph Node Assay with IDP-118 Lotion (Study # 7001-U6HP-02-10, GLP)

This study was conducted to determine if two IDP-118 Lotion formulations, Formula A and Formula B, would induce a hypersensitivity response in mice as measured by the proliferation of lymphocytes in the draining auricular lymph nodes.

A 3-fold or greater increase in stimulation index (SI) was considered a positive response. The positive control, 35% hexylcinnamaldehyde (HCA) in acetone olive oil (AOO), resulted in a SI of 39.7 when compared to the AOO control. The 35% HCA in IDP-118 Formula A Vehicle and Formula B Vehicle, resulted in a SI of 9.8 and 29.6 when compared to the Formula A Vehicle and Formula B Vehicle controls, respectively.

Treatment with IDP-118 Lotion Formula A and IDP-118 Lotion Formula B did not result in a SI of greater than or equal to 3 relative to the Formula A or Formula B vehicles or the AOO control. Therefore, these findings suggest IDP-118 Lotion Formula A and IDP-118 Lotion Formula B are not sensitizers.

Study 2 IDP-118 Lotion: Topical Application Ocular Irritation Screening Assay Using the EpiOcular Human Cell Construct (Study # 7001-U6HP-04-10, GLP)

This study was conducted to evaluate the potential ocular irritation of the test articles by measuring 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) dye conversion by the EpiOcular™ tissue construct after topical exposure to the test articles, i.e., IDP-118 Lotion Formula A, IDP-118 Lotion Formula B, halobetasol propionate and tazarotene.

IDP-118 Lotion Formula A and B as well as the drug substances (halobetasol propionate and tazarotene) were predicted to be minimally-irritating to non-irritating to the eye based on the results from this study.

Study 3 Phototoxicity Assay Using the EpiDerm™ Skin Model (Study # V01-118A-607, GLP)

The phototoxicity potential of IDP-118 Lotion was evaluated in the EpiDerm™ in vitro skin model by treating tissues and subsequently exposing to ultraviolet-A (UVA)/visible light, and measuring tissue viability. According to the prediction model presented by (b) (4) IDP-118-A Lotion (lot # DP1615) and IDP-118-A Lotion Vehicle (lot # DP1612) did not show phototoxic potential; whereas Tazorac Cream 0.1% (lot # 81464) exhibited a phototoxic potential (i.e., test article induced ≥30% decrease in viability in the presence of UVA compared to the viability in the absence of UVA). The positive control, 0.02% chlorpromazine, met the acceptance criterion for a positive phototoxic response and validated the assay sensitivity.

5.6. Nonclinical Deficiencies

A Complete Response is recommended for this NDA from a Pharmacology/Toxicology perspective based on 21 CFR §314.125(b)(4), i.e., there is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling.

Specifically, the applicant did not provide sufficient nonclinical toxicology data to support NDA approval since it was determined that an adequate clinical bridge to the Listed Drugs, Ultravate (halobetasol propionate) Cream, 0.05% and Tazorac (tazarotene) Cream, 0.05%, was not established based on the clinical studies the applicant submitted in the NDA. Refer to the Clinical Pharmacology section of this review for the details.

The following nonclinical information is needed to resolve the Complete Response deficiencies.

5. Adequate data from a complete battery of genetic toxicology studies for both monads.

6. Adequate data from systemic embryofetal development studies in a rodent and a nonrodent species for both monads. It is recommended that embryofetal development studies involve systemic dosing to ensure adequate exposure to the drug substances.

7. Adequate data from a study or studies in male and female rodents for effects upon fertility, reproductive function, or early embryonic development for both monads.

8. Adequate data from a study in rodents for effects on pre- and postnatal development for both monads.

9. Potential of your drug product or drug substances to induce carcinogenicity should be evaluated in two species for both monads. One study should be conducted using a systemic route of administration and the other by the dermal route of administration. It is recommended that protocols for carcinogenicity studies be submitted to the Division for evaluation by the Executive Carcinogenicity Assessment Committee of CDER.

5.7. Labeling

The labeling will not be addressed in this time. The labeling for this drug product will be addressed when the NDA is resubmitted to address the nonclinical deficiencies identified above.

6 Clinical Pharmacology

6.1. Executive Summary

The applicant submitted the current NDA seeking for approval for DUOBRII Lotion which is a combination product of halobetasol propionate and tazarotene 0.01%/0.045% for the topical treatment of plaque psoriasis.

The applicant is following a 505(b)(2) regulatory pathway and has identified Ultravate (halobetasol propionate) Cream, 0.05% (NDA 019967) and Tazorac (tazarotene) Cream, 0.05% (NDA 021184) as listed drugs for halobetasol propionate and tazarotene, respectively. The applicant proposed to rely on the Agency's findings of safety from the listed drugs. To support the NDA, the applicant conducted 11 clinical studies that included two identically designed Phase 3 pivotal trials, a long-term safety study, a maximal use pharmacokinetic (PK)/hypothalamic-pituitary-adrenal (HPA) axis suppression study, and a topical corticosteroid potency classification study.

To support a clinical bridge, a relative bioavailability assessment was conducted by assessing the PK of halobetasol propionate, tazarotene (prodrug), and tazarotenic acid (an active metabolite of tazarotene) following application of the proposed product under maximal use conditions and administration of the listed drugs as per the approved labeling. The study results demonstrated that under maximal use conditions, following once daily application of halobetasol propionate and tazarotene lotion, 0.01%/0.045%, the values of C_{max} and AUC of halobetasol propionate were higher than those following once daily application of one of the listed drugs, Ultravate (halobetasol propionate) Cream, 0.05%; and the values of C_{max} and AUC of the active metabolite of tazarotene, tazarotenic acid, were higher compared to those of the other list drug, Tazorac (tazarotene) Cream, 0.05%. In conclusion, the study results did not support establishment of a clinical bridge; however, the applicant has conducted two Phase 3 trials and a long-term safety study to support the safety of the proposed combination product. Furthermore, the HPA axis suppression rate of the proposed combination product was 15%. The incidence of HPA axis suppression was sufficiently low to allow for further assessment in pediatric subjects, which will be requested as a post-marketing requirement (PMR). In addition, there were no notable systemic safety findings in the maximal use PK study, the Phase 3 trials, and the long-term safety study (see Section 7.3 Review of Safety for further details on safety assessments).

The totality of these evidences suggests that this NDA is acceptable from a Clinical Pharmacology perspective, even though the clinical bridge with the listed drugs was not established. Lack of clinical bridge would affect the ability to rely on the Agency's findings of certain nonclinical safety information. Refer to pharmacology-toxicology review for further details regarding the nonclinical deficiencies identified for this NDA submission.

There is an agreed initial pediatric study plan (iPSP) dated 6/16/2016. The iPSP included a deferral of a PK/HPA axis suppression study in pediatric population (b) (4) to 16 years 11 months. This trial will be included as a PREA PMR.

6.1.1. Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds NDA 209354 acceptable, provided that the applicant adequately addresses the nonclinical deficiencies identified above in Section 5 Nonclinical Pharmacology/Toxicology.

6.1.2. Post-Marketing Requirements

Conduct a maximal use PK/HPA axis suppression study in pediatric subjects (b) (4) to less than 17 years of age with moderate to severe plaque psoriasis.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

6.2.1.1. Bioavailability and HPA axis suppression

The applicant conducted a study (V01-118A-501) in subjects with moderate to severe plaque psoriasis affecting at least 20% body surface area (BSA) to compare the systemic exposure of the proposed combination product of halobetasol propionate and tazarotene lotion, 0.01%/0.045% to the listed drugs. In addition, the applicant compared the HPA axis suppression potential of the combination product to the listed drug, Ultravate (halobetasol propionate) Cream, 0.05%. As stated in the approved labelling of the listed drug Ultravate Cream, the applicant also proposed that the total dosage should not exceed 50 grams per week for the proposed product. The applicant did not propose a limitation for the treatment duration for the proposed drug product, whereas the approved labeling of the listed drug Ultravate Cream states that treatment beyond two consecutive weeks is not recommended and suggests that reassessment of diagnosis may be necessary if no improvement is seen within 2 weeks of treatment. The approved labelling of the other listed drug, Tazorac cream, 0.05%, does not have treatment duration limitation.

Following topical application, tazarotene undergoes esterase hydrolysis to form its active metabolite, tazarotenic acid, which has higher systemic exposure than the parent drug. The median amount of halobetasol propionate and tazarotene lotion, 0.01%/0.045% applied once daily during the 8-week treatment period was approximately 8.9 grams. Plasma PK samples were collected on Days 1, 14, and 28 at pre-dose, and at 1, 2, 4, 8, 12, and 24 hours post-dose. The results showed that many of the PK samples had concentrations below the limit of quantification (BLQ) for halobetasol propionate and tazarotene (50 pg/mL and 5 pg/mL, respectively); however, tazarotenic acid was measurable (> 5 pg/mL) in most PK samples and in all the subjects. For halobetasol propionate, mean (SD) C_{max} and AUC_{last} values were 87.2 (96.6) pg/mL and 1145 (1501) pg*hr/mL on Day 14, respectively; mean (SD) C_{max} and AUC_{last} values were 101.9 (135.4) pg/mL and 1300 (1959) pg*hr/mL on Day 28,

respectively. For tazarotenic acid, mean (SD) C_{max} and AUC_{last} values were 466.1 (390.0) pg/mL and 8513 (7096) pg*hr/mL, respectively, on Day 14; mean (SD) C_{max} and AUC_{last} values were 523.4 (523.3) pg/mL and 9954 (10091) pg*hr/mL on Day 28, respectively. These results indicated that by Day 28, the systemic exposure of the proposed product was at or near steady state.

To assess the relative bioavailability, the study evaluated the systemic exposure of the listed drugs by including a 2-week Ultravate (halobetasol propionate) Cream, 0.05% once daily treatment group and a 4-week Tazorac (tazarotene) Cream, 0.05% once daily treatment group. The baseline disease severity and % BSA involved to be treated of the study subjects among different treatment groups were similar. The median amount used per once daily application was approximately 8.1 grams, and 8.0 grams, in the treatment groups of Ultravate (halobetasol propionate) Cream, 0.05% and Tazorac (tazarotene) Cream, 0.05%, respectively. These values were similar to the median once daily amount used per application of 8.2 grams in the treatment group of halobetasol propionate and tazarotene lotion, 0.01%/0.045%.

The relative bioavailability results showed that under maximal use conditions, following once daily application, the systemic exposure (both C_{max} and AUC) of halobetasol propionate in the treatment group of halobetasol propionate and tazarotene lotion, 0.01%/0.045 was higher than that in the treatment group of the listed drug Ultravate (halobetasol propionate) Cream, 0.05%; furthermore, the systemic exposure (both C_{max} and AUC) of the active metabolite of tazarotene, tazarotenic acid, was higher when compared to the list drug Tazorac (tazarotene) Cream, 0.05%. These results indicated that the clinical bridge between the proposed new combination product and the listed drugs was not established. In addition, the applicant assessed the HPA axis suppression potential of the proposed drug product and Ultravate Cream under maximal use conditions. The results indicated that the rate of HPA axis suppression for the proposed drug product was 15% (3 out of 20 subjects) on Day 29 but no subjects (0%) had suppression on Day 57 during the 8-week treatment period. In contrast, in the Ultravate (halobetasol propionate) Cream, 0.05% treatment group, 5% (1 of 20) subjects had HPA axis suppression on Day 15. The incidence of HPA axis suppression in the proposed combination product treatment group was sufficiently low to allow for further assessment in pediatric subjects, which will be requested as a post-marketing requirement (PMR).

In conclusion, the relative bioavailability assessment showed that the bioavailability of the combination product was higher than the listed drugs. This indicates that the clinical bridge is not established. Despite higher systemic exposure of the new combination product compared to the listed drugs, study results of the two Phase 3 clinical trials and a long-term safety study did not raise systemic safety concerns (see Section 7.3 Review of Safety for further details). Therefore, from a Clinical Pharmacology standpoint, this application is acceptable. However, the failure of establishing a clinical bridge to the listed drugs would impact the applicant's ability to rely on the Agency's findings of safety (i.e. nonclinical safety data) from the listed drugs. See pharmacology-toxicology review for further details regarding the nonclinical deficiencies identified for this NDA.

6.2.1.2. Potency classification

The potency classification study was a single point vasoconstrictor (VCA) study using both visual assessment (primary endpoint) and chromameter assessment (secondary endpoint). The results of visual assessment were inconclusive in that the proposed drug was not statistically different from Ultravate Cream, 0.05% (Class 1, supper high), Fluocinonide Cream, 0.05% (Class 2, potent), and Betamethasone dipropionate cream, 0.05% (Class 3, upper mid-strength). The chromameter results indicated that the potency of the proposed product is upper mid-strength to high. Whether a VCA study should be conducted as a post-marketing commitment to draw a definitive conclusion of the potency for the proposed drug will be decided at the resubmission.

6.2.1.3. Formulation

The applicant stated that all 11 clinical studies conducted in the development program used the final to-be marketed halobetasol propionate and tazarotene lotion, 0.01%/0.045% formulation, including the maximal use PK/HPA axis suppression trial, two Phase 3 safety and efficacy studies, one long-term safety study, the corticosteroid potency classification study, and dermal safety studies.

6.2.1.4. QT

A thorough QT/QTc (TQT) study waiver request was submitted in the NDA and reviewed by the QT Interdisciplinary Review Team. It was determined that a TQT study was not required for halobetasol propionate and tazarotene lotion, 0.01%/0.045% (for more details, refer to the review by Dr. Dhananjay D. Marathe dated 02/15/2018 in DARRTS).

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The applicant has proposed a dosing regimen of applying a thin layer of halobetasol propionate and tazarotene Lotion, 0.01%/0.045% to the affected area once daily. This regimen is supported by efficacy data from two Phase 3 trials (V01-118A-301 and V01-118A-302). Refer to Clinical and Statistics reviews for efficacy findings.

Therapeutic Individualization

No studies were conducted for assessment of the effects of various intrinsic or extrinsic factors on the safety or efficacy of the proposed topical drug.

Outstanding Issues

The relative bioavailability assessment showed that the bioavailability of the new combination product of halobetasol propionate and tazarotene lotion, 0.01%/0.045% was higher than the listed drugs (individual monads). This indicates that the clinical bridge was not established. The applicant has provided clinical safety data to support the safety of the higher systemic exposure with the combination product; however, the

non-establishment of the clinical bridge would impact the applicant's ability to provide animal toxicity data from the listed drugs. From a Clinical Pharmacology standpoint, this application is acceptable as the applicant has provided safety data for their product from the two Phase 3 trials and long term safety study.

Summary of Labeling Recommendations

The labeling will not be addressed in the current review cycle. The labeling for this drug product will be addressed when the NDA is resubmitted to address the nonclinical deficiencies identified above.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

A summary of PK, HPA axis suppression potential, and potency of halobetasol propionate and tazarotene Lotion, 0.01%/0.045% is provided in the table below.

Pharmacokinetics	
Drug exposure under maximal use conditions	In the maximal use study V01-118A-501, systemic exposure of halobetasol propionate and tazarotene Lotion, 0.01%/0.045% was characterized in adult subjects with moderate to severe plaque psoriasis affecting at least 20% BSA following once daily application to the affected area for 8 weeks. Many of the PK samples collected on Days 14 and 28 had concentrations below the lower limit of quantification (LLOQ) for halobetasol propionate and tazarotene (50 pg/mL and 5 pg/mL, respectively); however, tazarotenic acid was measurable (>5 pg/mL) in most the PK samples and in all the subjects. For halobetasol propionate, mean (SD) C_{max} and AUC_{last} values were 87.2 (96.6) pg/mL and 1145 (1501) pg*hr/mL on Day 14, respectively; mean (SD) C_{max} and AUC_{last} values were 101.9 (135.4) pg/mL and 1300 (1959) pg*hr/mL on Day 28, respectively. For tazarotenic acid, mean (SD) C_{max} and AUC_{last} values were 466.1 (390.0) pg/mL and 8513 (7096) pg*hr/mL, respectively, on Day 14; mean (SD) C_{max} and AUC_{last} values were 523.4 (523.3) pg/mL and 9954 (10091) pg*hr/mL on Day 28, respectively. These results indicated that by Day 28, the systemic exposure of the proposed product was at or near steady state.
Pharmacodynamics	
HPA axis suppression	In the maximal use study V01-118A-501, cosyntropin stimulation test was performed at screening, and on Days 29 and 57 (24 hours since the last dose administration on Day 56) to evaluate the HPA axis suppression potential of halobetasol propionate and tazarotene Lotion, 0.01%/0.045% during the 8-week treatment

	period. The results demonstrated that 15% (3 out of 20) had abnormal response on Day 29 and no subjects had abnormal response on Day 57.
Potency classification	The potency of the proposed product in the to-be-marketed formulation was determined to be between upper mid-strength to high using chromameter assessments in a single-point vasoconstriction assessment study (V01-118A-101) that compared the proposed product to four currently marketed topical corticosteroid formulations of known potency and a vehicle lotion formulation.
Bioanalytical methods	
PK assays and cortisol assay	The results of cortisol assay validation and PK assay validation and incurred sample reanalysis are acceptable. Sample storage time was within the documented long-term matrix stability range.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Not applicable. The pivotal Clinical Pharmacology study for topical corticosteroids included the maximal use PK and HPA axis suppression study which provided information to support the systemic safety of the topical product and not efficacy.

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

Yes, provided that the applicant adequately addresses the nonclinical deficiencies identified above in Section 5 Nonclinical Pharmacology/Toxicology. See Section 7 for the evaluation of the effectiveness and safety.

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

The applicant did not assess intrinsic factors in the current NDA. The applicant requested a deferral of pediatric studies for subjects (b) (4) o 16 years 11 months of age. There is an agreed iPSP dated 6/16/2016. As per th agreed iPSP, the applicant will conduct a PK/HPA axis suppression trial in pediatric subjects (b) (4) to 16 years 11 months of age with moderate to severe plaque psoriasis. This trial will be included as a Pediatric Research Equity Act (PREA) post marketing requirement. A waiver has been granted for studies in pediatric subjects (b) (4) years of age in the agreed iPSP.

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

Food-drug or drug-drug interaction studies were not performed for this topical product. No drug interactions are listed in the labels for the approved listed products for Ultravate

Cream or Tazorac Cream (Ultravate Cream and Ointment [US Prescribing Information] 2012, Tazorac Cream [US Prescribing Information] 2013). No inhibition or induction of cytochrome P450s (CYP) enzymes has been reported for halobetasol propionate. Tazarotene is converted to tazarotenic acid by esterases following topical application. Tazarotenic acid is the major circulating metabolite in blood. Tazarotenic acid is oxidized to an inactive sulfoxide metabolite by CYP2C8, flavin-containing mono-oxygenase enzyme 1 (FMO1), and FMO3 [*Attar M et al. Drug Metab Dispos. 2003 Apr;31(4):476-81*]. Following once daily application of halobetasol propionate and tazarotene lotion, 0.01%/0.045% under maximal use conditions, the highest mean observed C_{max} of halobetasol propionate, tazarotene, and tazarotenic acid were 101.9 pg/mL (on Day 28), 44.7 pg/mL (on Day 1), and 523.4 pg/mL (on Day 28). These values were within 2-fold of the highest observed mean C_{max} of the corresponding listed drug (Ultravate Cream, 0.05% for halobetasol propionate and Tazorac Cream, 0.05% for tazarotene, respectively) in the same study. Tazarotenic acid is a weak inhibitor of CYP enzymes in vitro with a $K_i \geq 4800$ ng/mL which is several thousand times higher than the observed highest mean observed C_{max} of tazarotenic acid (i.e. 523.4 pg/mL) in the maximal use PK trial. Taking all the information into account, the drug interaction potential for the proposed drug as a perpetrator is expected to be low; the interaction potential for the proposed drug as a victim drug is unknown. This issue can be handled by labeling and would not need further investigation as a PMC/PMR as both the moieties are not new molecular entities and have been marketed for more than 20 years.

What is the systemic bioavailability of halobetasol propionate and tazarotene lotion, 0.01%/0.045% under maximal use conditions and what is the relative bioavailability compared to Ultravate (halobetasol propionate) Cream, 0.05% and Tazorac (tazarotene) Cream, 0.05%?

The systemic exposure of halobetasol propionate and tazarotene lotion, 0.01%/0.045% was evaluated and compared to the listed drugs: Ultravate (halobetasol propionate) Cream, 0.05% and Tazorac (tazarotene) Cream, 0.05% under maximal use conditions in Trial V01-118A-501. This was a multicenter, open-label, randomized, parallel group study. Adult subjects with moderate to severe plaque psoriasis with ≥20% treatable body surface area (BSA) involvement were randomized at 1:1:1:1 ratio to receive an 8-week treatment of halobetasol propionate and tazarotene lotion, 0.01%/0.045%, an 8-week treatment of halobetasol propionate lotion, 0.01% (another formulation that this sponsor is developing), a 2-week treatment of Ultravate (halobetasol propionate) Cream, 0.05%, or a 4-week treatment of Tazorac (tazarotene) Cream, 0.05%. These investigational products were applied once daily to all affected area on the body excluding face, scalp, axillae, and intertriginous areas. The results of the treatment of halobetasol propionate lotion, 0.01% will not be discussed in this review as this formulation was not submitted for review under this NDA.

The median amount used per application was approximately 8.2 grams, 8.1 grams, and 8.0 grams, for halobetasol propionate and tazarotene lotion, 0.01%/0.045%, Ultravate (halobetasol propionate) Cream, 0.05%, and Tazorac (tazarotene) Cream, 0.05%,

respectively. Plasma PK samples were collected on Days 1, 14, and 28 at pre-dose, and at 1, 2, 4, 8, 12, and 24 hours post-dose.

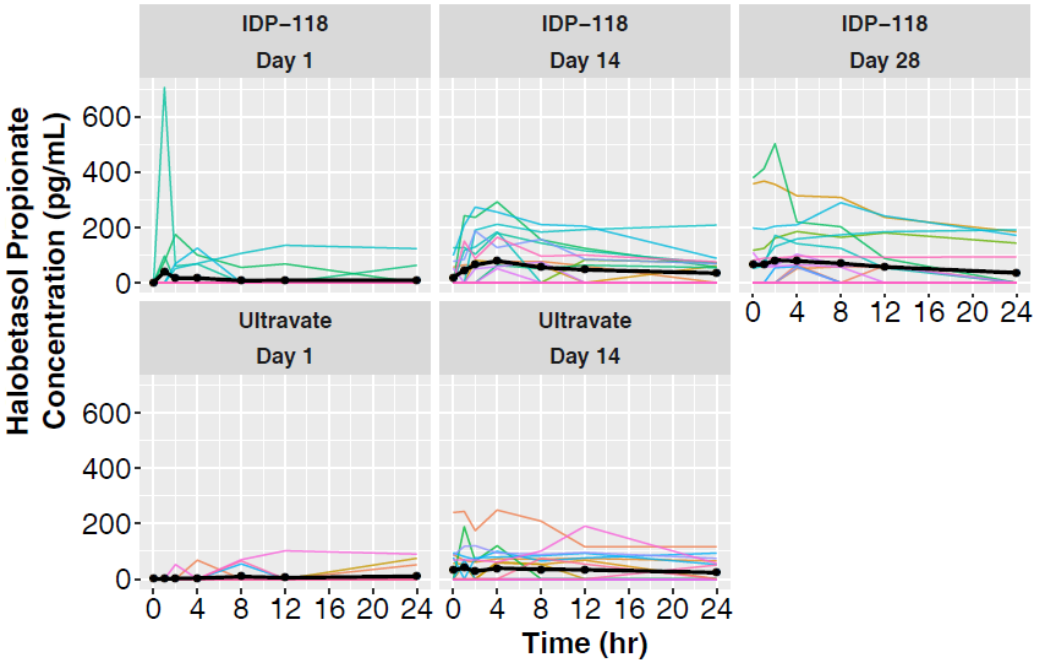
Pharmacokinetics of halobetasol propionate: The majority of samples taken on Day 1 had no measurable plasma concentration of halobetasol propionate (< 50 pg/mL). On Day 14, the number of subjects who had measurable concentrations of halobetasol propionate doubled in both treatment groups [13/22 and 12/23 in halobetasol propionate and tazarotene lotion, 0.01%/0.045% treatment group and Ultravate (halobetasol propionate) Cream, 0.05%, respectively]; the mean values of both C_{max} and AUC were higher in the halobetasol propionate and tazarotene lotion, 0.01%/0.045% treatment group when compared to the treatment group of the listed drug Ultravate Cream (halobetasol propionate), 0.05% (Table 5). The mean C_{max} and AUC_{last} of halobetasol propionate was slightly higher on Day 28 than on Day 14 in the halobetasol propionate and tazarotene lotion, 0.01%/0.045% treatment group, indicating that exposure of halobetasol propionate was at or close to the steady state by Day 28. The individual PK profiles of halobetasol propionate are shown in Figure 1.

Table 5: Mean (SD) PK parameters of halobetasol propionate following once daily administration in Trial V01-118A-501.

	Halobetasol propionate PK parameters	Halobetasol propionate and tazarotene lotion, 0.01%/0.045% (N = 22)	Ultravate Cream, 0.05% (N = 23)	GMR (90% CI) (%)[1]
Day 1	C_{max} (pg/mL)	56.2 (154.5)	15.8 (31.7)	-
	AUC_{last} (pg*hr/mL)	233 (592)	130 (384)	-
Day 14	C_{max} (pg/mL)	87.2 (96.6)	58.8 (72.8)	126.85 (86.77, 185.43)
	AUC_{last} (pg*hr/mL)	1145 (1501)	713 (1104)	156.52 (65.20, 375.73)
Day 28	C_{max} (pg/mL)	101.9 (135.4)	-	-
	AUC_{last} (pg*hr/mL)	1300 (1959)	-	-

Source: reviewer's analysis using data provided by the applicant.
(1) GMR (90% CI) (%): geometric mean ratio % (90% confidence interval) of halobetasol propionate and tazarotene lotion, 0.01%/0.045% to the listed drug, Ultravate Cream, 0.05%; the values were calculated using non-zero values of the corresponding parameter.
AUC_{last}: area under the plasma concentration curve from time zero to the time of the last measurable plasma concentration.

Figure 1: Individual halobetasol propionate plasma concentration-time profiles (colored lines) with mean profiles (black lines) in Trial V01-118A-501.



Source: Reviewer's Analysis.
The proposed product halobetasol propionate and tazarotene lotion, 0.01%/0.045% is labeled as IDP-118, the name of the product during development; the listed drug, Ultravate (halobetasol propionate) Cream, 0.05% is labeled as Ultravate. The black dots represent the arithmetic mean of the concentrations at the corresponding nominal time.

Pharmacokinetics of tazarotene and tazarotenic acid: Approximately a half of the total samples had no measurable plasma concentration of the parent pro-drug, *tazarotene* (< 5 pg/mL) while the active metabolite, tazarotenic acid, was measurable (≥ 5 pg/mL) in all subjects. Therefore, the bioavailability analysis will focus on the tazarotenic acid concentrations.

PK parameters of tazarotenic acid are shown in Table 6. For both treatment groups, accumulation of tazarotenic acid was observed when comparing C_{max} and AUC_{last} values on Day 14 to Day 1; the mean values of C_{max} and AUC_{last} values were slightly higher on Day 28, respectively, when compared to those on Day 14, indicating that exposure of tazarotenic acid was at or close to steady state by Day 28. On both Days 14 and 28, the values of C_{max} and AUC_{last} of tazarotenic acid in the treatment group of halobetasol propionate and tazarotene lotion, 0.01%/0.045% were higher than those in the treatment group of the listed drug, Tazorac Cream, 0.05%. The highest point of estimate values for the geometric ratio of C_{max} and AUC_{last} were 182.32% and 180.95%, respectively (on Day 14). Individual PK profiles of tazarotenic acid are shown in Figure 2.

For the prodrug, tazarotene, in the halobetasol propionate and tazarotene lotion, 0.01%/0.045% group, 55% (12/22), 82% (18/22), and 82% (18/22) of the subjects had measurable concentrations on Days 1, 14, and 28, respectively, during a 24 hr period

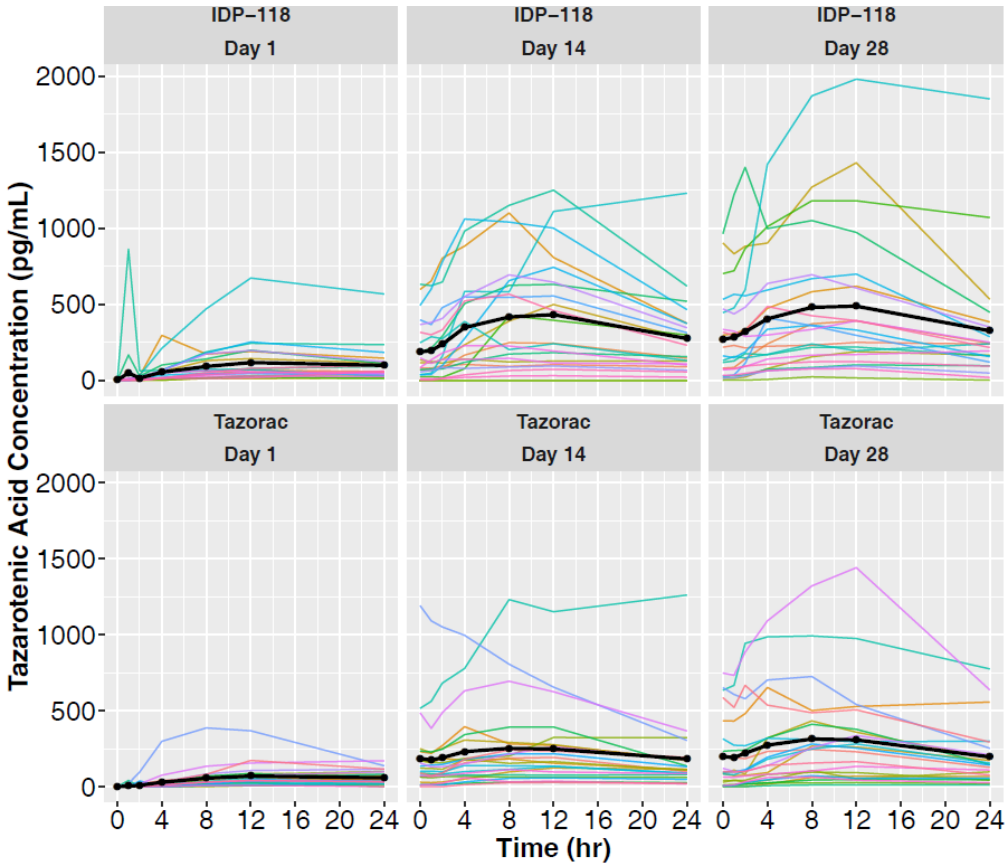
after dose administration; in the Tazorac (tazarotene) Cream, 0.05% group, 46% (11/24), 48% (11/23), and 61% (14/23) subjects had measurable concentrations. The mean (SD) values of C_{max} and AUC_{last} of tazarotene on Days 14 and 28 are shown in Table 7. The exposure of tazarotene was higher in the halobetasol propionate and tazarotene lotion, 0.01%/0.045% group than in the Tazorac Cream, 0.05% group on Day 14 but similar on Day 28. Individual PK profiles of tazarotene are shown in Figure 3.

Table 6: Mean (SD) PK parameters of tazarotenic acid following once daily administration of the proposed product and Tazorac Cream, 0.05% in Trial V01-118A-501.

	Tazarotenic acid PK parameters	Halobetasol propionate and tazarotene lotion, 0.01%/0.045% (N = 22)	Tazorac Cream, 0.05% (N = 24)	GMR (90% CI) (%)[2]
Day 1	C_{max} (pg/mL)	158.0 (213.8)	77.3 (79.3)	-
	AUC_{last} (pg*hr/mL)	2109 (2523)	1208 (1272)	-
Day 14	C_{max} (pg/mL)	466.1 (390.0)	288.8 (327.5) (N=23)[1]	182.32 (108.57, 306.16)
	AUC_{last} (pg*hr/mL)	8513 (7096)	5331 (5932) (N=23)[1]	180.95 (108.99, 300.43)
Day 28	C_{max} (pg/mL)	523.4 (523.3)	340.3 (351.8) (N=23)[1]	164.27 (92.19, 292.70)
	AUC_{last} (pg*hr/mL)	9954 (10091)	6419 (6842) (N=23)[1]	161.63 (87.35, 299.08)

Source: reviewer's analysis using data provided by the applicant.
(1) Number of subjects with available data
(2) GMR (90% CI) (%): geometric mean ratio % (90% confidence interval) of halobetasol propionate and tazarotene lotion, 0.01%/0.045% to the listed drug, Tazorac Cream, 0.05%
AUC_{last}: area under the plasma concentration curve from time zero to the time of the last measurable plasma concentration

Figure 2: Individual tazarotenic acid plasma concentration-time profiles (colored lines) with mean profiles (black lines) in Trial V01-118A-501.



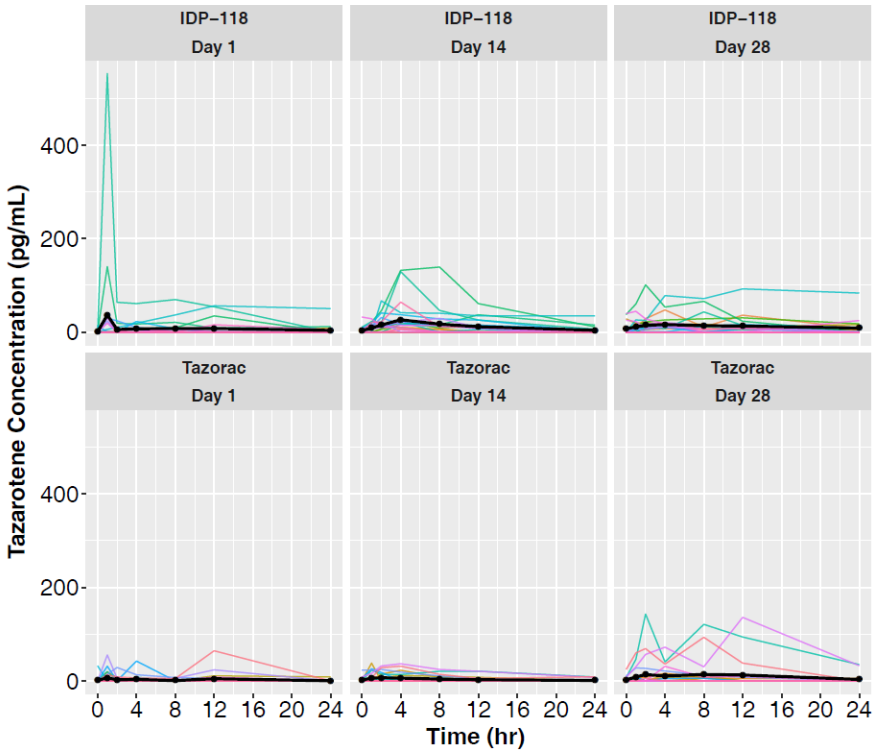
Source: Reviewer's Analysis.
The proposed product halobetasol propionate and tazarotene lotion, 0.01%/0.045% is labeled as IDP-118, the name of the product during development; the listed drug, Tazorac (tazarotene) Cream, 0.05% is labeled as Tazorac. The black dots represent the arithmetic mean of the concentrations at the corresponding nominal time.

Table 7: Mean (SD) PK parameters of tazarotene following once daily administration of the proposed product and Tazorac Cream, 0.05% in Trial V01-118A-501.

	#Tazarotene PK parameters	Halobetasol propionate and tazarotene lotion, 0.01%/0.045% (N = 22)	Tazorac Cream, 0.05% (N = 23)	#GMR (90% CI) (%)
Day 1	C_{max} (pg/mL)	44.7 (120.7) (N=21)[&]	11.7 (18.8)	-
	AUC_{last} (pg*hr/mL)	157 (331) (N=21)[&]	33 (59)	-
Day 14	C_{max} (pg/mL)	31.8 (38.1)	10.2 (13.5)	148.40 (84.97, 259.17)
	AUC_{last} (pg*hr/mL)	267 (392)	72 (136)	251.94 (89.73, 707.39)
Day 28	C_{max} (pg/mL)	24.6 (27.3)	22.3 (42.0)	122.32 (67.28, 222.36)
	AUC_{last} (pg*hr/mL)	273 (403)	218 (527)	314.28 (107.39, 919.76)

[&]Number of subjects with available data
#GMR (90% CI) (%): geometric mean ratio % (90% confidence interval) of halobetasol propionate and tazarotene lotion, 0.01%/0.045% to the listed drug, Tazorac Cream, 0.05%
AUC_{last}: area under the plasma concentration curve from time zero to the time of the last measurable plasma concentration

Figure 3: Individual tazarotene plasma concentration-time profiles (colored lines) with mean profiles (black lines) in Trial V01-118A-501.



Source: Reviewer's Analysis.
The proposed product halobetasol propionate and tazarotene lotion, 0.01%/0.045% is labeled as IDP-118, the name of the product during development; the listed drug, Tazorac (tazarotene) Cream, 0.05% is labeled as Tazorac. The black dots represent the arithmetic mean of the concentrations at the corresponding nominal time.

What is the effect of halobetasol propionate and tazarotene lotion, 0.01%/0.045% on suppressing the hypothalamic pituitary adrenal (HPA) axis?

In Trial V01-118A-501 described above, subjects were tested for HPA axis function using the adrenocorticotropin (ACTH) stimulation test (0.25 mg cosyntropin injected intravenously or intramuscularly) at the Screening Visit (2 weeks prior to Baseline Visit), at the end of treatment in the Ultravate Cream group on Day 15 (last dose administered on Day 14), and on Days 29 and 57 (last dose administered on Day 56), in the halobetasol propionate and tazarotene lotion, 0.01%/0.045% group.

All subjects were in the normal range for adrenal function, defined as a cortisol level of > 18 µg/dL, after stimulation with Cosyntropin at the Screening Visit. In the halobetasol propionate and tazarotene lotion, 0.01%/0.045% group, 15% (3 of 20) and 0% (0 of 20) subjects had HPA axis suppression on Days 29 and 57, respectively. In the Ultravate Cream group, 5% (1 of 20) subjects had HPA axis suppression on Day 15; this suppressed subject returned to normal on Day 44 at a follow-up visit.

What is the potency classification for halobetasol propionate and tazarotene lotion, 0.01%/0.045%?

The corticosteroid potency of halobetasol propionate and tazarotene lotion, 0.01%/0.045% was compared to the listed drug, Ultravate (halobetasol propionate) Cream, 0.05%, and other corticosteroids of known potency using a single point vasoconstrictor assay (Trial V01-118A-101). The chromameter assessment results suggested that halobetasol propionate and tazarotene lotion, 0.01%/0.045% was an upper mid-strength to high potent corticosteroid (Table 8).

Table 8: Potency ranking results based on chromameter assessment score from study V01-118A-101.

Formulations		N	Mean and Standard Deviation	REGWQ Grouping*
Product 3	Ultravate® (halobetasol propionate) Cream, 0.05%; RANBAXY Super potent-Class 1 Lot No: 94614; Expiration Date: 06/17	30	2.2743 ± 0.9760	A
Product 5	BETAMETHASONE DIPROPIONATE CREAM USP, 0.05%; Upper mid-strength potent-Class 3 E. FOUGERA & CO., A division of Fougera Pharmaceuticals Inc. Lot No: FU6538; Expiration Date: NOV 18	30	1.8147 ± 0.9760	B
Product 1	IDP-118 (halobetasol propionate 0.01% / tazarotene 0.045%) Lotion; Dow Pharmaceutical Sciences, a division of Valeant Pharmaceuticals North America LLC Lot No: 8083850; Manufacture Date: 03/10/15	30	1.5275 ± 0.7537	B C
Product 4	Fluocinonide Cream USP, 0.05%; (high) potent-Class 2 Mfd. by: Taro Pharmaceuticals Inc.; Dist. by: Taro Pharmaceuticals U.S.A., Inc. Lot No: K510921749; Expiration Date: APR 2017	30	1.3052 ± 0.9494	C D
Product 6	TRIAMCINOLONE ACETONIDE CREAM USP, 0.1%; Lower mid-strength potent-Class 5 E FOUGERA & CO., A division of Fougera Pharmaceuticals Inc. Lot No: FR1170; Expiration Date: OCT 18	30	0.9092 ± 0.8186	D
Product 7	Vehicle Lotion; Dow Pharmaceutical Sciences, a division of Valeant Pharmaceuticals North America LLC Lot No: 8083428; Manufacture Date: 02/20/15	30	0.0263 ± 0.5661	E
Untreated	No Treatment	30	0.0013 ± 0.0027	E

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

Source: adapted from Table 11.4.1.3 of study report; red colored text was added by the reviewer. Halobetasol propionate and tazarotene lotion, 0.01%/0.045% is denoted as Product 1.

7 Statistical and Clinical Evaluation

7.1. Sources of Clinical Data and Review Strategy

7.1.1. Table of Clinical Studies

Table 9: Listing of Clinical Trials Relevant to NDA 209354

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
V01-118A-301	Phase 3, multicenter, double-blind, randomized, vehicle-controlled clinical trial	DUOBRII ((HP 0.01%, Taz 0.045%) Lotion or DUOBRII Vehicle Lotion topically, once daily for 8 weeks	Primary efficacy: Percentage of subjects who achieved success defined as at least a 2-grade improvement from baseline in IGA score and an IGA score of 0 or 1 at Week 8	8 Weeks / 12 Weeks	planned: N=210 140:70 Analyzed: N=203 135:68	Male and Female subjects age ≥ 18 years with moderate or severe plaque psoriasis defined as IGA= 3 or 4 3% ≤ BSA ≤ 12%	16 sites in the U.S.
V01-118A-302	Phase 3, multicenter, double-blind, randomized, vehicle-controlled clinical trial	DUOBRII ((HP 0.01%, Taz 0.045%) Lotion or DUOBRII Vehicle Lotion topically, once daily for 8 weeks	Primary efficacy: Percentage of subjects who achieved success defined as at least a 2-grade improvement from baseline in IGA score and an IGA score of 0 or 1 at Week 8	8 Weeks / 12 Weeks	planned: N=210 140:70 Analyzed: N=215 141:74	adult subjects with moderate to severe plaque psoriasis (IGA = 3 or 4) 3% ≤ BSA ≤ 12%	16 sites in the U.S.

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
V01-118A-201	Phase 2, multicenter, double-blind, randomized, vehicle-controlled clinical trial	•DUOBRII (HP 0.01%, Taz 0.045%) Lotion •DUOBRII Monad (HP 0.01%) Lotion •DUOBRII Monad (Taz 0.045%) Lotion •DUOBRII Vehicle Lotion applied topically, once daily for 8 weeks.	•Efficacy: Percentage of subjects with treatment success, defined as at least a 2-grade improvement from Baseline in IGA score and an IGA score of 0 or 1 at Week 8;	8 Weeks	Planned: N=210 in a ratio of 2:2:2:1 Analyzed: N=212 as 59:63:59:31	adult subjects with moderate to severe plaque psoriasis (IGA = 3 or 4) 3% ≤ BSA ≤ 12%	18 sites in the U.S.
V01-118A-202	Phase 2, multicenter, double-blind, randomized, vehicle-controlled clinical trial: Clinical bridge to Tazorac cream, 0.05%	•DUOBRII (HP 0.01%, Taz 0.045%) Lotion •Tazorac Cream, 0.05% •Vehicle Lotion •Vehicle Cream applied topically, once daily for 12 weeks.	•Efficacy: Percentage of subjects with treatment success, defined as at least a 2-grade improvement from baseline in IGA score and an IGA score of 0 or 1 at Weeks 2, 4, 8, and 12 (Week 12 is the primary time point of analysis)	12 Weeks	Planned: N=150 in a ratio of 4:4:1:1 Analyzed: N=152 62:58:15:17	adult subjects with moderate to severe plaque psoriasis (IGA = 3 or 4) 3% ≤ BSA ≤ 12%	15 sites in the U.S.
V01-118A-203	Phase 2, multicenter, double-blind, randomized, vehicle-	•DUOBRII (HP 0.01%, Taz 0.045%) Lotion •Ultravate (HP)	•Efficacy: Percentage of subjects with treatment success, defined as at least a 2-grade improvement	2 Weeks	Planned: N=150 in a ratio of 4:4:1:1	adult subjects with moderate to severe plaque psoriasis (IGA	15 sites in the U.S.

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
	controlled clinical trial: Clinical bridge to halobetasol propionate cream (HP), 0.05%	Cream, 0.05% •Vehicle Lotion •Vehicle Cream Applied topically, once daily for 2 weeks.	from Baseline in IGA score and an IGA score of 0 or 1 at Week 2		Analyzed: N=154 61:63:16:14	= 3 or 4) 3% ≤ BSA ≤ 12%	
Studies to Support Safety							
V01-118A-303	A Phase 3, multicenter, open-label study to evaluate the long term safety of IDP-118 Lotion in the treatment of Plaque Psoriasis	•DUOBRII ((HP 0.01%, Taz 0.045%) Lotion, applied topically, once daily for 8 weeks, and then as needed up to 1 year Reference Therapy: •None	•Efficacy: Percentage of subjects with an IGA = 0 or 1 , or ≥ 2-point decrease in IGA from baseline at Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52 •Safety: AEs, clinical laboratory (chemistry and hematology) abbreviated physical examination local skin reactions assessed at baseline and subsequent study visits	8 weeks for all subjects intermittent treatment up to 1 year	Planned: N = 500 Analyzed: N = 555 N = 391 completed 6 months N = 138 completed 1 year	adult subjects with moderate to severe plaque psoriasis (IGA = 3 or 4) 3% ≤ BSA ≤ 12%	45 sites in the U.S.
V01-118A-501	Phase 1b open-label, randomized study to evaluate the absorption and systemic PK and HPA axis	•DUOBRII Lotion (HP 0.01%, Taz 0.045%) QD x 8 Weeks •IDP-122 Lotion (HP 0.01%) QD x 8 Weeks •Ultravate Cream	•PK: Plasma concentrations HP, Taz, and tazarotenic acid •PD/Safety: Percentage of subjects manifesting HPA axis suppression	2 Weeks, 4 Weeks, 8 Weeks	Planned: N=90 in a ratio of 1:1:1:1 Analyzed: N=94 23:24:22:25	adult subjects with moderate to severe plaque psoriasis (IGA = 3 or 4) BSA ≥ 20%	12 sites in the U.S.

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
	suppression potential of topically applied IDP-118 Lotion and HP monad Lotion: (MuST study)	(HP 0.05%) QD x 2 Weeks •Tazorac Cream (Taz 0.05%) QD x 4 Weeks	defined as a cortisol level of ≤18 µg/dL measured at 30 minutes after stimulation with cosyntropin •safety: AEs, local skin reactions, physical examinations, vital signs, and safety laboratory tests •Efficacy: IGA scores				
DPSI-IDP-118-P2-01	Phase 2 Dose Ranging, Evaluator-blinded study of the safety, Including Adrenal Suppression of topical IDP-118: Proof of concept	•Low-dose DUOBRII Lotion (HP 0.01%, Taz 0.045%) QD •High-dose DUOBRII Lotion (HP 0.025%, Taz 0.045%) QD •Comparator 1: Ultravate Cream (HP, 0.05%) QD •Comparator 2: Tazorac Cream (Taz 0.1%) QD Cohorts 1 and 3: 6 W Cohorts 2, 4, 6:8 W Cohort 5: 2 W	•Efficacy: Percentage of subjects with treatment success: (Investigator's Global Evaluation (IGE) score or Investigator's Assessment of the Target Lesion (IATL) of 0 (clear) or 1 (almost clear) and >=2 grade improvement at each study visit •Safety: AEs, local skin Reactions, clinical laboratory tests, and HPA axis suppression results •PK: Plasma drug	2 weeks in cohort 5 6 weeks in cohorts 1,3 8 weeks in cohorts 2,4,6	Planned: N = 50 Analyzed: N = 51 16 subjects in cohorts 1,3,6 randomized at ratio of 6:5:5 35 subjects in cohorts 2,4,5 Randomized at ratio of 13:11:11	adult subjects with moderate to severe plaque psoriasis (IGA = 3 or 4) 10% ≤ BSA ≤ 20%	7 sites in the U.S.

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
			levels				
V01-118A-101	randomized, evaluator-blinded, within-subject, study to determine the Potency of DUOBRII Compared to four topical corticosteroids and a vehicle Lotion: Steroid potency Vasoconstrictor Assay (VCA)	•DUOBRII Lotion (HP 0.01%, Taz 0.045%) •IDP-122 Lotion (HP 0.01%) •Ultravate Cream (HP 0.05%) •betamethasone dipropionate cream 0.05% •fluocinonide cream 0.05% •triamcinolone acetonide cream 0.1% •vehicle lotion •No treatment A single dose applied topically, remained on the skin for 16 hours	•PD: Vasoconstriction, assessed as skin blanching and measured using visual scoring (primary) and a Chromameter (informational) •Safety: AEs	16 hours	N= 30	healthy adult male and female subjects	1 site in the U.S.
V01-118A-102 Cumulative irritancy Patch test	21-Day, randomized, controlled study to evaluate the skin irritation potential of DUOBRII lotion (halobetasol propionate 0.01% and tazarotene	Test Products: •DUOBRII Lotion (HP 0.01%, Taz 0.045%) •IDP-122 Lotion (HP 0.01%) •Vehicle Lotion Reference Therapy: •Tazorac Cream (Taz 0.05%) • Sodium lauryl	safety: Skin irritation, assessed as a mean cumulative irritation score, calculated from the total observed scores for each subject on Days 2 through 22 AEs	21 days	N = 40	healthy subjects	1 site in the U.S.

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
	0.045%) and IDP-122 lotion (halobetasol propionate 0.01%)	sulfate 0.5% aqueous solution •Saline 0.9% semi-occlusive 0.2 mL patches applied once daily for 21 days					
V01-118A-103 RIPT: Repeat Insult Patch Testing	randomized, (within-subject) controlled study to evaluate the sensitizing potential of DUOBRII lotion and IDP-122 lotion	•DUOBRII Lotion (HP 0.01%, Taz 0.045%) •IDP-122 Lotion (HP 0.01%) •Vehicle Lotion •Saline 0.9% Applied topically on the infrascapular area as semi-occlusive 0.2 mL patches, 9 times over 3 weeks (induction phase), no application for 10 to 14-days (rest phase) applied to naïve sites for 48-hour (challenge phase)	•Safety: Sensitization, assessed at 30 minutes and at 24, 48, and 72 hours after patch removal from the challenge phase cumulative irritation scores during the induction phase AEs	3 weeks (induction Phase) followed by 10 to 14-day (rest phase) followed by 48-hour (challenge Phase)	N = 244	healthy subjects	1 site in the U.S.

Source: adapted from Sponsor's Submission, Tabular Listings of All Clinical Studies, Section 2.7.6.1.1

7.1.2. Review Strategy

Data Sources

The applicant provided CSRs and datasets by electronic submission at the following network path: \\CDSESUB1\evsprod\NDA209354\209354.enx

A consultation for review of data fitness was obtained from CDER Office of Computational Sciences (OCS). OCS performed exploratory safety analysis and data fitness analysis for trials -A201, -301, -302, and -303 for this NDA and found the data quality acceptable.

Data and Analysis Quality

In collaboration with the OCS (JumpStart Data Fitness Consult Response dated 11/3/2017), the statistical and clinical teams evaluated the data fitness, whether certain common analyses could be performed, and other data quality metrics including:

- Availability of appropriate variables
- Variables populated by expected data points
- Appropriate use of standard terminology
- Data well described by metadata

In general, the data submitted by the applicant to support the efficacy and safety of DUOBRII lotion for the proposed indication appeared adequate.

7.2. Review of Relevant Individual Trials Used to Support Efficacy

7.2.1. Study Design and Endpoints

The applicant conducted two identically-designed Phase 3 trials (Trials 301 and 302). Both were identically-designed, randomized, multicenter, double-blind, vehicle-controlled, parallel-group trials to investigate the safety and efficacy of DUOBRII (halobetasol propionate and tazarotene) lotion, 0.01%/0.045% for the treatment of moderate to severe plaque psoriasis. For enrollment, subjects should have met the following key inclusion criteria:

- Male or females at least 18 years of age
- Body surface area (BSA) of 3% to 12% (excluding the face, scalp, palms, soles, axillae and intertriginous areas)
- Investigator Global Assessment (IGA) score of 3 or 4 (excluding the face, scalp, palms, soles, axillae and intertriginous areas), see Table 35 in Section 13.3 for details on the IGA scale
- Has a target lesion that meets the following criteria:
    - Measures between 16-100 cm^2 inclusive
    - A score of at least 3 for at least 2 of the 3 different psoriasis signs (erythema, plaque elevation, and scaling); with a sum of the three scores at least eight (8) and cannot have a score of 0 or 1 on any one of the signs, see Table 36 in Section 13.3
    - Target lesions cannot be on excluded areas or areas covering bony prominences (i.e., elbows and knees)

Each trial was designed to enroll and randomize approximately 210 subjects in a 2:1 ratio to either DUOBRII lotion (n=140) or vehicle lotion (n=70). Subjects applied study product to the affected areas (as determined by the investigator at baseline) once daily for 8 weeks. Subjects were scheduled to be evaluated at the following 7 visits: screening (Day -30 to -1), baseline (Day 0), and Weeks 2, 4, 6, 8 (end of treatment [EOT]), and 12 (follow-up).

The protocol-specified primary efficacy endpoint was the proportion of subjects with "treatment success" at Week 8, where treatment success is defined as an IGA score of 0 (clear) or 1 (almost clear) with at least 2-grade improvement from baseline. The IGA was assessed by the evaluator for the overall affected areas with plaque psoriasis. The protocol specified that the face, scalp, palms, soles, axillae, and intertriginous areas were to be excluded in the assessments.

The protocol specified the following as secondary efficacy endpoints:

- Proportion of subjects with treatment success at Week 12 (4 weeks after EOT)
- Proportion of subjects with treatment success at Week 6
- Proportion of subjects with treatment success at Week 4
- Proportion of subjects with treatment success at Week 2

The protocol specified several "tertiary" and "other" efficacy endpoints; however, as these endpoints were not included in the multiplicity testing strategy, the results of these endpoints are considered exploratory and are not included in this review.

7.2.2. Statistical Methodologies

The protocol-specified primary analysis population is the intent-to-treat (ITT) population, defined as all subjects who are randomized and dispensed study drug. The protocol also specified conducting supportive analyses using the per-protocol (PP) population, defined as all subjects in the ITT population who complete the Week 8 visit without any of the following major protocol violations:

- Violated the inclusion/exclusion criteria
- Used an interfering concomitant medication
- Did not attend the Week 8 visit
- Missed more than one post-baseline study visit prior to Week 8
- Have not been compliant with the dosing regimen (i.e., subjects must apply 80-120% of the expected applications of study product during the study)
- Out of visit window at the Week 8 visit by more than ±5 days

The protocols specified that the trials were to be conducted in a manner such that a minimum of 15 subjects will be randomized in each center. Centers that do not enroll a minimum of 15 subjects were specified to be pooled by ordering these centers and combining the smallest with the largest, second smallest with second largest, and so on. After pooling, the centers (pooled and un-pooled) will be termed "analysis centers."

The protocol-specified analysis method for the primary efficacy endpoint (i.e., proportion of subjects with treatment success at Week 8) was the Cochran-Mantel-Haenszel (CMH) test stratified by analysis center.

The protocol-specified analysis method for the secondary efficacy endpoints (all binary) was the CMH test stratified by analysis center. To control the Type I error rate for testing multiple secondary endpoints, the protocol specified analyzing the secondary endpoints using a sequential gatekeeping approach. The secondary endpoints were specified to be analyzed in the order listed in Section 7.2.1 and the testing will stop once a non-statistically significant value is observed (i.e., a p-value > 0.05).

The protocol-specified primary method for handling missing data is the multiple imputation (MI) approach. The protocol specified that missing data will be within each treatment arm independently using the Markov Chain Monte Carlo (MCMC) method. The protocol specified the following two sensitivity analyses for the handling of missing data:

- Impute missing data using the last observation carried forward (LOCF)
- Analyze observed data using a repeated measures logistic regression (i.e., generalized estimate equations [GEE]) with treatment arm, analysis center, and visit (Weeks 2, 4, 6, and 8) as factors in the model

The protocol specified that the consistency of treatment response across analysis centers will be investigated using a logistic regression with treatment, analysis center, and the interaction between treatment and analysis center in the model. If the p-value for the interaction is significant at the 0.10 level, the protocol specified that a sensitivity analysis will be conducted where analysis centers with "extreme" efficacy results will be excluded. Extreme analysis centers will be identified by analyzing all the possible subsets that can be created by excluding one analysis center. Each data subset will be analyzed using the above logistic regression to see if the interaction between treatment and analysis center remains significant at the 0.10 level. If one or more of the subsets result in an interaction p-value greater than or equal to 0.10, then the analysis center excluded that resulted in the largest interaction p-value is deemed to be the extreme analysis center. If all subset interaction p-values are less than 0.10, then the process will continue with all subsets that can be created by excluding two analysis centers. The process of identifying the extreme analysis centers will continue in stepwise manner (excluding one, two, three, etc.) until the p-value of the interaction exceeds 0.10.

The protocols also specified investigating the center-to-center variability prior to pooling. Specifically, the protocol specified:

> "Prior to investigating the treatment effect within the analysis centers, the magnitude of the site main effect will be investigated to determine if the main site-to-site variability is such that it could mask the analysis center effects. Thus, prior to pooling, the percent of subjects with treatment success at Week 8 will be analyzed with a logistic regression with factors of treatment group, site, and the interaction term of treatment group by site. If the analysis is not computationally feasible due to some sites having very few subjects enrolled, the low-enrolling sites will be excluded from the analysis."

7.2.3. Subject Disposition, Demographics and Baseline Disease Characteristics

Trial 301 enrolled and randomized a total of 203 subjects (135 to DUOBRII and 68 to vehicle) from 16 centers in the United States. Trial 302 enrolled and randomized a total of 215 subjects (141 to DUOBRII and 74 to vehicle) from 16 centers in the United States. Table 10 presents the disposition of subjects for Trials 301 and 302. The discontinuation rates were generally similar between the treatment arms within each trial and between each trial.

Table 10: Disposition of Subjects for Trials 301 and 302

	Trial 301		Trial 302	
	DUOBRII (N=135)	Vehicle (N=68)	DUOBRII (N=141)	Vehicle (N=74)
Discontinued	23 (17%)	11 (16%)	21 (15%)	13 (18%)
Adverse Event	6 (4%)	0	5 (4%)	4 (5%)
Subject Request	7 (5%)	7 (10%)	10 (7%)	5 (7%)
Protocol Violation	1 (1%)	0	2 (1%)	0
Lost to Follow-Up	6 (4%)	4 (6%)	3 (2%)	2 (3%)
Worsening Condition	2 (2%)	0	1 (1%)	2 (3%)
Other	1 (1%)	0	0	0

Source: Reviewer's Analysis (same results as Applicant's Analysis); Intent-to-Treat (ITT) population: all randomized subjects.

The demographics and baseline disease characteristics for Trials 301 and 302 are presented in Table 11. The demographics and baseline disease characteristics were generally balanced across the treatment arms within each trial. The age of subjects in Trial 301 was on average slightly lower than subjects in Trial 302. In addition, Trial 301 had a slightly higher proportion of subjects with an IGA score of 4 (severe) at baseline compared to Trial 302.

Table 11: Demographics and Baseline Disease Characteristics for Trials 301 and 302

	Trial 301		Trial 302	
	DUOBRII (N=135)	Vehicle (N=68)	DUOBRII (N=141)	Vehicle (N=74)
Age (years)				
Mean (SD)	48.1 (13.3)	50.0 (13.3)	51.8 (14.8)	51.8 (13.2)
Median	48.0	49.5	54.0	54.0
Range	19 to 80	20 to 83	21 to 82	23 to 78
Categories				
< 65	121 (90%)	60 (88%)	115 (82%)	63 (85%)
≥ 65	14 (10%)	8 (12%)	26 (18%)	11 (15%)
Sex				
Male	89 (66%)	47 (69%)	86 (61%)	50 (68%)
Female	46 (34%)	21 (31%)	55 (39%)	24 (32%)
Race				
White	119 (88%)	63 (93%)	113 (80%)	63 (85%)
Black or African American	9 (7%)	2 (3%)	9 (6%)	7 (9%)
Asian	3 (2%)	2 (3%)	13 (9%)	3 (4%)
Other	4 (3%)	1 (1%)	6 (4%)	1 (1%)
Baseline IGA				
3 – Moderate	112 (83%)	56 (82%)	125 (89%)	63 (85%)
4 – Severe	23 (17%)	12 (18%)	16 (11%)	11 (15%)
% BSA				
Mean (SD)	6.5 (3.0)	5.5 (2.6)	5.4 (2.6)	5.9 (2.5)
Median	6.0	5.0	4.0	5.0
Range	3 to 12	3 to 12	3 to 12	3 to 12

Source: Reviewer's Analysis (same results as Applicant's Analysis); Intent-to-Treat (ITT) population: all randomized subjects.

7.2.4. Results of the Primary Efficacy Endpoint

Table 12 presents the results for the primary efficacy endpoint (i.e., proportion of subjects with treatment success at Week 8) for the ITT and PP populations. For both trials, DUOBRII lotion was statistically superior to vehicle lotion for the primary endpoint at Week 8 (p-values < 0.001). The response rates were higher in Trial 302 compared to Trial 301. While the results for the ITT and PP populations were similar in Trial 301, the results for the PP population were slightly higher compared to the ITT population in Trial 302.

Table 12: Results of the Primary Efficacy Endpoint at Week 8 for Trials 301 and 302

	Trial 301		Trial 302	
	DUOBRII	**Vehicle**	**DUOBRII**	**Vehicle**
ITT(1)	N=135	N=68	N=141	N=74
Treatment Success(2)	35.8%	7.0%	45.3%	12.5%
P-Value(3)	<0.001		<0.001	
PP(4)	N=117	N=55	N=112	N=65
Treatment Success(2)	35.9%	5.5%	50.0%	13.8%
P-Value(3)	<0.001		<0.001	

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

(1) Intent-to-Treat (ITT) population: all randomized subjects. Missing data was imputed using multiple imputation (MI). The values displayed are the averages over the 75 and 105 imputed datasets for Trials 301 and 302, respectively.
(2) Treatment success is defined as an IGA score of 0 or 1 with at least a 2-grade improvement from baseline.
(3) P-value is based on a CMH test stratified by analysis center.
(4) Per-Protocol (PP) population: see Section 7.2.2 for details on the PP population.

For both trials, the primary imputation method was the multiple imputation (MI) approach using the Markov Chain Monte Carlo (MCMC) method to impute the missing data. The protocol specified the following two sensitivity analyses for the handling of missing data: (i) not impute missing data and analyze using a repeated-measures logistic regression (GEE) with treatment, analysis center, and visit (i.e., Weeks 2, 4, 6 and 8) in the model and (ii) impute missing data using the last observation carried forward (LOCF). This reviewer conducted an additional sensitivity analysis where missing data is imputed as failures. Table 13 presents the number of subjects with missing IGA data at Week 8 along with the results for the primary endpoint at Week 8 across the various imputation methods. For both trials, the results were generally similar across the various methods for handling missing data.

Table 13: Results for the Primary Efficacy Endpoint at Week 8 with Different Approaches for Handling Missing Data

	Trial 301			Trial 302		
	DUOBRII (N=135)	Vehicle (N=68)	P-Value	DUOBRII (N=141)	Vehicle (N=74)	P-Value
Subjects with Missing Data	15 (11%)	9 (13%)		21 (15%)	12 (16%)	
MI-MCMC (primary)(1)	35.8%	7.0%	<0.001	45.3%	12.5%	<0.001
Observed Data(2)	32.1%	5.0%	<0.001	45.4%	11.4%	<0.001
LOCF(3)	34.1%	5.9%	<0.001	42.6%	12.2%	<0.001
Failure(4)	32.6%	5.9%	<0.001	41.1%	12.2%	<0.001

Source: Reviewer's Analysis (same results as Applicant's Analysis(1,2,3))
(1) Multiple imputation (MI) where missing data imputed the MCMC method. The values displayed are the averages over the 75 and 105 imputed datasets for Trials 301 and 302, respectively. P-value is based on a CMH test stratified by analysis center.
(2) Missing data is not imputed. P-value based on GEE analysis with treatment, analysis center, and visit (i.e., Weeks 2, 4, 6, and 8) in the model. The rates displayed are based on the GEE model. The observed response rates are 36.7% and 6.8% for Trial 301 and 48.3% and 14.5% for Trial 302.
(3) Last observation carried forward (LOCF). P-value based on a CMH test stratified by analysis center.
(4) Missing data imputed as failures. P-value based on a CMH test stratified by analysis center.

7.2.5. Results of the Secondary Efficacy Endpoints

Table 14 presents the results for the secondary efficacy endpoints in both trials for the ITT population. DUOBRII lotion was statistically superior to vehicle lotion for treatment success at Weeks 4, 6 and 12 in both trials (p-values ≤ 0.008). While DUOBRII lotion was statistically superior to vehicle lotion at Weeks 2 in Trial 302 (p-value = 0.004), it was not statically superior to vehicle lotion in Trial 301 (p-value = 0.098). The results for the PP population (not shown) were similar to those obtained using the ITT population.

Table 14: Results of the Secondary Efficacy Endpoints for Trials 301 and 302 [ITT(1), MI(2)]

	Trial 301		Trial 302	
	DUOBRII (N=135)	Vehicle (N=68)	DUOBRII (N=141)	Vehicle (N=74)
Treatment Success(3) at Week 12(4)	33.3%	8.5%	33.4%	8.8%
P-Value(5)	<0.001		<0.001	
Treatment Success(3) at Week 6	37.8%	6.7%	37.5%	8.2%
P-Value(5)	<0.001		<0.001	
Treatment Success(3) at Week 4	24.9%	9.3%	30.0%	1.4%
P-Value(5)	0.008		<0.001	
Treatment Success (3) at Week 2	9.2%	3.0%	9.8%	0%
P-Value(5)	0.098		0.004	

Source: Reviewer's Analysis (same results as Applicant's Analysis)
(1) Intent-to-Treat (ITT) population: all randomized subjects.
(2) Missing data was imputed using multiple imputation (MI). The values displayed are the averages over the 75 and 105 imputed datasets for Trials 301 and 302, respectively.
(3) Treatment success is defined as an IGA score of 0 or 1with at least a 2-grade improvement from baseline.
(4) Four weeks after end of treatment.
(5) P-value is based on a CMH test stratified by analysis center.

7.2.6. Patient Reported Outcomes (PROs)

The protocols for both trials included the Dermatology Life Quality Index (DLQI). Endpoints based on this PRO were designated as "other" endpoints and not included in the multiplicity testing strategy; therefore, these endpoints are considered exploratory and not included in this review.

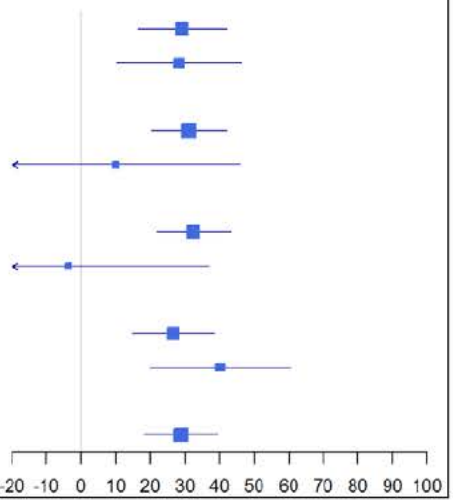
7.2.7. Findings in Special/Subgroup Populations

7.2.7.1. Sex, Age, Race, and Baseline IGA Score

Figure 4 and Figure 5 present the results of the primary efficacy endpoint at Week 8 by sex, age (<65 and ≥65), race (White and Non-White), and baseline IGA score for Trials 301 and 302; respectively. For sex, the treatment effect was similar between males and females in Trial 301; however, in Trial 302, the treatment effect was greater in females compared to males. In both trials, the number of subjects in the ≥ 65 years of age subgroup and Non-White subgroup were relatively small; therefore, it would be difficult to detect differences in efficacy to their complement subgroup (i.e., < 65 years subgroup and White subgroup). For baseline IGA score, the treatment effect was greater for subjects with an IGA score of 4 (severe) compared to those with an IGA score of 3 (moderate) in Trial 301; however, in Trial 302, the treatment effect was greater for subjects with an IGA score of 3 (moderate).

Figure 4: Results of the Primary Efficacy Endpoint at Week 8 by Sex, Age, Race and Baseline IGA Score for Trial 301 [ITT(1), MI(2)]

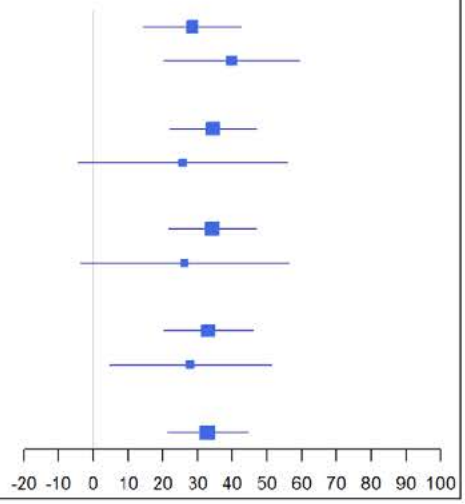
Subgroups (n[D], n[V])	DUOBRII (N=135)	Vehicle (N=68)	Difference	Difference and 95% CI
Sex				
Males (89, 47)	36.3%	7.2%	29.1%	
Females (46, 21)	34.7%	6.4%	28.3%	
Age				
18-64 (121, 60)	37.0%	5.9%	31.1%	
65+ (14, 8)	25.0%	15.0%	10.0%	
Race				
White (119, 63)	38.4%	5.9%	32.5%	
Non-White (16, 5)	16.5%	20.5%	-4.0%	
Baseline IGA				
3 - Moderate (112, 56)	34.9%	8.5%	26.4%	
4 - Severe (23, 12)	40.1%	0%	40.1%	
Overall	35.8%	7.0%	28.8%	



Source: Reviewer's Analysis
(1) Intent-to-Treat (ITT) population: all randomized subjects.
(2) Missing data was imputed using multiple imputation (MI). The values displayed are the averages over the 75 and 105 imputed datasets for Trials 301 and 302, respectively.

Figure 5: Results of the Primary Efficacy Endpoint at Week 8 by Sex, Age, Race and Baseline IGA Score for Trial 302 [ITT(1), MI(2)]

Subgroups (n[D], n[V])	DUOBRII (N=141)	Vehicle (N=74)	Difference	Difference and 95% CI
Sex				
Males (86, 50)	40.5%	12.2%	28.3%	
Females (55, 24)	52.9%	13.1%	39.8%	
Age				
18-64 (115, 63)	45.7%	11.5%	34.2%	
65+ (26, 11)	43.9%	18.4%	25.5%	
Race				
White (113, 63)	45.6%	11.5%	34.1%	
Non-White (28, 11)	44.4%	18.4%	26.0%	
Baseline IGA				
3 - Moderate (125, 63)	47.6%	14.7%	32.9%	
4 - Severe (16, 11)	27.7%	0%	27.7%	
Overall	45.3%	12.5%	32.8%	



Source: Reviewer's Analysis
(1) Intent-to-Treat (ITT) population: all randomized subjects.
(2) Missing data was imputed using multiple imputation (MI). The values displayed are the averages over the 75 and 105 imputed datasets for Trials 301 and 302, respectively.

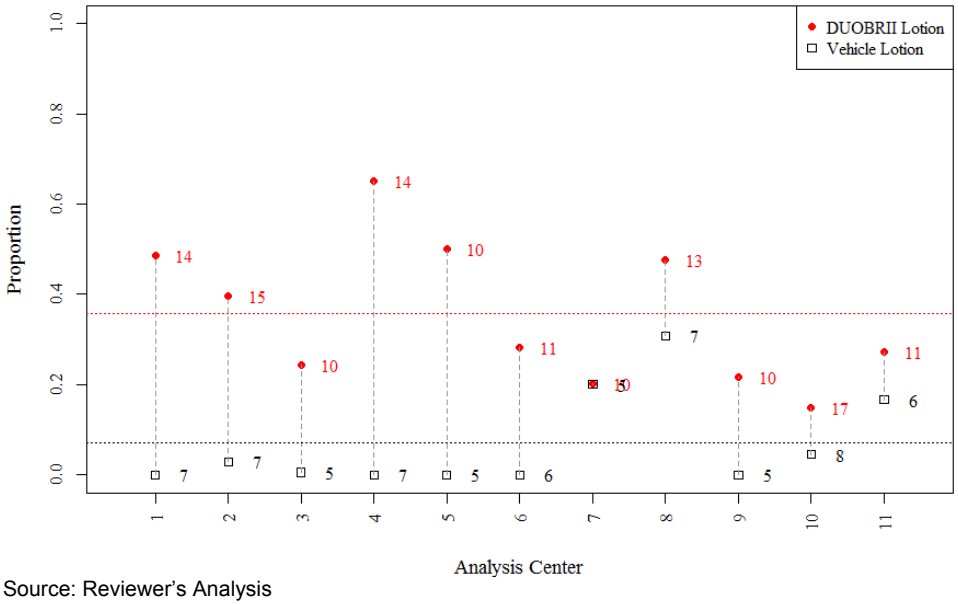
7.2.7.2. Center

Trial 301 randomized a total of 203 subjects (135 to DUOBRII and 68 to vehicle) from 16 centers in the United States and Trial 302 randomized a total of 215 subjects (141 to DUOBRII and 74 to vehicle) from 16 centers in the United States. The protocol specified a pooling strategy for centers that enrolled less than 15 subjects. These centers were pooled by ordering and combining the smallest with the largest. The process repeated until all centers had at least 15 subjects. For Trial 301, 7 of the 16 centers enrolled less than 15 subjects and the pooling process yielded 11 analysis centers (9 unpooled and 2 pooled). For Trial 302, 9 of the 16 centers enrolled less than 15 subjects and the pooling process yielded 11 analysis centers (7 unpooled and 4 pooled).

Figure 6 and Figure 7 present the results of the primary efficacy endpoint at Week 8 by analysis centers for Trials 301 and 302; respectively. In both trials, most centers had higher efficacy with DUOBRII lotion than vehicle lotion. The applicant investigated the consistency of results across analysis centers by testing the treatment by analysis center interaction in a logistic regression model. If the interaction was significant at the 0.10 level, the protocol specified a sensitivity analysis where the data will be analyzed excluding one analysis center at a time to identify the impact of each analysis center on the overall results. The p-values for the treatment by analysis center interaction were 0.834 and 0.940 for Trials 301 and 302, respectively. The applicant also evaluated the interaction based on the original centers (i.e., without pooling centers); however, this included only centers with at least 2 subjects per treatment arm (i.e., centers #112 and #114 in Trial 301 and center #208 in Trial 302 were not included). The p-values for the

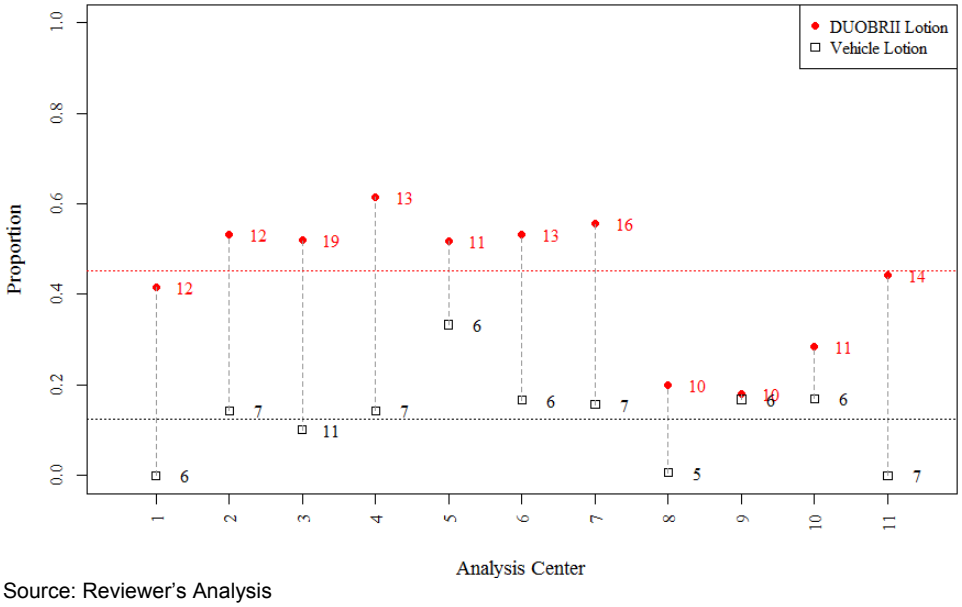
treatment by center interaction were 0.944 and 0.994 for Trials 301 and 302, respectively.

Figure 6: Results of the Primary Efficacy Endpoint at Week 8 by Analysis Centers for Trial 301 [ITT(1), MI(2)]



Source: Reviewer's Analysis
(1) Intent-to-Treat (ITT) population: all randomized subjects.
(2) Missing data was imputed using multiple imputation (MI). The values displayed are the averages over the 75 and 105 imputed datasets for Trials 301 and 302, respectively.

Figure 7: Results of the Primary Efficacy Endpoint at Week 8 by Analysis Centers for Trial 302 [ITT(1), MI(2)]



Source: Reviewer's Analysis
(1) Intent-to-Treat (ITT) population: all randomized subjects.
(2) Missing data was imputed using multiple imputation (MI). The values displayed are the averages over the 75 and 105 imputed datasets for Trials 301 and 302, respectively.

7.3. Review of Safety

7.3.1. Safety Review Approach

The primary review of safety for DUOBRII lotion relied on the evaluation of pooled safety data from two Phase 3 (-301 and -302) controlled trials that comprised the applicant's Integrated Summary of Safety (ISS) database, and shared identical inclusion/exclusion criteria, study designs (except ECG testing was conducted only in trial -301), dosing regimen, primary, and secondary efficacy endpoints. Trial -303 was not included in the ISS database. During the pre-NDA meeting with the applicant, the Agency agreed that the applicant's SAP for the ISS appeared reasonable. An overview of the Phase 3 trials is presented below:

Trials -301 and -302:
Phase 3 trials -301 and -302 included a DUOBRII lotion arm and a placebo comparator arm (DUOBRII vehicle lotion). The study drug was applied once daily for 8 weeks. Safety assessments included AEs, local skin reactions, abbreviated physical examinations, clinical laboratory measurements, and ECG (only for trial -301). For a detailed description of the study designs, refer to section 7.2, Review of relevant individual trials used to support efficacy.

Trial -303:
A Phase 3, open-label study to evaluate long-term safety of DUOBRII lotion applied once daily for 8 weeks, followed by intermittent application (as needed) for a total duration of 1 year. The study was conducted in 555 subjects with moderate-to-severe plaque psoriasis. Safety assessments included AEs, laboratory parameters, abbreviated physical examinations, and local skin reactions.

7.3.2. Review of the Safety Database

For the pivotal Phase 3 trials (-301 and -302), the safety population was defined to include all subjects randomized, received at least one dose of the study drug, and had at least one post-baseline safety assessment.

Overall Exposure

Overall exposure to DUOBRII lotion in terms of frequency, duration and target population was adequate for the evaluation of safety.

The number of subjects exposed to the to-be-marketed formulation of DUOBRII lotion in the Phase 2 and Phase 3 trials are presented in the following table:

Table 15: Overall Exposure to DUOBRII lotion (Phase 2 and 3 trials)

Number of Subjects		
Exposure to Drug	**With Study P201**	**Without Study P201**
≥ 28 days	926	893
≥ 56 days	800	785
≥ 84 days	487	487
≥ 168 days	324	324
≥ 365 days	34	34

Source: Analysis by Matthew Guerra, Ph.D., Biostatistics Reviewer.

Relevant characteristics of the safety population:

For the characterization of safety population, refer to the review of demographic and other baseline characteristics in the efficacy section of this review (Section 7.2).

Adequacy of the safety database:

The size of safety database is adequate. The number of subjects exposed to the to-be-marketed formulation of DUOBRII included 926 subjects for ≥ 4 weeks, 800 subjects for ≥ 8 weeks, 487 for ≥ 12 weeks, 324 subjects for ≥ 24 weeks, 34 subjects for ≥ 52 weeks, and 1369 subjects to at least 1 dose of DUOBRII lotion.

7.3.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Overall, the quality of data submitted is adequate to characterize the safety and efficacy of DUOBRII. Data quality and fitness were evaluated in conjunction with the JumpStart team. We discovered no significant deficiencies that would impede a thorough analysis of the data presented by the applicant.

Categorization of Adverse Events

An Adverse Event (AE) was defined as any untoward medical occurrence, including illness, sign, symptoms, clinically significant laboratory abnormalities, or disease temporally associated with the use of the drug, in a subject administered the drug product. AEs did not necessarily have a causal relationship to the study drug. AEs were recorded from the time the informed consent was signed. Treatment Emergent Adverse

Events (TEAEs) were AEs that occurred after the first administration of the study drug. AEs were documented at each study visit as observed by the investigators or reported by subjects.

The investigators categorized AEs by system-organ-class (SOC) and preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.0 (MedDRA version 15.0 was used in Phase 2 studies -A201 and -P201). The applicant assessed TEAEs by the number of subjects reporting one or more adverse events. Each subject reporting a TEAE was counted once at each level of MedDRA summarization (PT or SOC). Both verbatim terms and preferred terms were included in the data files for phase 3 trials, and there was good correlation between the verbatim and preferred terms used. No safety signal emerged from the review of TEAEs.

Investigators categorized AEs for seriousness, causality, event name (diagnosis/signs and symptoms), duration, maximum intensity (severity), action taken regarding the study drug (including any treatment given), and outcome of AEs. Subjects were followed to resolution of the AE (return to normal/baseline or stabilization) by the investigators.

Serious Adverse Events (SAEs) were any AE that resulted in death, was immediately life-threatening, required (or prolonged) hospitalization, resulted in persistent disability or incapacity, resulted in a congenital anomaly or birth defect, or a medically important event that may have required medical or surgical intervention to prevent one of the outcomes listed above.

Severity of AEs were assessed by investigators as mild, moderate, or severe. Causality was assessed as related or unrelated based on positive temporal relationship to the study drug, reasonable possibility of association of AE with underlying or concomitant illness or therapy, whether the AE was related to study procedures or lack of efficacy, and existence of a likely alternative etiology/lack of temporal relationship of the AE to the study drug.

The applicant's assessment of adverse events, conducted for all the studies in the DUOBRII development program, appears reasonable and appropriate. The applicant reported accurate definitions of treatment emergent adverse events, serious adverse events, and severity of adverse events.

Routine Clinical Tests

The applicant performed chemistry and hematology laboratory evaluations, physical examinations, and vital signs measurements in all Phase 2 and Phase 3 trials. Trials P201 and -501 included HPA axis suppression evaluation, and trial -301 included ECG monitoring.

7.3.4. Safety Results

Deaths

One death was reported during the clinical development program for DUOBRII. Subject (# (b) (6)) in study V01-118A-201 received vehicle lotion and died from severe congestive heart failure. The investigators considered his death not related to the study drug.

Reviewer's comment: This reviewer agrees with the applicant's assessment that death of this subject was not related to the study drug (vehicle lotion).

Serious Adverse Events

Combined Trials 301 and 302:

This pooled safety analysis set of 410 subjects included 270 subjects in the DUOBRII group and 140 subjects in the vehicle group. Four (4) SAEs of Staphylococcal cellulitis, pneumonia, anemia, and asthma were reported in 3(1.1%) of subjects in the DUOBRII group, compared to no SAEs in the vehicle group. The investigators assessed all SAEs as not related to the study drug:

1. **Anemia** (Subject (b) (6), DUOBRII arm): A 73-year-old white female with history of gastroesophageal reflux disease was hospitalized and received blood transfusion because of severe anemia on Day 24 of trial (Hemoglobin=7.4, repeat Hemoglobin = 10.1 at Week 8). Adverse events that occurred within a 3-day window of the SAE included moderate gastrointestinal hemorrhage. It is not known from the case report form whether therapeutic measures were administered to treat the subject. The subject requested to discontinue the trial on Day 57. The final outcome of this SAE was reported as unresolved.

2. **Asthma** and **pneumonia** (Subject (b) (6), DUOBRII arm): A 47-year-old African American female with history of asthma and tracheostomy (for treatment of respiratory failure related to asthma exacerbation), was hospitalized for asthma exacerbation on Day 59 and diagnosed with pneumonia on Day 69. The investigators assessed the SAEs as unrelated to study drug. The SAEs resolved on Day 83 and the subject completed the trial on Day 86.

3. **Facial cellulitis** due to Methicillin Sensitive Staphylococcus Aureus (Subject (b) (6), DUOBRII arm): A 48-year-old white female hospitalized on Day 47 and discontinued from the trial. This SAE was reported resolved on Day 76.

Reviewer's comment: This reviewer agrees with the investigators' assessments that the SAEs were not related to the study drug. Plausible explanations for the occurrences of these SAEs include the subjects' medical histories and concomitant medications. The fact that the study drug was not applied to the subjects' faces also argues against a drug-related AE in the SAE case of facial cellulitis.

Trial 303:

Eighteen (3.3%) of subjects experienced SAEs in trial -303. The investigators considered no SAEs to be related to the study drug. No subject experienced more than 1 SAE, as presented in the following table:

Table 16: Summary of Treatment-Emergent SAEs (Safety Population, Trial -303)

Trial -303	SAE
DUOBRII (halobetasol propionate [HP] 0.01%, tazarotene [Taz] 0.045%) Lotion	**Count (%)**
Dictionary-Derived Term (PT)	1 (0.2)
Cellulitis gangrenous	1 (0.2)
Diverticulitis	1 (0.2)
Sepsis	1 (0.2)
Tonsillitis	1 (0.2)
Colitis ulcerative	1 (0.2)
Incarcerated umbilical hernia	1 (0.2)
Pancreatitis acute	1 (0.2)
Colon cancer	1 (0.2)
Prostate cancer	1 (0.2)
Small intestine adenocarcinoma	1 (0.2)
Ankle fracture	1 (0.2)
Clavicle fracture	1 (0.2)
Anaemia	1 (0.2)
Pericardial effusion	1 (0.2)
Type 2 diabetes mellitus	1 (0.2)
Cerebrovascular accident	1 (0.2)
Nephrolithiasis	1 (0.2)
Intervertebral disc operation	1 (0.2)

Source: Applicant's submission, CSR V01-118A-303, Table 15, p. 85 and Reviewer's table by JMP Clinical, safety population for trial -303 using filters "AESER=Y and AE. AETRTEM". MedDRA version 18.0.

Reviewer's comment:
This reviewer agrees with the investigator's assessments that the SAEs were not related to the study drug. Each SAE was reported in a single subject. There is an absence of a clear safety signal. However, the absence of a vehicle arm does not allow for comparison of incidence rates for the reported SAEs with an untreated group of subjects.

Trial A201:

A total of 6 SAEs occurred in 4 subjects during this trial. The investigators considered no SAE as related to the study drug:

1. Infection(unspecified) and Congestive cardiac failure (Subject (b) (6), vehicle lotion arm): A 64-year-old white male hospitalized on Day 48 for infection and diagnosed with CHF during hospitalization. The subject died on Day 75.

2. Coronary artery disease and acute myocardial infarction (subject (b) (6), Monad HP, 0.01% lotion arm): A 54-year-old white male hospitalized on Day 78 with myocardial infarction, resolved on Day 79.

3. Colorectal adenocarcinoma (Subject (b) (6), Monad Taz 0.045% lotion arm): A 55-year-old white female, with SAE reported on Day 48 after a polypectomy, outcome of SAE was reported as resolved.

4. Hernia (obstructive incarcerated recurrent incisional) (Subject (b) (6), vehicle lotion arm): A 59-year-old white male hospitalized on Day 11 with the SAE. The SAE resolved on Day 14.

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

Trial 202:
The investigators considered the following SAEs unrelated to study drug:

1. Chest pain (Subject (b) (6)) in DUOBRII lotion arm (1.7%): A 48-year-old white male, with history of coronary artery stent, experienced an SAE of severe atypical chest pain and was hospitalized on Day 12. No action was taken regarding the study medication. No final diagnosis for this SAE was reported in the CRF. The SAE resolved on Day 13.

2. Chest pain (Subject (b) (6)) in Taz 0.05% cream arm (1.8%): A 47-year-old African American male with history of hypertension experienced an SAE of chest pain and was hospitalized on Day 60. Subject was evaluated with chest radiography, chest CT scan, echocardiogram, bilateral leg Doppler, ECG, and cardiac stress test. No action was taken regarding the study medication. No final diagnosis for this SAE was reported in the CRF. The SAE resolved on Day 64.

Reviewer's comment: This reviewer agrees with the investigators' assessments that the

SAEs were not related to the study drug.

Trial 203:
No SAEs occurred during the conduct of this trial.

Trial P201:
Malignant melanoma (Subject (b) (6)): A 53-year-old female (9.1%) in the Ultravate arm was diagnosed on Day 34 with malignant melanoma. This SAE was reported as resolved with surgery. The investigators considered this SAE unrelated to the study drug.

Reviewer's comment: This reviewer agrees with the investigator's assessment that the SAE was not related to the study drug.

Trial 501:
Cerebrovascular accident (Subject (b) (6)): A 55-year-old white male (4.3%) in the HP, 0.01% lotion (IDP-122) arm, hospitalized on Day 23. The SAE resolved on Day 36. The investigators considered this SAE unrelated to the study drug.

Reviewer's comment: This reviewer agrees with the investigator's assessment that the SAE was not related to the study drug.

Study 101:
No SAEs occurred during the conduct of this trial.

Study 102:
No SAEs occurred during the conduct of this trial.

Trial 103 (RIPT):
The investigators assessed the following SAEs as unrelated to the study drugs:

1. Abdominal pain, dehydration, vomiting (Subject (b) (6)): a 54-year-old African American female hospitalized on Day 34. The SAEs resolved on Day 36.
2. Pyelonephritis (Subject: (b) (6)): a 21-year-old white female hospitalized on Day 34. The SAE resolved on Day 48.
3. Colitis (Subject: (b) (6)): A 54-year-old African American female hospitalized on Day 7. The SAE resolved on Day 11.

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

Dropouts and/or Discontinuations Due to Adverse Effects

The most frequent TEAEs leading to study drug discontinuations during Phase 2 and Phase 3 trials were application site reactions and skin-related TEAEs.

Combined Trials 301 and 302:

The incidence of TEAEs that led to drug discontinuation was 17/270 (6.3%) in DUOBRII lotion group, compared to 5/140 (3.6%) in the vehicle lotion group. Most common TEAEs that led to discontinuation were psoriasis (1.1% vs. 1.4%) and contact dermatitis (1.9% vs. 0) in DUOBRII lotion group compared to vehicle lotion group. Subject disposition is summarized below:

Table 17: Summary of Subject Disposition (All Randomized Subjects, Combined Trials -301 and -302)

Parameter	DUOBRII lotion, N (%)	Vehicle lotion, (N%)
Subjects Included	276	142
Study Status		
Completed Study	232 (84.1)	118 (83.1)
Discontinued Study	44 (15.9)	24 (16.9)
Reasons for Discontinuation		
Adverse Event	11 (4.0)	4 (2.8)
Subject Request	17 (6.2)	12 (8.5)
Protocol Violation	3 (1.1)	0
Lost to Follow-Up	9 (3.3)	6 (4.2)
Worsening Condition	3 (1.1)	2 (1.4)
Other	1 (0.4)	0

Source: Applicant's submission, Section 2.7.4, Modified from Table 14.0.1

Reviewer's comment:

The proportion of subjects who completed studies -301 and -302, and the proportion of subjects who discontinued the studies were similar in the DUOBRII lotion group compared to the Vehicle lotion group. However, slightly higher proportion of subjects in DUOBRII treatment group discontinued the trial due to adverse events than in the vehicle group.

Trial 303:
In trial 303, 41 of 550 subjects (7.5%) discontinued the study drug due to TEAEs. TEAEs that led to study drug discontinuation, in more than 1 subject each, were the following: application-site dermatitis (7), application-site pruritus (7), application-site pain

(6), application-site reaction (5), psoriasis (4), urticaria (2), and application-site irritation (2).

Five hundred and three (90.6%) subjects completed 3 months, 391 (70.5%) completed 6 months, and 138 (24.9%) completed 12 months of treatment.

Table 18: Summary of Subject Disposition (All Treated Subjects, Trial -303)

Parameter	DUOBRII lotion, N (%)
Subjects Included	555
Reason for Discontinuation	
Lack of Efficacy	151 (27.2)
Subject Request	87 (15.7)
Other	45 (8.1)
Lost to Follow-Up	41 (7.4)
Sponsor Request	39 (7.0)
Adverse Event	33 (5.9)
Worsening Condition	16 (2.9)
Protocol Violation	6 (1.1)
Pregnancy	1 (0.2)

Source: Applicant's submission, Study V01-118A-303 CSR, Modified from Table 8, page 57.

Reviewer's comment:

Twenty five percent (25%) of subjects completed this study. The most frequent reason for study discontinuation was lack of efficacy (27%).

The proportion of subjects who discontinued trial -303 because of adverse events (5.9%) was similar to the proportion of subjects who discontinued the combined trials -301 and -302 because of adverse events (4%).

Trial A201:

TEAEs that led to study drug discontinuation were more common in the Taz monad group. The following number of subjects discontinued the study drug, in each group, because of TEAEs:

- DUOBRII monad (Taz 0.045%) lotion group: application-site pain in 2 (3.4%) subjects, application-site pruritus in 4(6.9%) subjects, and one (1) subject each with application-site erythema, application-site dermatitis, application-site discoloration, application-site swelling and psoriasis.
- DUOBRII lotion group: One (1) subject each for the following TEAEs: application-site erythema, application-site pruritus, and cellulitis.
- DUOBRII vehicle lotion group: one subject for congestive cardiac failure.

Trial 202:

TEAEs that led to study drug discontinuation in this trial were the following:

- DUOBRII lotion group: one (1) subject (1.7%) each, with TEAE of contact dermatitis, skin atrophy, skin reaction, and Staphylococcal impetigo.
- Tazarotene cream, 0.05% group: one (1) subject (1.8%) with skin rash.
- Vehicle lotion group: One (1) subject (6.7%) for TEAE of administration site condition aggravated.

Trial 203:
No TEAEs led to discontinuation of the study drug in this trial.

Trial P201:

Five (5) subjects discontinued the study drug in this trial because of TEAEs:

- Cohort #2 (low-dose DUOBRII x 8 weeks) - 2 subjects: subject ((b) (6)) with urticaria, subject ((b) (6)) with application site pain, application-site pruritus, application-site dryness, folliculitis and psoriasis.
- Cohort #4: (high-dose DUOBRII x 8 weeks) - 1 subject ((b) (6)) with application-site pain, application-site dryness, application-site pruritus
- Cohort #6 (Tazarotene cream, 0.1% x 8 weeks) - 2 subjects: subject ((b) (6)) for psoriasis, subject ((b) (6)) for application-site folliculitis.

Trial 501:
One (1) subject each in DUOBRII lotion and IDP-122 lotion groups discontinued treatment for TEAEs of cerebrovascular accident and abdominal discomfort.

Study 101:
No TEAEs led to subject discontinuation of the study drug.

Study 102:
No TEAEs led to subject discontinuation of the study drug.

Study 103:
One subject (0.4%) discontinued the study drug because of application site dermatitis.

Reviewer's comment:
Most subjects discontinued the study drug in the Phase 2 trials because of local skin reactions, which appears consistent with irritation due to Tazarotene.

Significant Adverse Events

In the combined -301 and -302 trials, the incidence of grade 3 (severe) treatment-emergent local skin reactions (LSRs) was lower in the DUOBRII lotion group, compared to vehicle lotion group: Itching (14.5% vs. 20.7%), dryness (3.7% vs. 13.6%), and burning/stinging (8.2% vs. 14.3%).

Treatment Emergent Adverse Events and Adverse Reactions

Combined Trials -301 and -302:

Two hundred and seventy (270) subjects were included for analysis in the DUOBRII group and 140 subjects in the vehicle group for the combined trials -301 and -302. At the Week 8 visit, the incidence of TEAEs in DUOBRII group was 97/270 (35.9%), compared to 30/140 (21.4%) in the vehicle group.

TEAEs with > 1% incidence above the vehicle group included contact dermatitis (7.4%/0), application site pain (2.6%/0.7%), upper respiratory tract infection (1.9% / 0.7%), excoriation (1.9% / 0), skin atrophy (1.9%/0), folliculitis (1.9%/0), and rash (1.5%/0). The results are summarized in the following table:

Table 19: Summary of TEAEs occurring in ≥ 1% of subjects in either treatment group through Week 8 (Safety population, Studies 301 and 302 combined), and higher in the DUOBRII treatment group compared to vehicle group by ≥ 1%

Trials -301 and -302 combined	DUOBRII (N=270)	Vehicle (N=140)
Any TEAE	97 (35.9%)	30 (21.4%)
PT	**Count (%)**	**Count (%)**
Dermatitis contact	20 (7.4)	0
Application site pain	7 (2.6)	1 (0.7)
Upper respiratory tract infection	5 (1.9)	1 (0.7)
Excoriation	5 (1.9)	0
Skin atrophy	5 (1.9)	0
Folliculitis	5 (1.9)	0
Rash	4 (1.5)	0
Skin abrasion	3 (1.1)	0
Sinusitis	3 (1.1)	0

Source: Applicant's submission, section 2.7.4, modified from Tables 9, page 43. MedDRA version 18.0, and JMP Clinical Additional Filter to include Adverse Events: FUPFL ne 'Y', Analysis Population: Safety.

Adverse Reactions

Adverse reactions occurred at a higher incidence in the DUOBRII lotion group (20.4%), compared to vehicle lotion group (7.9%). The results are summarized in the following table:

Table 20: Summary of Adverse Reactions (ARs) occurring in ≥ 1% of subjects in either treatment group through Week 8 (Safety population, Studies 301 and 302 combined), and higher in the DUOBRII treatment group compared to vehicle group by ≥ 1%

Trials -301 and -302 combined	DUOBRII (N=270)	Vehicle (N=140)
Any Adverse Reaction	55 (20.4%)	11 (7.9%)
PT	**Count (%)**	**Count (%)**
Dermatitis contact	17 (6.3)	0
Application site pain	7 (2.6)	1 (0.7)
Skin atrophy	5 (1.9)	0
Folliculitis	5 (1.9)	0
Rash	4 (1.5)	0
Excoriation	3 (1.1)	0

Source: Applicant's submission, section 2.7.4, modified from Tables 10, page 44. MedDRA version 18.0, and **JMP** Clinical Additional Filter to include Adverse Events: FUPFL ne 'Y', Analysis Population: Safety.

Reviewer's comment:

The higher incidence of application-site pain and contact dermatitis in the DUOBRII lotion group, compared to the vehicle lotion group, is consistent with adverse reactions reported with the use of tazarotene.

Trial 303:

Table 21: Summary of the most frequent (≥ 1%) TEAEs (Safety population, Trial -303)

Trial -303	DUOBRII lotion (N=550)
Any TEAE	314 (57)
PT	**Count (%)**
Application site dermatitis	59 (11)
Application site pruritus	33 (6)
Application site pain	29(5)
Nasopharyngitis	28 (5)
Influenza	17 (3)
Upper respiratory tract infection	16 (3)
Application site irritation	14 (3)
Application site folliculitis	14 (3)
Application site erosion	12 (2)
sinusitis	11 (2)

Application site rash	9 (2)
Application site erythema	8 (2)
Back pain	8 (2)
Dermatitis contact	8 (2)
Psoriasis	8 (2)
Hypertension	8 (2)
cellulitis	8 (2)
Application site infection	7 (1)
Arthralgia	7 (1)
Headache	7 (1)
Nausea	7 (1)
Application site reaction	6 (1)

Source: Applicant's submission: Tables 12, page 47, section 2.7.4. MedDRA version 18.0, and JMP Clinical: Study DUOBRII-303, Analysis population: Safety, Select Where (: Percent Occurrence >= 1 &: Percent Occurrence, = 10.7), Treatment emergence determined using AE.AETRTEM.

All subjects were treated with DUOBRII lotion. No subject was treated with vehicle lotion in this open-label trial. Of the five hundred and fifty (550) subjects included in the analysis, 57.1 % experienced TEAEs.

The three most frequently observed TEAEs were related to application-site dermatitis (10.7%), application-site pruritus (6.0%), and application-site pain (5.3%).

Table 22: Summary of the most frequent (≥ 1%) Adverse Reactions (Safety population, Trial -303) (Rounded)

Trial -303	DUOBRII lotion (N=550)
PT	**Count (%)**
Application site dermatitis	56 (10)
Application site pruritus	33 (6)
Application site pain	28(5)
Application site irritation	13(2)
Application site folliculitis	11(2)
Application site erosion	9 (2)
Application site erythema	8 (2)
Application site rash	7 (1)

Source: Applicant's submission: Tables 13, page 49, section 2.7.4. MedDRA version 18.0, and JMP Clinical: Study DUOBRII-303, Analysis population: Safety, Select Where (: Percent Occurrence >= 1 &: Percent Occurrence, = 10.7), Treatment emergence determined using AE.AETRTEM.

Reviewer's comment:
The reported incidence of application-site pain, application-site pruritus, and contact dermatitis in the DUOBRII lotion group in trial -303 is consistent with adverse reactions reported with the use of tazarotene.

Trial A201:

The overall incidence of TEAEs in the DUOBRII lotion group (33.9%) was higher than in HP monad group (21%) and vehicle lotion group (22.6%), but lower than in Taz 0.045% monad group (46.6%).

Application site TEAEs had a greater incidence in DUOBRII lotion group (10.2%) and Taz 0.045% monad group (22.4%), compared with HP 0.01% monad group (0%) or vehicle lotion group (3.2%).

The investigators considered most application site TEAEs to be related to study drugs. Most frequent adverse reactions (ARs) occurred in the Taz 0.045% monad group; with application site pain (8.6%), application site pruritus (6.9%), and application site erythema (3.4%), as summarized in the following table:

Table 23: Summary of Adverse Reactions occurring in ≥ 1% of subjects in any treatment group (Safety population, Study A201) (Rounded)

Trial -A201	Taz 0.045% monad (N=58)	DUOBRII (N=59)	HP 0.01% monad (N=62)	Vehicle (N=31)
PT	**Count (%)**	**Count (%)**	**Count (%)**	**Count (%)**
Application site pain	5 (9)	2 (3)	0	1 (3)
Application site pruritus	4 (7)	0	0	0
Application site erythema	2 (3)	1(2)	0	0
Application site dermatitis	1 (2)	0	0	0
Application site discolouration	1 (2)	1 (2)	0	0
Application site irritation	1 (2)	1 (2)	0	0
Psoriasis	1 (2)	0	0	0
Dermatitis contact	1 (2)	0	0	0
Application site folliculitis	0	2 (3)	0	0

Source: Applicant's submission synopsis 2.7.4, modified from Table 16, page 54. MedDRA version 17.0, and Reviewer's analysis: JMP Clinical Study: DUOBRII-201, Analysis Population: Safety Select Where (: Percent Occurrence >= 1 &: Percent Occurrence <= 3.8) Treatment emergence determined using AE.AETRTEM.

Trial 202:

Most frequent TEAEs in DUOBRII lotion group, compared to Tazorac cream group, were application site pain (6.7% vs. 5.3%), skin atrophy (5% vs. 0), pruritus (5% vs. 3.5%), and headache (5% vs. 1.8%). TEAE of contact dermatitis in Tazorac cream group was more frequent than in DUOBRII lotion group (7.0% vs. 1.7%).

Most frequent ARs in DUOBRII lotion group were application site pain (6.7%) and skin atrophy (5.0%), compared to application site pain (5.3%) and contact dermatitis (5.3%) in Tazorac, 0.05% cream group. Adverse reactions that occurred in trial -202 are summarized in the following table:

Table 24: Summary of Adverse Reactions occurring in ≥ 1% of subjects in either treatment group (Safety population, Trial -202)

Trial -202	DUOBRII lotion (N=60)	Tazorac 0.05% cream (N=57)	DUOBRII vehicle lotion (N=15)	vehicle cream (N=16)
PT	**Count (%)**	**Count (%)**	**Count (%)**	**Count (%)**
Application site pain	4 (7)	3 (5)	2 (13)	0
Skin atrophy	3 (5)	0	0	0
Application site pruritus	2 (3)	2 (4)	2 (13)	0
folliculitis	2 (3)	1 (2)	0	0
Dermatitis contact	1 (2)	3 (5)	0	0
Rash	1 (2)	1 (2)	0	0
Psoriasis	1 (2)	0	0	0
Diarrhoea	1 (2)	0	0	0

Source: Applicant's submission, Section 2.7.4, modified from Table 17, page 65, MedDRA version 18.0, and Reviewer's analysis, JMP Clinical: DUOBRII-202, Analysis Population: Safety. Select Where (: Percent Occurrence >= 1 &: Percent Occurrence <= 6.1), Treatment emergence determined using AE.AETRTEM.

Trial 203:

Most frequent TEAEs and ARs were application site conditions which occurred with similar frequency in the DUOBRII lotion group (6.6%), compared to Ultravate cream group (6.5%). The only AR reported by more than one subject was application site pain in 3 subjects in the Ultravate cream group.

Table 25: Summary of Adverse Reactions occurring in ≥ 1% of subjects in any treatment group (Safety population, Trial -203)

Trial -203	DUOBRII lotion (N=61)	Ultravate cream 0.05% (N=62)	DUOBRII vehicle lotion (N=16)	vehicle cream (N=14)
PT	**Count (%)**	**Count (%)**	**Count (%)**	**Count (%)**
Application site pain	1 (2)	3 (5)	0	0
Application site dryness	1 (2)	1 (2)	0	0
Application site pruritus	1 (2)	1 (2)	0	0
Application site atrophy	1 (2)	0	0	1 (7)

Source: Applicant's submission, Section 2.7.4, modified from Table 18, page 56. MedDRA version 18.0, and Reviewer's analysis, JMP Clinical: Study: DUOBRII-203, Analysis Population: Safety, Select Where (: Percent Occurrence >= 1 &: Percent Occurrence <= 2.6), Treatment emergence determined using AE.AETRTEM.

Trial P201:

No adverse reactions occurred in the high strength DUOBRII lotion (6 Weeks) group or the low strength DUOBRII lotion (6 Weeks) group. These two cohorts were excluded from the AR table. All adverse reactions in this trial were related to application-site conditions, and occurred in one or two subjects in each treatment group. Two subjects in Tazorac, 0.1% cream group experienced application site pain and pruritus.

Table 26: Summary of Adverse Reactions (Safety population, Trial P201)

Trial -P201	DUOBRII lotion, Low-strength (HP 0.01/Taz 0.045%), 8 weeks (N=13)	Ultravate, 0.05% cream, 2 weeks (N=11)	Tazorac cream, 0.1%, 8 weeks (N=5)	DUOBRII lotion, High-strength (HP 0.025%/ Taz 0.045%), 8 weeks (N=11)
PT	**Count (%)**	**Count (%)**	**Count (%)**	**Count (%)**
Application site pain	1 (8)	0	2 (40.0)	2 (18)
Application site pruritus	1 (8)	0	2 (40.0)	2 (18)
Application site dryness	1 (8)	0	1 (20.0)	1 (9)
Application site hypersensitivity	1 (8)	0	0	0
Chills	0	0	1 (20.0)	0
Application site folliculitis	1 (8)	1 (9)	1 (20.0)	1 (9)
Telangiectasia	1 (8)	0	0	0
Psoriasis	1 (8)	0	1 (20.0)	1 (9)
Urticaria	1 (8)	0	0	0
Sunburn	1 (7.7)	0	0	0

Source: Applicant's submission, Section 2.7.4, modified from Table 15, page 53. MedDRA version 15.0, and JMP Clinical 12.2.0, Study DUOBRII-P2-01, Analysis Population: Safety, select where (: Percent Occurrence >= 2 &: Percent Occurrence <= 13.7), Treatment Emergence determined using AE. AETRTEM.

Reviewer's comment:
The adverse reactions reported in Phase 2 trials for DUOBRII lotion are related to the application site reactions, and are consistent with the adverse effects generally associated with the use of tazarotene and halobetasol.

Trial 501:

The only adverse reactions in this trial occurred in DUOBRII lotion group. No ARs were reported for IDP-122 lotion group, Tazorac cream group, or Ultravate cream group. ARs of headache, application site folliculitis, application site irritation, and application site pain each occurred in one subject (4.3%). One subject (4.3%) reported ARs of abdominal discomfort, nausea and vomiting as presented in table below:

Table 27: Summary of Adverse Reactions (Safety Population, Trial-501)

Trial -501	DUOBRII lotion
PT	**Count (%)**
Application site folliculitis	1 (4)
Application site irritation	1 (4)
Application site pain	1 (4)
Headache	1 (4)
Abdominal discomfort	1 (4)
Nausea	1 (4)
Vomiting	1 (4)

Source: Applicant's submission, CSR V01-118A-501, Table 14.3.1.2.5, and JMP clinical: Study: DUOBRII-501 Analysis Population: Safety Select Where (: Percent Occurrence >= 1.1 &: Percent Occurrence <= 5.3) Treatment emergence determined using AE.AETRTEM.

Study 102:

No adverse reactions were reported for this study.

Study 103:

No adverse reactions were reported for this study.

Laboratory Findings

HPA axis suppression: Results are discussed in section 7.3.5.

Trials -101, -102, -103: No laboratory tests were conducted in healthy subjects.

Combined trials -301 and -302: No clinically significant, treatment-related abnormalities occurred in the hematology and clinical chemistry laboratory results.

Trial -303: One (1) subject discontinued treatment for mildly elevated ALT and AST, determined as unrelated to study drug by the investigator.

Trial P201: In cohort 2, One (1) subject had a decrease in hemoglobin and an increase in urobilinogen, determined as unrelated to the study drug by the investigator.

Trials -201, -202, -203, -501:

The applicant reported no clinically meaningful changes in any laboratory parameters.

Reviewer's comment:
No clinically significant changes in chemistry and hematology laboratory parameters related to the drug were observed during the development program of DUOBRII, consistent with the mechanism of action and topical route of administration for this drug

product.

Vital Signs

Trials -102 and -103: Vital signs data were not collected.

Trials P201, -201, -202, -203, -501, -301, -302, and -303:
Vital signs data were unremarkable and did not raise safety concerns. Blood pressure and heart rate parameters for combined trials -301 and -302 are summarized in the following table:

Table 28: Summary of Vital Signs and Change From Baseline (Safety Population, Combined Trials -301 and -302) at Week 8

Parameter	DUOBRII lotion (N=270), (N=240) at Week 8	Vehicle lotion (N=140), (N=121) at Week 8
Baseline Diastolic Blood Pressure (mmHg)		
Mean (±SD)	79.9 (11.25)	78.9 (9.38)
Min, Max	50, 110	44, 101
DBP: Change from Baseline to Week 8		
Mean (±SD)	0 (10.36)	1.2 (8.82)
Min, Max	-31, 85	-22, 21
Baseline Systolic Blood Pressure (mmHg)		
Mean (±SD)	127.5 (14.67)	127.1 (14.82)
Min, Max	93,207	89, 179
SBP: Change from Baseline to Week 8		
Mean (±SD)	0.2 (12.97)	-0.9 (12.94)
Min, Max	-48, 42	-38, 36
Baseline Pulse (bpm)		
Mean (±SD)	75.5 (10.15)	76.4 (11.32)
Min, Max	55, 99	50, 108
Pulse: Change from Baseline to Week 8		
Mean (±SD)	1.0 (9.87)	1.6 (9.83)
Min, Max	-32, 28	-28, 25

Source: Applicant's submission, ISS Table 14.3.1.6

Reviewer's comment:
This reviewer agrees with the applicant's assessment that no clinically significant changes in vital signs were observed in DUOBRII lotion group, compared to the vehicle lotion group, during the treatment period.

Electrocardiograms (ECGs)

The only ECG data for this submission were recorded during trial V01-118A-301. The applicant reported no abnormal findings in the ECG data.

QT

The applicant requested a waiver to conduct a thorough QT/QTc clinical study for DUOBRII lotion, and provided the following reasons in support of their request:

- Non-clinical study V01-118A-608 conducted by the applicant showed that Tazarotenic acid and halobetasol propionate inhibited hERG current minimally, and hERG inhibition observed was due to Tazarotene. the applicant concluded that this degree of hERG inhibition would not be clinically significant, since tazarotene is rapidly metabolized to tazarotenic acid and has a high degree of plasma protein binding.

- Lack of ECG abnormalities observed a 3-month dermal toxicity study in Gottingen minipigs (V01-118A-605)

- The applicant cited the long marketing history of halobetasol propionate (> 25 years) and tazarotene (> 18 years) and the absence of any post-marketing reports of cardiovascular safety signals, including arrhythmias possibly related to QT/QTc prolongation, in several public databases (the FDA Postmarket drug safety information for patients and providers, FAERS database, CredibleMeds organization QT drug database)

- The applicant performed a literature search (Pubmed April/May 2015) which did not identify an increased risk of QT/QTc prolongation associated with the use of topical halobetasol propionate, tazarotene, or other corticosteroids and retinoids.

In an advice letter of 4/22/2016, the Agency informed the applicant that a determination for waiver would be made after submission of the study results from the maximal use PK trial in subjects with psoriasis. The Agency stated that a waiver of thorough QT trial would be reasonable if the results from the maximal use PK trial confirm that the systemic exposure of halobetasol propionate, tazarotene, and tazarotenic acid following DUOBRII lotion treatment under maximal use conditions was low, and less than or similar to those following treatment with listed drugs Tazorac cream, 0.1% and Ultravate cream, 0.05%.

Reviewer's comment:

A consultation was obtained from DCRP QT-Interdisciplinary Review Team(QT-IRT) regarding the TQT waiver request. In a memorandum of 2/15/2018, the QT-IRT determined that a TQT study was not required for DUOBRII lotion, based on the following rationale:

"a waiver of thorough QT trial would be reasonable if the results from the maximal use PK trial confirm that the systemic exposure of halobetasol propionate, tazarotene and tazarotenic acid following DUOBRII lotion treatment under maximal use conditions is

low and less than or similar to those following treatment with listed drugs Tazorac cream, 0.1% and Ultravate cream, 0.05%."

In the sponsor's maximal use PK study in patients, the steady state Cmax for halobetasol propionate was higher by 1.5-fold (87.2/58.2 pg/mL), for tazarotenic acid was higher by ~1.6-fold (471/286 pg/mL on Day 14 and 525/340 pg/mL on Day 28) and for tazarotene was higher by 1.1- to 3.1-fold (31.6/10.2 pg/mL on Day 14 and 24.1/22.3 pg/mL on Day 28) for DUOBRII lotion compared to the corresponding listed drugs (Ultravate cream (0.05%) and Tazorac cream (0.1%)).

However, there is sub-nanomolar systemic exposure (Cmax) of halobetasol propionate and tazarotene and ~1.6 nM systemic exposure of tazarotenic acid with DUOBRII lotion. The preclinical data suggested a safety margin of at least 4-orders of magnitude over observed Cmax in patients for all these moieties for hERG inhibition (IC50 for halobetasol propionate, tazarotenic acid and tazarotene are >10 μM, >10 μM and 5.7 μM respectively). Furthermore, tazarotene and tazarotenic acid are highly bound to human plasma proteins (>90%) which further increases the safety margin corresponding to the free drug concentration in plasma for these moieties towards hERG inhibition. Also, no large QTc outliers (QTcF > 500 ms or ΔQTcF ≥ 60 ms) or higher mean changes in QTc compared to vehicle control were seen in ECG assessments in Phase 3 study for DUOBRII. Postmarketing experience of 25 years for halobetasol propionate and 18 years for tazarotene did not identify significant cardiovascular adverse effects with topical use. Thus, the totality of evidence suggests minimal risk for QTc prolongation for DUOBRII lotion despite the findings of higher exposures compared to listed drugs in the maximal use PK study."

This reviewer recommends granting the TQT waiver request, and agrees with the assessment of the QT-IRT that the totality of evidence suggests minimal risk for QTc prolongation for DUOBRII lotion; despite the findings in the sponsor's maximal use PK study that the steady state Cmax for halobetasol propionate, tazarotenic acid, and tazarotene were higher for DUOBRII lotion compared to the corresponding listed drugs (Ultravate cream,0.05% and Tazorac cream, 0.1%).

Immunogenicity

Not applicable.

7.3.5. Analysis of Submission-Specific Safety Issues

HPA axis suppression studies

Study -501:
Study -501 was a Phase 1, 8-week, open-label, randomized study to evaluate the absorption and systemic pharmacokinetics (PK) and HPA axis suppression potential of once daily topical applications of DUOBRII lotion (Taz 0.045% and HP 0.01%, 8 weeks),

IDP-122 lotion (HP monad 0.01%, 8 weeks), Ultravate cream, 0.05% (2 weeks), and Tazorac cream, 0.05% (4 weeks) in adult subjects with moderate to severe plaque psoriasis. Subjects were randomized in a (1:1:1:1) ratio. Safety assessment included pre-stimulation and post-stimulation cortisol concentrations, local skin reactions (LSRs), AEs, laboratory tests, pregnancy tests, physical examinations and vital signs measurements. Efficacy assessment included IGA evaluations. PK assessments were also included.

Twenty-three (23) subjects were randomized at screening visit to each of the following groups in this trial:

1. In the Ultravate cream group, 1 (5%) of subjects had an abnormal HPA axis suppression test on Day 15 (N=20).
2. In the DUOBRII lotion group, 3 (15%) of subjects had an abnormal HPA axis suppression test on Day 29 (N=20), with normal repeat test for all subjects on Day 57 on continued treatment (N=20).
3. In the IDP-122 lotion group, 1 (5.6%) of subjects had an abnormal HPA axis suppression test on Day 29 (N=18), with abnormal repeat tests for 3 (15.8%) subjects on Day 57 (N=19) (including the subject with abnormal test on Day 29). All repeat HPA axis suppression test results at an unscheduled follow-up visit were normal).

Table 29: Summary of HPA Axis Suppression Tests by Visit (Safety Population)

Study # V01-118A-501		N (%) of subjects with abnormal HPA axis suppression test			
Cohort	Subjects	Screening	Day 15	Day 29	Day 57
DUOBRII lotion	N = 23	0		3(15.0%)	0
IDP-122 lotion	N = 23	0		1(5.6%)	3(15.8%)
Ultravate cream	N = 23	0	1(5.0%)		

Note: Poststimulation cortisol levels ≤18 µg/dL considered abnormal.
Source: modified from applicant's submission, Study V01-118A-501 CSR, Table 27, p. 106.

Reviewer's comment:
A higher proportion of subjects treated with DUOBRII lotion for 4 weeks, compared to subjects treated with IDP-122 lotion for 4 weeks or subjects treated with Ultravate cream for 2 weeks, had abnormal HPA axis suppression test results.

The results of this trial show that all subjects in the DUOBRII lotion group (including all subjects with HPA axis suppression on Day 29 that received continued treatment) had normal HPA axis suppression test results after 8 weeks of treatment.

The proportion of subjects with HPA axis suppression treated with IDP-122 lotion for 8 weeks was similar to the proportion of subjects with HPA axis suppression treated with

DUOBRII lotion for 4 weeks.

Study P201:

Trial P201 was a Phase 2, dose-ranging, evaluator-blinded study to evaluate safety and adrenal suppression potential of DUOBRII lotion in adult subjects with moderate to severe psoriasis. Subjects received once daily topical application of one of the two formulations of DUOBRII lotion, Ultravate cream, or Tazarotene cream.

Safety assessment included AEs, LSRs, laboratory tests (chemistry, hematology, and urinalysis), and HPA axis suppression tests. PK and efficacy were also assessed.

The following 6 cohorts were enrolled in this study (cohorts 1, 3, and 6 were discontinued):

1. Cohort 1: Low dose DUOBRII (HP 0.01% and Taz 0.045%) lotion, QD x 6 weeks
2. Cohort 2: Low dose DUOBRII (HP 0.01% and Taz 0.045%) lotion, QD x 8 weeks
3. Cohort 3: High dose DUOBRII (HP 0.025% and Taz 0.045%) lotion, QD x 6 weeks
4. Cohort 4: High dose DUOBRII (HP 0.025% and Taz 0.045%) lotion, QD x 8 weeks
5. Cohort 5: Ultravate (HP 0.05%) cream, QD x 2 weeks
6. Cohort 6: Tazarotene (Taz 0.1%) cream, QD x 8 weeks

At the end of treatment, the percentage of subjects with HPA axis suppression was lowest (20%) in Cohort 2 (Low dose DUOBRII, treated for 8 weeks with to-be-marketed formulation), compared to (50%) in cohort 4 (High dose DUOBRII, treated for 8 weeks), and (45%) in cohort 5 (Ultravate 0.05%, treated for 2 weeks). This study was conducted in subjects with affected BSA = 10% - 20%, while DUOBRII is planned for use in subjects with affected BSA ≤ 12%, with anticipated reduced exposure and lower incidence of HPA axis suppression. The results are presented in table below:

Table 30: Summary of HPA Axis Suppression by Visit (Safety)

Study DPSI-IDP118-P2-01			N (%) of subjects with abnormal HPA axis suppression test				
Cohort	N	Weeks	screening	Week 2	Week 4	Week 6	Week 8
#1	6	6	2	1(17)		3(50)	
#2	13	8	0		3(23)		2(20)
#3	5	6	1	2(40)	3 (60)	4(80)	
#4	11	8	0		5(45)		5(50)
#5	11	2	0	5(46)			0
#6	5	8	1	1(20)	0		0

Note: HPA axis suppression was defined as a plasma cortisol level 30 minutes after Cortrosyn® administration < 18 ug/dL. Source: modified from applicant's submission, Study DPS-IDP118-P2-01 CSR, Table 12-9, p. 88.

Reviewer's comment:

The results of this study suggest that a lower proportion of subjects (20%) treated with low-dose (to-be-marketed formulation) of DUOBRII, compared to subjects treated with the high-dose DUOBRII formulation (50%), had HPA axis suppression at 8 weeks.

The *proportion of subjects treated with low-dose DUOBRII, with HPA axis suppression at 8 weeks (20%), was less than half of the proportion of subjects treated with Ultravate cream for 2 weeks (46%).*

Comparison of the results of studies -501 and P201 shows highly variable rates of abnormal HPA axis suppression test results in subjects treated with DUOBRII lotion for a period of 8 weeks.

7.3.6. Safety Analyses by Demographic Subgroups

The safety population (combined Phase 3 trials -301 and -302), included 270 subjects treated with DUOBRII lotion.

Race:
Because the majority of subjects were white (84%), no meaningful conclusions could be drawn by comparing incidences of AEs among racial subgroups.

Age:
Examination of TEAEs by age (≤ 65 years and > 65 years of age) did not reveal any clinically significant age-related differences in the incidence of TEAEs. Of the 270 subjects, 37 (14%) were > 65 years of age, and 233 (86%) were 65 years of age or younger (by this reviewer's analysis). The applicant's subgroup analysis, based on age groups of < 51 years of age and ≥ 51 years of age, was consistent with the same findings. The small number of TEAEs made comparisons of the incidence between different age subgroups not clinically meaningful.

Gender:
Examination of TEAEs by gender did not reveal any significant gender-related differences in the incidence of TEAEs. The safety population included 171 (63%) male and 99 (37%) female subjects. The results are listed in the following table:

Table 31: Summary of TEAEs (in ≥ 2% of Subjects) in DUOBRII lotion Group by Gender, Through Week 8 (Safety Population, Combined Trials -301, -302)

Preferred Term	Male (N=171), N (%)	Female (N=99), N (%)
Dermatitis contact	14 (8.2)	6 (6.1)
Pruritus	4 (2.3)	4 (4.0)
Skin atrophy	3 (1.8%)	2 (2.0%)
Psoriasis	4 (2.3%)	0
Rash	2 (1.2%)	2 (2.0%)
Nasopharyngitis	2 (1.2%)	3 (3.0%)
Upper respiratory tract infection	2 (1.2%)	3 (3.0%)
Folliculitis	3 (1.8%)	2 (2.0%)
Sinusitis	1 (0.6%)	2 (2.0%)
Excoriation	5 (2.9%)	0
Application site pain	3 (1.8%)	4 (4.0%)
Pain	0	2 (2.0%)
Burning sensation	1 (0.6%)	3 (3.0%)
Seasonal allergy	0	2 (2.0%)

Source: Applicant's submission, modified from ISS Table 14.3.1.2.3.3. MedDRA version 18.0.

7.3.7. Specific Safety Studies/Clinical Trials

Clinical photosafety studies:

(b) (4) The applicant submitted UV-visible spectra and in-vitro phototoxicity study (V01-118A-607) results for DUOBRII lotion, Tazorac cream, 0.1%, Tazarotene, 0.045% monad lotion, and DUOBRII vehicle lotion (b) (4). The absorption spectra evaluation of the drug product and its components showed light absorption in the 290-700 nm wavelength.

Reviewer's comment:
Because DUOBRII lotion absorbs light in the 290-700 nm range, (b) (4) .

This reviewer recommends that the applicant conduct phototoxicity and photoallergenicity studies for DUOBRII lotion.

Clinical dermal safety studies:

The applicant conducted two Phase 1, provocative dermal safety studies in healthy adult subjects (V01-118A-102 and V01-118A-103) with the to-be-marketed formulation to support the dermal safety of DUOBRII lotion. The trials evaluated the potential of DUOBRII lotion for irritation and sensitization. The results are presented in this section.

Study V01-118A-102 (Cumulative irritancy patch test)

This study was a 21-day, randomized, controlled, evaluator-blinded, within-subject study to evaluate the skin irritation potential of DUOBRII lotion in healthy adult male and female subjects ≥ 18 years of age. Forty (40) subjects were randomized and 36 subjects completed the study.

Each subject received 0.2 mL per patch of each of the following test drugs: DUOBRII lotion, IDP-122 lotion (Halobetasol propionate, 0.01% lotion), Vehicle lotion, Tazarotene cream, 0.05%, 0.5% SLS (positive control), 0.9% saline (negative control).

Semi-occlusive patches were applied to one side of the infrascapular area of each subject once daily for 21 consecutive days (21 applications). Dermal reactions at the application sites were assessed daily, before each patch application, using a visual scale for erythema, edema, and irritation. The actual patch test grades were calculated as the sum of numerical grades and letter grades (converted to numerical equivalents), according to the following tables:

Table 32: Integer Grading scale of Dermal Response

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

Table 33: Effects on Superficial Layers of the Skin

Symbol	Numerical Equivalent	Response
A	0	Slight glazed appearance
C	1	Marked glazing
E	2	Glazing with peeling and cracking
F	3	Glazing with fissures
G	3	Film of dried serous exudate covering all or portion of the patch
H	3	Small petechial erosions and/or scabs

Source: Applicant's submission, protocol V01-118A-102, Tables 9-1 and 9-3.

Results:

Under the exaggerated conditions of this dermal provocative irritancy study, The DUOBRII lotion showed evidence of irritation (categorized by investigators as slightly irritating), but was less irritating than Tazorac cream, 0.05%. DUOBRII lotion was more irritating than 0.5% SLS, 0.9% Saline, vehicle lotion, and IDP-122 lotion. The results are summarized in the following table:

Table 34: Summary of Mean and Total Irritation Scores (Safety Population, DUOBRII Lotion)

Study -102 (N=40)	Mean (SD) Irritation Score	Total Irritation Score: Mean(SD)
Tazorac Cream	0.56 (0.45)	11.60 (9.60)
DUOBRII Lotion	0.36 (0.36)	7.55 (7.53)
0.5% SLS	0.23 (0.26)	4.73 (5.49)
0.9% Saline	0.04 (0.12)	0.88 (2.62)
Vehicle Lotion	0.03 (0.07)	0.63 (1.41)
IDP-122 Lotion	0.01 (0.04)	0.30 (0.76)

Source: Applicant's submission, protocol V01-118A-102, Table 14.2.2.1

Two subjects experienced 4 TEAEs. One subject had cough and one subject had 3 TEAEs related to dental surgeries. All TEAEs were mild and unrelated to the study drugs.

Reviewer's comment:
The results of this cumulative irritancy study show that DUOBRII lotion is irritating. This reviewer recommends this information be included in the label.

Study V01-118A-103 (RIPT):

This study was a 6-week, randomized, controlled, evaluator-blinded, within-subject comparison study of sensitization potential of DUOBRII lotion and IDP-122 (halobetasol propionate, 0.01%) lotion using a repeat insult patch test (RIPT) design.

Two hundred forty-four (244) healthy male and female subjects, 18-years of age or older, were randomized. Two hundred and twenty (220) subjects completed the induction phase, and 208 subjects completed the challenge phase of study. A rechallenge Phase was not performed in this study.

Each subject received a total of 10 applications of each of the following solutions (0.2 mL of each test drug was applied to semi-occlusive patches): DUOBRII lotion, IDP-122 lotion, Vehicle lotion, 0.9% Saline (negative control).

During the induction phase of the study, patches were applied to randomly assigned, adjacent sites on the infrascapular areas of the subjects on Mondays, Wednesdays, and Fridays of 3 consecutive weeks (9 applications) and remained in place until removed and the next patch was applied. Dermal reactions were assessed using a visual scale, similar to the scale used for study -102, after each patch removal and prior to application of an identical patch to the same patch site. A 10 to 14-day rest period (with no patch application) followed the completion of the induction phase, prior to the start of the challenge phase.

During the challenge phase, a 48-hour application of each test patch was performed at a naïve site on the opposite side of the subjects' infrascapular areas. Test sites were evaluated, using the same dermal irritation scoring grade used in the induction phase, at 30 minutes, 24-hours, 48-hours, and 72-hours after patch removal. During this phase, no subject had a score of > 1, and no subject required a rechallenge.

Thirty subjects (12.3%) had 43 TEAEs. The applicant considered none as related to study drugs. Five (5) SAEs occurred in 3 subjects: Subject (b) (6)) experienced lower abdominal pain, dehydration, and vomiting. Subject (b) (6)) experienced pyelonephritis. Subject (b) (6)) experienced colitis. All SAEs resolved and the investigators considered none as related to study drugs.

Reviewer's comment:
This reviewer agrees with the applicant's conclusion of that DUOBRII lotion did not

show potential for skin sensitization in this study.

7.3.8. Additional Safety Explorations

Not applicable.

Human Carcinogenicity or Tumor Development

One event of malignant melanoma was identified in the Ultravate arm of the trial P201. Given the short duration of treatment, it is this reviewer's opinion that the study drug was not a causative agent.

Pediatrics and Assessment of Effects on Growth

Clinical studies were conducted only in adults. Because DUOBRII is a new fixed-combinations product, This NDA is required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients, under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c).

On 6/16/2016, the Division agreed to the Agreed initial pediatric study plan (Agreed iPSP) submitted by the sponsor, following a Pediatrics Review Committee (PeRC) meeting held on 6/8/2016. The Agreed iPSP included the following:

- Partial waiver to conduct PK and clinical safety studies for children from 0 to less than (b) (4) years of age. The prevalence of moderate to severe psoriasis in pediatric population in this age group is low. Therefore, studies in psoriasis patients less than (b) (4) years of age would be impossible or highly impracticable (Section 505B (a)(4)(B)(i) of the Act).

- Deferral to conduct PK/HPA axis suppression studies for children from (b) (4) to Less than 17 years of age.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable to this review.

7.3.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

DUOBRII lotion has not been marketed in any country. Therefore, postmarketing safety data are not available.

Expectations on Safety in the Postmarket Setting

Analysis of safety data did not identify any safety signals. There are no safety concerns that are expected to change the favorable benefits/risk assessment or lead to increased risk for DUOBRII lotion in the postmarket setting. However, additional safety data is required to characterize the safety profile of DUOBRII lotion in the pediatric population.

7.3.10. Integrated Assessment of Safety

The safety profile for DUOBRII lotion was adequately characterized during the drug development program. The primary safety database included 270 subjects from the Phase 3 trials (-301 and -302) treated with DUOBRII lotion, once daily for 8 weeks. In the long-term safety trial (-303), of the 550 subjects treated with DUOBRII lotion, 391 completed 6 months and 138 completed 12 months of treatment.

There was one death reported during the DUOBRII development program, in a subject treated with vehicle lotion in the Phase 2 trial, -201.

During the Phase 3 trials (-301 and -302), SAEs occurred in 1.1% of subjects treated with DUOBRII lotion, compared to no subjects in the vehicle group.

During the Phase 3 trials (-301 and -302), adverse reactions (AR)s occurred in 20.4% of subjects in the DUOBRII lotion group, compared to 7.9% of subjects in the vehicle lotion group. The most common ARs in subjects treated with DUOBRII lotion were contact dermatitis (6.3%), application site pain (2.6%), skin atrophy (1.9%), folliculitis (1.9%), rash (1.5%), and excoriation (1.1%).

The effect of DUOBRII on pregnant or lactating women are unknown. Pregnant or lactating women were excluded from participation in any clinical studies for DUOBRII lotion. Two pregnancies occurred during the development program:

- In trial -303, one subject had a positive urine pregnancy test and discontinued treatment. The outcome of this pregnancy was reported as a spontaneous abortion.
- In study -103, one subject had a positive urine pregnancy test at the end of the study visit. The subject underwent elective termination of her pregnancy.

7.4. Summary and Conclusions

7.4.1. Statistical Issues

There were no major statistical issues affecting overall conclusions. The treatment effects were generally consistent across trials and endpoints. There were no substantial differences in efficacy among subgroups. For handling of missing data, the results were similar across the various methods investigated to impute the missing data (see Table 13).

7.4.2. Conclusions and Recommendations

To establish the effectiveness of DUOBRII, the applicant submitted data from two identically-designed, randomized, multicenter, vehicle-controlled, parallel-group, pivotal Phase 3 trials (Trials 301 and 302). The trials enrolled subjects 18 years of age and older with a clinical diagnosis of plaque psoriasis with body surface area (BSA) involvement of 3% to 12% (excluding the face, scalp, palms, soles, axillae and intertriginous areas) and an Investigator's Global Assessment (IGA) score of 3 (moderate) or 4 (severe). The protocol-specified primary efficacy endpoint was the proportion of subjects achieving treatment success at Week 8, where success was defined as an IGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline. The protocol specified evaluating treatment success at Weeks 2, 4, 6, and 12 (4 weeks after end of treatment) as secondary efficacy endpoints.

In both trials, DUOBRII was statistically superior to placebo (p-values < 0.001) for the primary efficacy endpoint at Week 8, see Section 7.2.4. DUOBRII lotion was statistically superior to vehicle lotion for treatment success at Weeks 4, 6 and 12 in both trials (p-values ≤ 0.008). While DUOBRII lotion was statistically superior to vehicle lotion at Weeks 2 in Trial 302 (p-value = 0.004), it was not statically superior to vehicle lotion in Trial 301 (p-value = 0.098), see Section 7.2.5.

Efficacy data submitted by the applicant support approval of this NDA for DUOBRII lotion, for the treatment of adults with plaque psoriasis.

To support the safety of DUOBRII lotion, the applicant pooled data from the two Phase 3 trials, -301 and -302. The applicant conducted a comprehensive assessment of the safety of DUOBRII lotion in the target population. The size of the safety database and the safety evaluations were adequate to identify common treatment-emergent adverse reactions.

However, the applicant did not establish a PK bridge / clinical bridge to the listed drugs. Therefore, the applicant can not rely on the Agency's finding of safety for the listed drugs via the 505 (b)(2) regulatory pathway, and thus the applicant has not addressed the safety of their product with regard to the risk of carcinogenicity, mutagenicity, and reproductive toxicity. These deficits are not remedied by the clinical trial data.

A **Complete Response** for this NDA is recommended, based on 21 CFR §314.125(b)(4), i.e., there is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling.

8 Advisory Committee Meeting and Other External Consultations

The Agency did not hold an Advisory Committee Meeting for this application.

9 Pediatrics

Refer to Section 7.3.8 of this review, Pediatrics and Assessment of Effects on Growth, for a discussion regarding the Pediatric Study Plan.

10 Labeling Recommendations

10.1. Prescribing Information

This application is recommended for Complete Response. Further discussions regarding labeling will not be conducted during this review cycle.

10.2. Patient Labeling

Refer to Section 10.1 of this review.

11 Risk Evaluation and Mitigation Strategies (REMS)

REMS are not applicable to this review.

11.1. Safety Issue(s) that Warrant Consideration of a REMS

Not applicable to this review.

11.2. Conditions of Use to Address Safety Issue(s)

Not applicable to this review.

11.3. Recommendations on REMS

Not applicable to this review.

12 Postmarketing Requirements and Commitments

Not applicable to this review.

13 Appendices

13.1. References

The references are included in footnotes.

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 for DUOBRII lotion. 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 Trial 118A-301, 118A-302, and 118A-201 which provided the primary data to establish effectiveness and safety of this product. Refer to Section 7.2.1 for the trial designs.

A total of one investigator from Trial 118A-301, one investigator from Trial 118A-302, and two investigators from Trial 118A-201 had disclosable financial interests and arrangements as listed in the following table:

Investigator	Study 118A-301	Study 118A-302	Study 118A-201
(b) (6)			

The applicant adequately disclosed financial interests involving clinical investigators. Because the number of investigators with financial disclosures was limited and assessments were blinded, the strategies employed by the applicant to minimize potential bias arising from investigator financial interests/arrangements appear reasonable.

Covered Clinical Study: 118A-301

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 50		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		

If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study: 118A-302

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 34		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)

Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study: 118A-201

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 43		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

13.3. Clinical/Biostatistics

Table 35: Investigator's Global Assessment (IGA) Scale

Grade	Score	Description
Clear	0	No evidence of scaling No evidence of erythema No evidence of plaque elevation above normal skin level
Almost Clear	1	Some plaques with fine scales Faint pink/light red erythema on most plaques Slight or barely perceptible elevation of plaque above normal skin level
Mild	2	Most to all plaques have some fine scales but are not fully covered, some plaques are completely covered with fine scale Most to all plaques are pink/light red to bright red in color Some plaques have definite elevation above normal skin level, typically with edges that are indistinct and sloped on some of the plaques
Moderate	3	Some plaques are at least partially covered with a coarse scale, most to all plaques are nearly covered with fine or course scale Most to all plaques are bright red, some plaque may be dark red in color Definite elevation of most to all plaques; rounded or sloped edges on most of the plaques
Severe	4	Most to all plaques are covered with coarse, thick scales Most or all plaques are bright, dark or dusky red Almost all plaques are raised and well-demarcated; sharp edges on virtually all plaques

Source: protocols for Trials 301 and 302

Table 36: Psoriasis Signs

Score	Grade	Description
Erythema:		
0	None	No erythema
1	Minimum	Pink discoloration, minimal erythema
2	Mild	Most plaques are light red to red in color
3	Moderate	Most or all plaques are bright red or dark red in color
4	Severe	Most plaques dusky red with purple hue
Plaque Elevation:		
0	None	No evidence elevation above the normal skin level
1	Minimum	Slight, just discernible elevation above normal skin level
2	Mild	Some plaques show definite elevation with indistinct edges
3	Moderate	Most plaques have definite elevation with distinct edges that are rounded or sloped
4	Severe	Almost all plaques are raised above normal skin level with sharp edges
Scaling:		
0	None	No scales on very few plaques
1	Minimum	Occasional fine scales hardly noticeable
2	Mild	Most plaques have fine scales
3	Moderate	Some plaques have coarse scales while most plaques have fine scales
4	Severe	Most plaques are covered by thick coarse scales

Source: protocols for Trials 301 and 302

13.4. Nonclinical Pharmacology/Toxicology

Literature References

1. (b) (4)

2. Duvic M, Nagpal S, Asano A T, and Chandraratna R A S. Molecular mechanisms of tazarotene action in psoriasis. Journal of the American Academy of Dermatology 1997; 37: S18 – S24.

3. Norris D A. Mechanisms of action of topical therapies and the rationale for combination therapy. Journal of the American Academy of Dermatology 2005; 53: S17 – S25.

4. Sebok B, Bonnekoh B, Kerenyib M, and Gollnicka H. Tazarotene Induces Epidermal Cell Differentiation in the Mouse Tail Test Used as an Animal Model for Psoriasis. Skin Pharmacology and Applied Skin Physiology 2000; 13:285-291.

5. Tadicherla S, Ross K, Shenefelt P D, and Fenske N A. Topical corticosteroids in dermatology. 2009; 8:1093 – 1105.

6. Yawalkar S, Wiesenberg-Boettcher I, Gibson J R, Siskin S B, and Pignat W. Dermatopharmacologic investigations of halobetasol propionate in comparison with clobetasol 17-propionate. Journal of the American Academy of Dermatology 1991; 25: 1137 – 1144.

13.5. OCP Appendices (Technical documents supporting OCP recommendations)

13.5.1. Summary of Bioanalytical Method Validation and Performance

13.5.2. PK assays: Methods for determination of halobetasol propionate, tazarotene, and tazarotenic acid

The concentrations of halobetasol propionate, tazarotene, and tazarotenic acid in PK plasma samples from the maximal use PK/relative bioavailability trial V01-118A-501 were measured using adequately validated high performance liquid chromatography and tandem mass spectrometry (LC-MS/MS) assays. The assay validation results are summarized in Table 37.

Table 37: Validation results of the LC-MS/MS bioanalytical methods used for measuring plasma concentrations of halobetasol propionate, tazarotene, and tazarotenic acid in Study V01-118A-501.

Analytes	Halobetasol Propionate	Tazarotene	Tazarotenic acid
Matrix	K_2EDTA Plasma	K_2EDTA Plasma	K_2EDTA Plasma
Standard curve assay range	50.0 to 12800 pg/mL	5.00 to 2500 pg/mL	5.00 to 2500 pg/mL
Intra-run precision	11.6 to 18.6% (LLOQ); 1.3 to 6.3% (above LLOQ)	7.1 to 11.7% (LLOQ); 1.7 to 9.3% (above LLOQ)	4.6 to 13.8% (LLOQ); 1.1 to 8.9% (above LLOQ)
Intra-run accuracy	-8.0 to 6.7% (LLOQ); 0.4 to 6.5% (above LLOQ)	-15.7 to 4.0% (LLOQ); -4.8 to 0.5% (above LLOQ)	-9.0 to 11.2% (LLOQ); -5.2 to -0.2% (above LLOQ)
Inter-run precision	15.1% (LLOQ); 3.0 to 5.2% (above LLOQ)	12.4% (LLOQ); 2.9 to 6.2% (above LLOQ)	13.2% (LLOQ); 3.4 to 6.6% (above LLOQ)
Inter-run accuracy	-0.2% (LLOQ); 1.1 to 4.8% (above LLOQ)	-7.5% (LLOQ); -2.6 to -0.6% (above LLOQ)	-0.6% (LLOQ); -3.8 to -1.8% (above LLOQ)
Freeze/thaw matrix stability	4 cycles at -20 °C and -70 °C;	4 cycles at -20 °C and -70 °C;	4 cycles at -20 °C and -70 °C;
Room temperature stability	9.25 hours	6.5 hours	6.5 hours
Processed-sample viability	2 day 20 hr at room temperature and refrigerated	3 day 21 hr at room temperature and refrigerated	3 day 21 hr at room temperature and refrigerated
Long term stability	448 days at -20°C and -70°C (the maximum sample storage time was 351 days at -20 °C or	330 days at -20°C and -70°C (the maximum sample	330 days at -20°C and -70°C (the maximum sample

	below)	storage time was 182 days at -20 °C or below)	storage time was 182 days at -20 °C or below)
Incurred sample reanalysis (ISR)	97% of 121 ISR samples (~10% of total) met the criteria of reproducibility (i.e., difference within ± 20% of average of original and repeat value).	97% of 94 ISR samples (~ 10% of total) met the criteria of reproducibility.	100% of 103 ISR samples (~ 11% of total) met the criteria of reproducibility.

13.5.3. Assay for serum cortisol levels

The analysis of serum cortisol samples from the maximal use pivotal study V01-118A-501 was conducted by (b) (4) using a commercially available Siemens Cortisol assay (a competitive immunoassay, 510k reference (b) (4)) on Siemens Advia Centaur XP platforms.

In response to Agency's information request, the applicant provided analytical reports and additional sample stability data. The assay measures serum cortisol concentration from 0.50 -75 µg/dL. The overall accuracy and precision ranged from -6.5% to 2.8% and from 1.62% to 5.45%, respectively. The ambient and refrigerated stability was 10 days; the frozen storage stability was 234 days. Four out of 422 cortisol serum samples from study V01-118A-501 were analyzed outside the 10-day stability window; however, these samples were stored and shipped frozen and analyzed within the manufacturer's recommended storage limit of four weeks which was within the established frozen storage stability of 234 days. Therefore, all samples were analyzed within the period with established storage stability.

13.5.4. Individual Study Reports

(Reviewer's note: Halobetasol propionate and tazarotene lotion, 0.01%/0.045% was referred to as IDP-118 Lotion, a name during development, in the below. The study results of another investigational drug IDP-122 Lotion will not be discussed in this NDA review).

13.5.5. Trial V01-118A-501

Title: Phase 1b Open-Label, Randomized Study Evaluating the Absorption and Systemic Pharmacokinetics and HPA Axis Suppression Potential of Topically Applied IDP-118 Lotion and HP Monad Lotion in Subjects with Moderate to Severe Plaque Psoriasis

Dates of the Study:
Date of first subject enrollment: 22 Dec 2015
Date of last subject completed: 03 Feb 2017

Objectives:
To evaluate the following in adult subjects with moderate to severe plaque psoriasis:

- Safety of IDP-118 Lotion and IDP-122 Lotion administered topically once daily for 8 weeks
- Systemic exposure of Halobetasol propionate (HP), tazarotene (Taz), and tazarotenic acid after administration of IDP-118 Lotion when applied once daily for 4 weeks compared with that of Ultravate Cream, 0.05% (with HP as the active ingredient) applied for 2 weeks and Tazorac Cream, 0.05% (with Taz as the active ingredient) applied for 4 weeks

- Systemic exposure of HP after administration of IDP-122 Lotion when applied once daily for 4 weeks compared with that of Ultravate Cream applied for 2 weeks
- Comparison of the HPA axis suppression potential for IDP-118 Lotion and IDP-122 Lotion when applied once daily for 8 weeks and Ultravate Cream when applied once daily for 2 weeks.

Methods:

This was a multicenter, open-label, randomized study. The study enrolled subjects who were at least 18 years of age and had a clinical diagnosis of moderate to severe plaque psoriasis (defined as an Investigator's Global Assessment [IGA] score of 3 or 4 graded on a scale ranging from 0 [clear] to 5 [very severe]), with at least 20% treatable BSA involvement of the disease at the Baseline visit. The investigator determined the selected areas to be treated with study drug (the face, scalp, axillae, and intertriginous areas were not included in this calculation) and assessed the extent of psoriasis involvement as a percentage of the subject's total BSA.

Approximately 90 subjects who met the study entry criteria were to be randomized in a 1:1:1:1 ratio to 1 of 4 treatment groups as follows:

- Investigational Drug Product 1: IDP-118 Lotion applied once daily for 8 weeks
- Investigational Drug Product 2: IDP-122 Lotion applied once daily for 8 weeks
- Comparator 1: Ultravate Cream, 0.05% applied once daily for 2 weeks
- Comparator 2: Tazorac Cream, 0.05% applied once daily for 4 weeks

The study visits included the following:

- Screening (Day -50 to 0), Day 1 (Baseline), Day 2, Day 14, and Day 15 (all groups)
- Day 28, Day 29 (IDP-118 Lotion, Tazorac Cream, and IDP-122 Lotion groups)
- Day 57 (IDP-118 Lotion and IDP-122 Lotion groups)

The investigator/evaluator assessed the overall severity of a subject's psoriasis (using the IGA) at Screening (Day -50 to 0), Baseline (Day 1), Day 14, Day 28, and Day 57 during the study period, as appropriate for each treatment group. The face, scalp, axillae, and intertriginous areas were to be excluded from this assessment. Any reported adverse events were recorded at each visit during the study period.

PK assessment:
Plasma samples for PK analysis were collected on Days 1, Days 14, and Days 28 at the following time points: predose, and at 1, 2, 4, 8 (± 15 minutes), 12 (± 30 minutes), and 24 hours (± 60 minutes) postdose. Note the Ultravate Cream group did not have plasma collected at Day 28. Plasma concentrations of HP, Taz, and tazarotenic acid (as appropriate for each treatment group) were analyzed using LC-MS/MS assays described in Section 13.4.1.1.

Plasma concentrations of HP, Taz, and tazarotenic acid (as appropriate for each treatment group) at each sampling time point were summarized for the PK population using descriptive statistics. The PK parameters were calculated from the individual plasma concentrations. Area under the concentration-time curve from time zero up to the sampling time corresponding to the last quantifiable concentration, $AUC_{(0-t)}$ calculated using the linear trapezoidal rule was calculated *if at least three consecutive quantifiable plasma concentrations were detected in the time interval*.

HPA suppression assessment:
Subjects were tested for HPA axis function using the adrenocorticotropin (ACTH) stimulation test (0.25 mg cosyntropin injected intravenously or intramuscularly), for Ultravate Cream at Screening and Day 15, and for IDP-118 Lotion and IDP-122 Lotion at Screening, Day 29, and Day 57. Subjects were to be in the normal range for adrenal function, defined as a cortisol level of > 18 µg/dL, after stimulation with Cosyntropin at the Screening visit. Adrenal function testing was not to occur at less than 4-week intervals. It was, therefore, recommended that the testing be performed 2 weeks prior to the Baseline visit. The serum concentrations of cortisol were analyzed using an assay described in Section 13.4.1.2.

Product and dose:
The batch numbers of the investigational products are shown in Table 38. Topical application of approximately 7 g per day (a cupful) of study drug was made to the identified minimum 20% BSA treatment area (excluding face, scalp, axillae, and intertriginous areas) once a day for a period of 2 weeks (Ultravate Cream), 4 weeks (Tazorac Cream), or 8 weeks (IDP-118 Lotion or IDP-122 Lotion). Sponsor-provided disposable dosing cups were supplied to the subject. The study drug was applied as a thin layer, enough to cover the entire affected area, and was gently rubbed into the skin. The subjects applied the drug to investigator-defined area throughout the study, even if psoriasis cleared. Subjects applied their daily treatments at home, except on the days of on-treatment study visits to the clinic (i.e., Baseline [Day 1], and Days 2, 14, 15, 28, and 29, as applicable for each treatment group). At these study visits, the study drug was applied at the clinic.

All subjects, irrespective of treatment group, were instructed to return their dispensed tubes to each subsequent study visit. Each tube was weighed (with the cap on) by a study coordinator or designee prior to dispensation and after collection at each study visit. Subjects were also asked to complete a diary calendar and questioned regarding their study drug use since the previous visit to assess subject compliance with study drug application.

Results:
There were two discrepancies between randomized treatment and treatment received. Subject (b) (6) was randomized to IDP-122 Lotion, but received IDP-118 Lotion and subject (b) (6) was randomized to IDP-118 Lotion, but received Ultravate Cream. Results below are summarized based on treatment received.

Table 38: The identity of IDP-118 Lotion and the comparator drugs used in Study V01-118A-501.

Product	Batch No.
IDP-118 Lotion	8083850
Ultravate Cream, 0.05%	94614
Tazorac Cream, 0.05%	89121

Demographics:
Demographic characteristics in the PK population were similar between the treatment groups (Table 39). In the PK population, across the treatment groups of IDP-118 Lotion and the comparator drugs, the mean age ranged from 48.7 to 49.8 years. A majority of subjects were White and male.

Table 39: Summary of subject demographic characteristics (PK population) in the treatment groups of IDP-118 Lotion and the comparator drugs in Study V01-118A-501.

	IDP-118 Lotion (N=22)	Tazorac Cream (N=24)	Ultravate Cream (N=23)
Age (years)			
N	22	24	23
Mean	48.7	49.8	49.2
SD	10.75	14.02	14.39
Median	47.0	53.0	47.0
Min. to Max.	32 to 69	20 to 75	27 to 77
Sex			
N	22	24	23
Male	17 (77.3%)	19 (79.2%)	18 (78.3%)
Female	5 (22.7%)	5 (20.8%)	5 (21.7%)
Ethnicity			
N	22	24	23
Hispanic or Latino	10 (45.5%)	12 (50.0%)	13 (56.5%)
Not Hispanic or Latino	12 (54.5%)	12 (50.0%)	10 (43.5%)
Race			
N	22	24	23
American Indian or Alaska Native	0 (0.0%)	0 (0.0%)	0 (0.0%)
Asian	0 (0.0%)	1 (4.2%)	0 (0.0%)
Black or African American	2 (9.1%)	1 (4.2%)	1 (4.3%)
Native Hawaiian or Other Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)
White	19 (86.4%)	21 (87.5%)	21 (91.3%)
Other/Multiple	1 (4.5%)	1 (4.2%)	1 (4.3%)

Source: study report Table 12.

Baseline disease chracteristics were similar across the treatment groups (Table 40). The BSA affected by psoriasis ranged between 20% and 68%, with a median of 24.0% to 25.0% across the treatment groups of IDP-118 Lotion and the comparator drugs. The majority of subjects had psoriasis of moderate severity. All subjects had normal ACTH stimulation test results at Screening.

Table 40: Summary of baseline disease characteristics (PK Population) in the treatment groups of IDP-118 Lotion and the comparator drugs in Study V01-118A-501.

	IDP-118 Lotion (N=22)	Tazorac Cream (N=24)	Ultravate Cream (N=23)
% BSA Affected by Psoriasis in the Allowed Treatment Areas			
N	22	24	23
Mean	26.4	30.1	30.8
SD	7.17	12.36	13.29
Median	25.0	24.0	25.0
Min. to Max.	20 to 52	20 to 62	20 to 68
Investigator's Global Assessment			
N	22	24	23
0 - Clear	0 (0.0%)	0 (0.0%)	0 (0.0%)
1 - Almost Clear	0 (0.0%)	0 (0.0%)	0 (0.0%)
2 - Mild	0 (0.0%)	0 (0.0%)	0 (0.0%)
3 - Moderate	17 (77.3%)	17 (70.8%)	18 (78.3%)
4 - Severe	5 (22.7%)	7 (29.2%)	5 (21.7%)
HPA Axis Suppression Test (Screening)			
N	22	24	23
Normal	22 (100.0%)	24 (100.0%)	23 (100.0%)
Abnormal	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: study report Table 14.

Dosing:

A summary of number of applications and amount of study drug used are summarized in Table 41. Taking all the weigt measurements into acount, the median amount of drug used during the study period was 424.25 g, 219.80 g and 121.20 g, respectively, in the 8-week treatment group with IDP-118 Lotion, the 4-week treatment group with Tazorac Cream, and the 2-week treatment group with Ultravate Cream.

Table 41: Summary of dose application data (PK Population) in the treatment groups of IDP-118 Lotion and the comparator drugs in Study V01-118A-501.

	IDP-118 Lotion (N=22)	Tazorac Cream (N=24)	Ultravate Cream (N=23)
Amount of Study Drug Used (g)[a]			
N	13	15	14
Mean	463.58	235.12	115.10
SD	93.086	50.423	37.012
Median	500.30	230.10	112.25
Min. to Max.	319.1 to 615.7	149.3 to 329.5	64.7 to 207.0
Minimum Amount of Study Drug Used (g)[b]			
N	22	24	23
Mean	405.96	216.04	116.91
SD	134.452	59.013	34.783
Median	424.25	219.80	121.20
Min. to Max.	99.0 to 615.7	106.3 to 329.5	40.5 to 207.0
Number of Applications			
N	22	24	23
Mean	51.6	27.8	14.4
SD	8.78	3.69	0.66
Median	56.0	28.0	14.0
Min. to Max.	29 to 57	13 to 37	14 to 16

Source: study report Table 14.3.0.2.3.
[a] Summary is restricted to subjects with an initial dispense weight and final return weigh for all dispensed tubes of study drug.

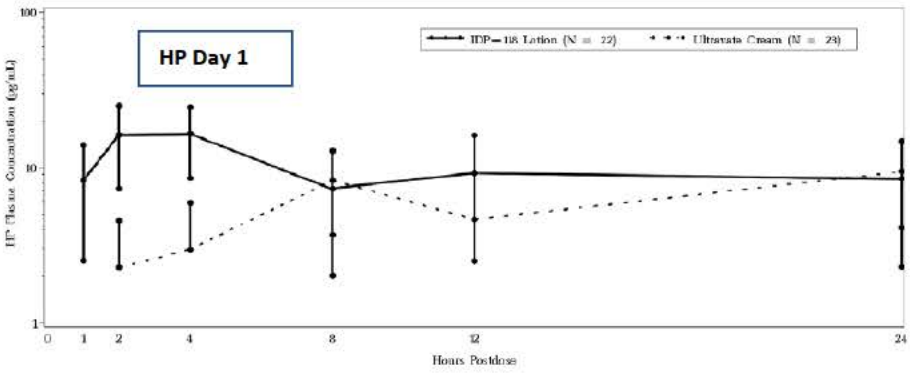
[b] Summary includes all subjects with at least one tube of study drug with two or more recorded weights. Minimum amount of study drug used is calculated by taking the difference between the maximum and minimum recorded weights for each tube of study drug, then summing across all tubes of study drug that have at least two recorded weights for each subject.

PK results: Tazarotenic acid was measurable in all collected PK samples (> LLOQ of 5 pg/mL) while HP and tazarotene were below the limit of quantification (BLQ) in many of the collected PK samples (LLOQ of 50 pg/mL and 5 pg/mL, respectively).

Pharmacokinetics of HP: The majority of samples taken on Day 1 had no measurable plasma concentration of HP. Among the Day 1 PK samples, 5/22 subjects in the IDP-118 Lotion group had at least one measurable concentrations with maximum value of 705 pg/mL; 5/23 subjects in the Ultravate Cream group had at least one measurable concentrations with maximum value of 102 pg/mL. On Day 14, the number of subjects who had measurable concentrations of HP doubled in both treatment groups (13/22 and 12/23 in IDP-118 Lotion group and Ultravate Cream, respectively).

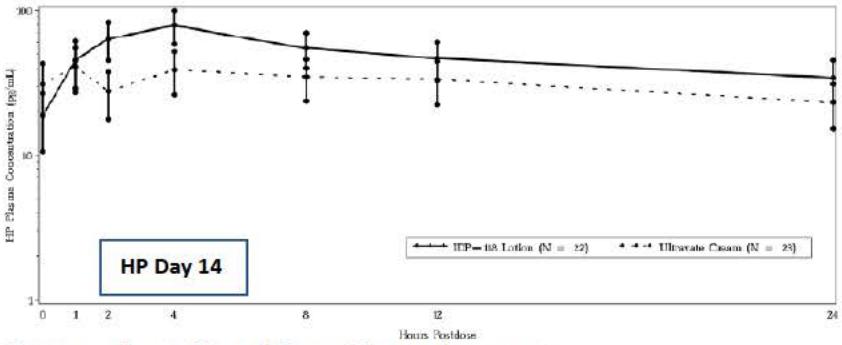
The mean HP plasma concentrations-time profiles of IDP-118 lotion with the comparator Ultravate Cream on Days 1, 14, and 28 (IDP-118 lotion only) are provided in Figure 8, Figure 9, and Figure 10, respectively.

Figure 8: Semi-Logarithmic plots of mean HP plasma concentrations (+/- standard errors) for IDP-118 Lotion and Ultravate Cream groups following dose administration on Day 1 (PK Population)



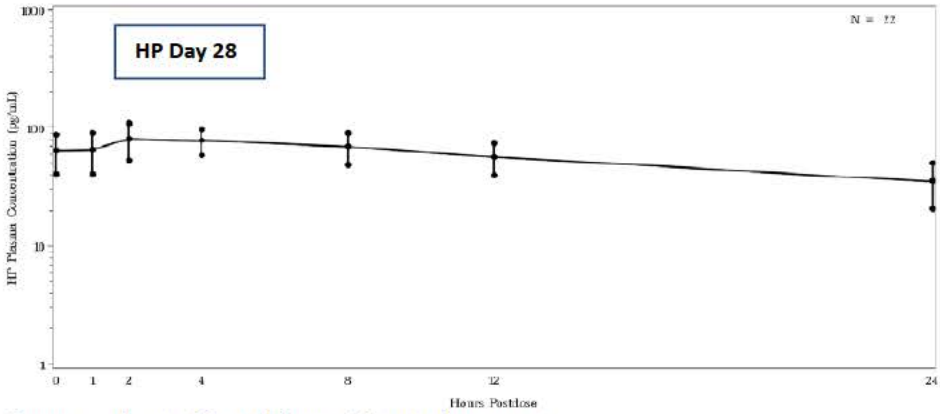
Source: adapted from Figure 1 in study report.

Figure 9: Semi-Logarithmic plots of mean HP plasma concentrations (+/- standard errors) for IDP-118 Lotion and Ultravate Cream groups before and after dose administration on Day 14 (PK Population).



Source: adapted from Figure 2 in study report.

Figure 10: Semi-Logarithmic plots of mean HP plasma concentrations (+/- standard errors) for IDP-118 Lotion group before and after dose administration on Day 28 (PK Population).



Source: adapted from Figure 3 in study report.
Only the IDP-118 Lotion group is presented because no corresponding data were collected for the Ultravate Cream, 0.05% treatment group on Day 28.

The PK parameters of HP in the IDP-118 Lotion treatment group are shown in Table 42. Mean values of C_{max} and $AUC_{(0\text{-}t)}$ of HP on Day 28 were higher than on Day 14 in the IDP-118 Lotion treatment group. The summary of C_{max} and $AUC_{(0\text{-}t)}$ ratios of IDP-118 Lotion to its comparator drug Ultravate Cream on Day 14 is shown in Table 43. Mean C_{max} of HP in the IDP-118 Lotion group was 50% higher than that in the Ultravate Cream group (87.2 pg/mL versus 58.2 pg/mL). More subjects had at least three measurable HP concentrations in the IDP-118 Lotion group than in the Ultravate Cream group (11 out of 22 versus 8 out of 23) and the mean value of $AUC_{(0\text{-}t)}$ in the IDP-118 Lotion group was 14% higher (2190 pg*hr/mL versus 1910 pg*hr/mL).

Table 42: Mean (SD) PK parameters of HP following once daily administration of IDP-118 Lotion in Trial V01-118A-501

	HP					
	Days 1-2		Days 14-15		Days 28-29	
Parameter	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
C_{max} (pg/mL)	22	27.2 (54.2)	22	87.2 (96.6)	22	100 (136)
C_{min} (pg/mL)	22	0 (0)	22	16.3 (31.1)	22	29.4 (59.2)
T_{max} (hr)	5	4.60 (4.34)	13	5.39 (3.50)	13	5.63 (5.93)
$AUC_{(0-t)}$ (pg*hr/mL)	2	1780 (1110)	11	2190 (1500)	10	2810 (2070)
$AUC_{(0-24h)}$ (pg*hr/mL)	0	---	3	3560 (843)	2	5830 (679)

Source: Table 15 in study report.

Table 43: Summary of HP Comparison Ratios of IDP-118 Lotion to Ultravate Cream (PK Population) following once daily administration in Trial V01-118A-501

HP	IDP-118 Lotion (N=22)	Ultravate Cream (N=23)	IDP-118 Lotion over Ultravate Cream Ratio
C_{max}(pg/mL)			
Day 14			
N	22	23	
Mean	87.2	58.2	1.50[a]
CV% Mean	111	125	
GM (90% CI)	NC	NC	NC[b]
CV% GM	65.2	54.5	
$AUC_{(0-t)}$(pg·hr/mL)			
Day 14			
N	11	8	
Mean	2190	1910	1.14[a]
CV% Mean	68.4	58.8	
GM (90% CI)	1650 (1040, 2630)	1550 (925, 2600)	1.07 (0.551, 2.06)[b]
CV% GM	102	90.2	

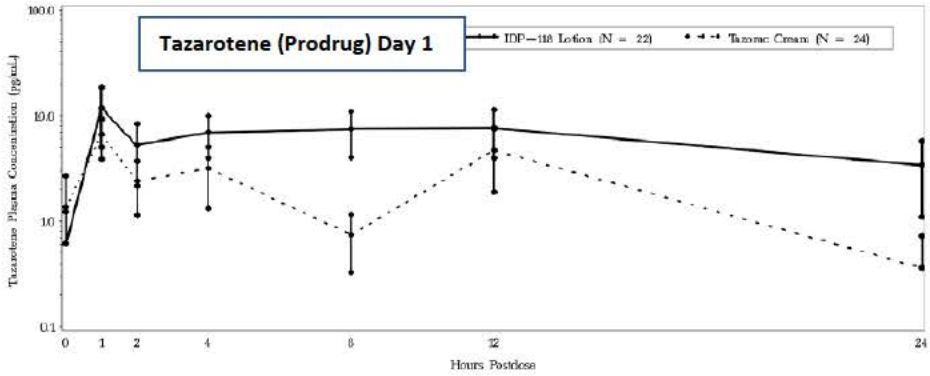
[a] Ratio of arithmetic means.
[b] Ratio (90% CI) of geometric means.
NC=not calculable
Source: adapted from Table 18 in study report.

***Reviewer's comment**: The applicant calculated $AUC_{(0-t)}$ only for subjects who had at least three consecutive quantifiable plasma concentrations were detected in the time interval. This approach excluded subjects who had one or two measurable concentrations. The reviewer recalculated the mean (SD) of this parameter (denoted as AUC_{last}) without excluding any subjects (see Table 5). For subjects who had measurable concentrations, the GMR (90% CI) values of Day 14 C_{max} and AUC_{last} for IDP-118 (i.e. halobetasol propionate and tazarotene lotion, 0.01%/0.045%) to the listed drug Ultravate Cream, 0.05% was 126.85% (86.77%, 185.43%) and 156.52% (65.20%, 375.73%), respectively. The results from recalculation suggested that the mean AUC_{last} of halobetasol propionate in the IDP-118 Lotion group was 60% higher than the listed drug Ultravate Cream, 0.05% group (1145 pg*hr/mL versus 713 pg*hr/mL) without excluding any subjects. The reanalysis results suggested that C_{max} values calculated by the reviewer are similar (except for C_{max} on Day 1) to the applicant's data which included all subjects without excluding subjects who had no measurable concentrations. Both analyses by the applicant and this reviewer showed that Day 14 C_{max} of halobetasol propionate in the IDP-118 (i.e. halobetasol propionate and tazarotene*

lotion, 0.01%/0.045%) group was higher than that in the listed drug Ultravate Cream, 0.05% group. Therefore, the systemic exposure of halobetasol propionate following application of halobetasol propionate and tazarotene lotion, 0.01%/0.045% was higher than following application of the listed drug Ultravate Cream, 0.05%.

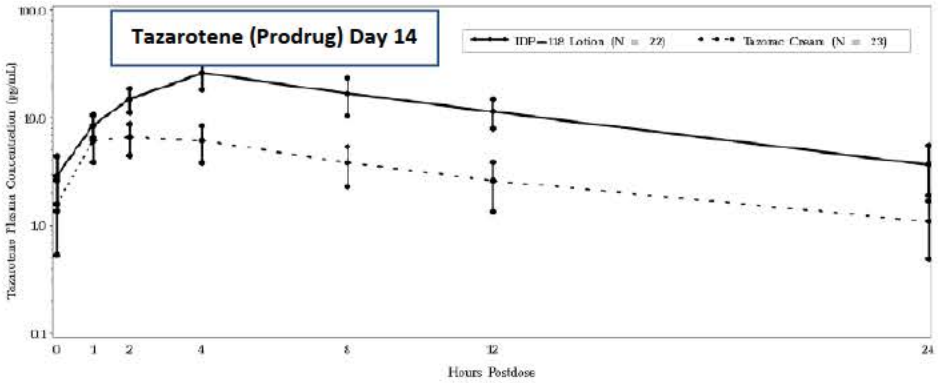
Pharmacokinetics of tazarotene and tazarotenic acid: Approximately a half of the total samples had no measurable plasma concentration of the parent prodrug, tazarotene (< 5 pg/mL) while the active metabolite, tazarotenic acid, was measurable (≥ 5 pg/mL) in all subjects. The mean plasma concentrations-time profiles of tazarotene and tazarotenic acid are shown in **Figure 11-Figure 16.**

Figure 11: Semi-Logarithmic plots of mean tazarotene plasma concentrations (+/- standard errors) for IDP-118 Lotion and Tazorac Cream groups following dose administration on Day 1 (PK Population)



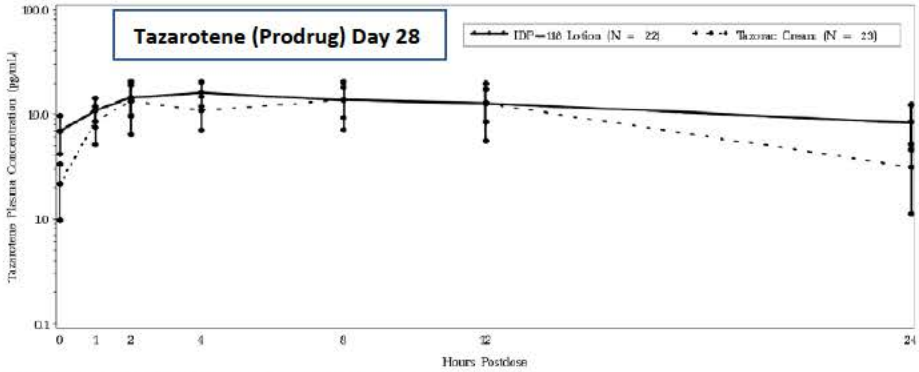
Source: adapted from Figure 4 in study report.

Figure 12: Semi-Logarithmic plots of mean tazarotene plasma concentrations (+/- standard errors) for IDP-118 Lotion and Tazorac Cream groups before and after dose administration on Day 14 (PK Population)



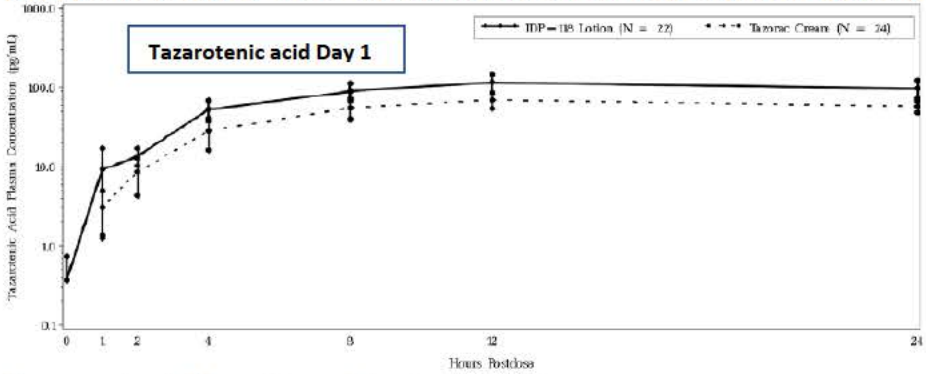
Source: adapted from Figure 5 in study report.

Figure 13: Semi-Logarithmic plots of mean tazarotene plasma concentrations (+/- standard errors) for IDP-118 Lotion and Tazorac Cream groups before and after dose administration on Day 28 (PK Population)



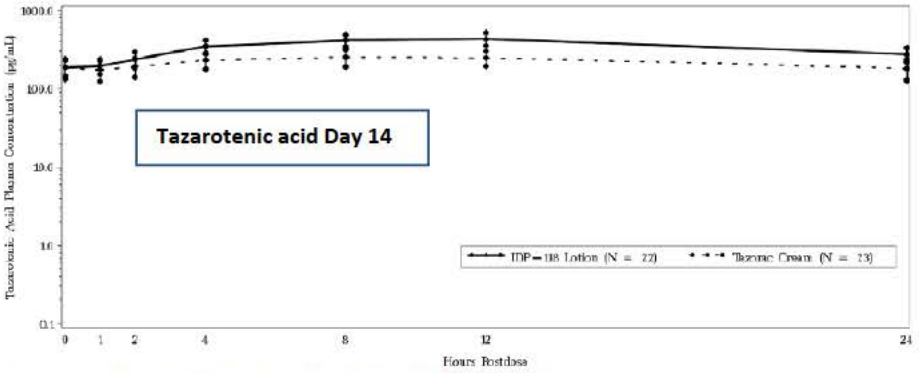
Source: adapted from Figure 6 in study report.

Figure 14: Semi-Logarithmic plots of mean tazarotenic acid plasma concentrations (+/- standard errors) for IDP-118 Lotion and Tazorac Cream groups following dose administration on Day 1 (PK Population)



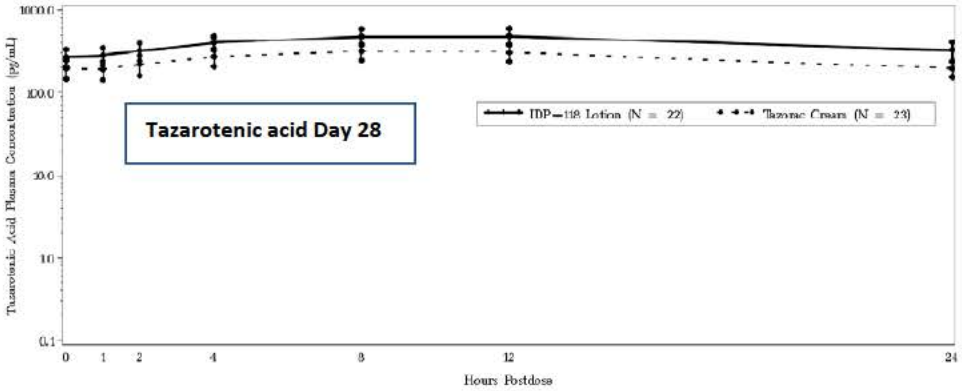
Source: adapted from Figure 7 in study report.

Figure 15: Semi-Logarithmic plots of mean tazarotenic acid plasma concentrations (+/- standard errors) for IDP-118 Lotion and Tazorac Cream groups before and after dose administration on Day 14 (PK Population)



Source: adapted from Figure 8 in study report.

Figure 16: Semi-Logarithmic plots of mean tazarotenic acid plasma concentrations (+/- standard errors) for IDP-118 Lotion and Tazorac Cream groups before and after dose administration on Day 28 (PK Population)



Source: adapted from Figure 9 in study report.

The PK parameters of tazarotene and tazarotenic acid in the IDP-118 Lotion treatment group are shown in Table 44. The summary of C_{max} and $AUC_{(0-t)}$ ratios of tazarotene and tazarotenic acid for IDP-118 Lotion to its comparator drug Tazorac Cream are shown in Table 45 and Table 46, respectively. For both treatment groups, the mean values of C_{max} and $AUC_{(0-t)}$ values were higher for the active metabolite, tazarotenic acid, on Day 28, respectively, when compared to those on Day 14. On both Days 14 and 28, the values of C_{max} and $AUC_{(0-t)}$ of tazarotenic acid in the treatment group of halobetasol propionate and tazarotene lotion, 0.01%/0.045% were higher than those in the treatment group of the listed drug, Tazorac Cream, 0.05%. The point of estimate values for the geometric ratio of $AUC_{(0-t)}$ were 181% and 161%, respectively, on Days 14 and 28. The point of estimate value for C_{max} on Day 28 was similar to that of $AUC_{(0-t)}$ on Day 28. Therefore, the systemic exposure of the active metabolite, tazarotenic acid, following application of IDP-118 Lotion was higher than following application of the listed drug, Tazorac Cream, 0.05%.

Table 44: Mean (SD) PK parameters of tazarotene and tazarotenic acid following once daily administration of IDP-118 Lotion in Trial V01-118A-501

	Days 1-2		Days 14-15		Days 28-29	
Parameter	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**
Taz						
C_{max} (pg/mL)	22	20.7 (33.0)	22	31.6 (38.1)	22	24.1 (27.3)
C_{min} (pg/mL)	22	0.635 (2.10)	22	1.02 (2.80)	22	3.08 (6.25)
T_{max} (hr)	12	6.82 (7.30)	18	4.06 (2.75)	18	5.56 (6.02)
$AUC_{(0-t)}$ (pg*hr/mL)	5	465 (384)	15	387 (426)	16	370 (437)
$AUC_{(0-24h)}$ (pg*hr/mL)	1	102 (---)	5	696 (580)	1	262 (---)
Taz Acid						
C_{max} (pg/mL)	22	130 (147)	22	471 (400)	22	525 (522)
C_{min} (pg/mL)	22	5.34 (14.2)	22	160 (166)	22	207 (197)
T_{max} (hr)	22	13.3 (6.69)	21	9.49 (4.62)	22	11.1 (5.24)
$AUC_{(0-t)}$ (pg*hr/mL)	22	2070 (2480)	21	8920 (7010)	22	9960 (10100)
$AUC_{(0-24h)}$ (pg*hr/mL)	3	1070 (166)	7	11000 (6440)	5	11000 (6590)

Source: Table 16 in study report.

Table 45: Summary of tazarotene comparison ratios of IDP-118 Lotion to Tazorac Cream (PK Population) following once daily administration in Trial V01-118A-501

Tazarotene	IDP-118 Lotion (N=22)	Tazorac Cream (N=24)	IDP-118 Lotion over Tazorac Cream Ratio
C_{max}(pg/mL)			
Day 14			
N	22	23	
Mean	31.6	10.2	3.11[a]
CV% Mean	120	132	
GM (90% CI)	NC	NC	NC[b]
CV% GM	NC	NC	
Day 28			
N	22	23	
Mean	24.1	22.3	1.08[a]
CV% Mean	113	189	
GM (90% CI)	NC	NC	NC[b]
CV% GM	NC	NC	
$AUC_{(0-t)}$(pg·hr/mL)			
Day 14			
N	15	7	
Mean	387	231	1.68[a]
CV% Mean	110	69.3	
GM (90% CI)	235 (145, 381)	184 (106, 319)	1.28 (0.592, 2.77)[b]
CV% GM	144	86.8	
Day 28			
N	16	6	
Mean	370	808	0.458[a]
CV% Mean	118	100	
GM (90% CI)	233 (150, 361)	471 (177, 1250)	0.495 (0.208, 1.18)[b]
CV% GM	132	177	

[a] Ratio of arithmetic means.
[b] Ratio (90% CI) of geometric means.
NC=not calculable

Source: Adapted from Table 19 in study report.

Table 46: Summary of tazarotenic acid comparison ratios of IDP-118 Lotion to Tazorac Cream (PK Population) following once daily administration in Trial V01-118A-501

Tazarotenic Acid	IDP-118 Lotion (N=22)	Tazorac Cream (N=24)	IDP-118 Lotion over Tazorac Cream Ratio
C_{max}(pg/mL)			
Day 14			
N	22	23	
Mean	471	286	1.65[a]
CV% Mean	84.9	112	
GM (90% CI)	NC	178 (124, 254)	NC[b]
CV% GM	NC	131	
Day 28			
N	22	23	
Mean	525	340	1.54[a]
CV% Mean	99.6	103	
GM (90% CI)	321 (215, 480)	194 (126, 299)	1.65 (0.929, 2.94)[b]
CV% GM	152	180	
$AUC_{(0-t)}$(pg·hr/mL)			
Day 14			
N	21	23	
Mean	8920	5330	1.67[a]
CV% Mean	78.6	111	
GM (90% CI)	6070 (4170, 8840)	3360 (2350, 4800)	1.81 (1.09, 3.00)[b]
CV% GM	131	131	
Day 28			
N	22	23	
Mean	9960	6420	1.55[a]
CV% Mean	101	106	
GM (90% CI)	5820 (3690, 9180)	3600 (2330, 5550)	1.62 (0.874, 2.99)[b]
CV% GM	192	183	

[a] Ratio of arithmetic means.
[b] Ratio (90% CI) of geometric means.
NC=not calculable

Source: Adapted from Table 21 in study report.

Reviewer's comment: *The applicant did not calculate the GMR (90%CI) of Day 14 C_{max} for IDP-118 (i.e. halobetasol propionate and tazarotene lotion, 0.01%/0.045%) to the listed drug Tazorac Cream, 0.05% because one subject did not have measurable concentrations. The reviewer calculated the GMR (90%CI) by excluding this subject (see reviewer's analysis results in Table 6). Both analyses by the applicant and this reviewer the systemic exposure (C_{max} and AUC_{last}) of tazarotenic acid on Days 14 and 28 following application of halobetasol propionate and tazarotene lotion, 0.01%/0.045% was higher than following application of the listed drug Tazorac Cream, 0.05%.*

HPA axis suppression results:

All subjects were in the normal range for adrenal function, defined as a cortisol level of > 18 µg/dL, after stimulation with Cosyntropin at the Screening Visit. In the IDP-118 Lotion group, 15% (3 of 20) and 0% (0 of 20) subjects had HPA axis suppression on Days 29 and 57, respectively. In the Ultravate Cream group, 5% (1 of 20) subjects had HPA axis suppression on Day 15; this suppressed subject returned to normal on Day 44 at a follow-up visit (Table 47).

Table 47: Summary of HPA axis suprresion data (Safety Population) in the treatment groups of IDP-118 Lotion and Ultravate Cream in Study V01-118A-501

	Screening	Day 29	Day 57
IDP-118 Lotion (N=23)			
N	23	20	20
Normal	23 (100.0%)	17 (85.0%)	20 (100.0%)
Abnormal	0 (0.0%)	3 (15.0%)	0 (0.0%)

	Screening	Day 15
Ultravate Cream (N=23)		
N	23	20
Normal	23 (100.0%)	19 (95.0%)
Abnormal	0 (0.0%)	1 (5.0%)

Note: Poststimulation cortisol levels ≤18 µg/dL considered abnormal.
Source: Table 27 of study report; compared to the PK population, the safety population included one more subject who had no PK data collection.

Summary of adverse events:
No deaths were reported in the study. In the IDP-118 Lotion group, no serious adverse Events (SAEs) were reported. A treatment-emergent adverse events (TEAE) leading to discontinuation of study drug was reported for 1 subject (4.3%). TEAEs were reported for 43.5% of subjects. In the Ultravate Cream group, no SAEs or TEAEs leading to discontinuation of study drug were reported. TEAEs were reported for 13.0% of subjects. In the Tazorac Cream group, no SAEs or TEAEs leading to discontinuation of study drug were reported. TEAEs were reported for 20.0% of subjects.

Assessments of local signs and symptoms demonstrated improvements in itching, dryness, and burning/stinging in the IDP-118 Lotion group, with greater percentages of subjects in the IDP-118 Lotion group having scores of either 0 or 1 (none or mild) for

itching, dryness, and burning/stinging on Day 57 compared with Baseline (Day 1). Treatment-emergent Grade 3 itching, dryness, and burning/stinging were reported by 26.1%, 17.4%, and 13.0% of subjects, respectively. One subject in the IDP-118 Lotion group had striae and telangiectasias post-Baseline; this subject also had striae and telangiectasias at Baseline. One subject in the IDP-118 Lotion group had folliculitis post-Baseline; this subject did not have folliculitis at Baseline. No subjects in the IDP-118 Lotion group had skin atrophy.

There were no clinically meaningful changes within the groups from Baseline to the final evaluation for any vital sign parameter.

13.5.6. Trial V01-118A-101

Title: A Randomized, Evaluator-Blinded, Within- Subject, Single-Center Vasoconstrictor Study to Determine the Potency of IDP-118 (halobetasol propionate 0.01% / tazarotene 0.045%) Lotion and IDP-122 (halobetasol propionate) Lotion, 0.01%, Compared to Four Different Currently Marketed Topical Corticosteroid Formulations of Known Potency and a Vehicle Lotion Formulation Under Non-Occluded Conditions in Healthy Adult Subjects

Dates of the study:
Date of first subject enrollment: 01 March 2016
Date of last subject completed: 02 March 2016

Objectives:
To use the vasoconstrictor response to determine the potency of IDP-118 (halobetasol propionate 0.01% / tazarotene 0.045%) Lotion (Dow Pharmaceutical Sciences, a division of Valeant Pharmaceuticals North America LLC) and IDP-122 (halobetasol propionate) Lotion, 0.01% (Dow Pharmaceutical Sciences, a division of Valeant Pharmaceuticals North America LLC) compared to four currently marketed topical corticosteroid formulations of known potency and a vehicle lotion formulation in healthy adult subjects.

The four currently marketed products were:

- Ultravate® (halobetasol propionate) Cream, 0.05% [RANBAXY] – Super Potent
- Fluocinonide Cream USP, 0.05% [Manufactured by: Taro Pharmaceuticals Inc.; Distributed by: Taro Pharmaceuticals U.S.A., Inc.] – (High) Potent
- Betamethasone Dipropionate Cream USP, 0.05% [E. FOUGERA & CO., A division of Fougera Pharmaceuticals Inc.] – Upper Mid-Strength Potent
- Triamcinolone Acetonide Cream USP, 0.1% [E. FOUGERA & CO., A division of Fougera Pharmaceuticals Inc.])– Mid-Strength Potent

Reviewer comments: *The bracketing using products of known potency class was adequate. It is noted that the potency of Ultravate® (halobetasol propionate) Cream,*

0.05% and Triamcinolone Acetonide Cream USP, 0.1% was classified into different categories in the study compared to other sources [i.e. the potency of Ultravate® (halobetasol propionate) Cream, 0.05% was classified as super high in the approved labeling of Ultravate® (halobetasol propionate) Cream, 0.05%; Triamcinolone Acetonide Cream USP, 0.1% was classified as lower mid-strength potent according to Jacob, et al. 2006]. This difference in the classification of Triamcinolone Acetonide Cream USP, 0.1% wouldn't result in different conclusion for the potency classification of IDP-118 Lotion because IDP-118 Lotion was determined to be in upper mid-strength potent to super potent in the study.

Study design:
This was a single-point, randomized, evaluator-blinded, within-subject, single-center study. The study was conducted in 30 healthy, non-tobacco-using adult male and female subjects with a Fitzpatrick skin type of 3 (III) or less who were pre-screened to show a vasoconstrictor response to triamcinolone acetonide cream USP, 0.1% (E. Fougera & Co.).

A 10 µL amount of each formulation was applied to a single application site on the flexor surfaces of each subject's ventral forearms (left and right) and kept in place for 16 hours. In addition, two untreated control sites were designated on each forearm as a ChromaMeter reference site. The degree of vasoconstriction was measured using visual scoring and a ChromaMeter (a-scale reading) at pre-dose (baseline assessments; in duplicate for ChromaMeter only) and at approximately 18 hours after the application of the formulations (2 hours [± 15 minutes]) after washing of the test sites to remove study drug). Assessments were performed under standard fluorescent lighting and at room temperature. The visual evaluator(s) and the ChromaMeter operator(s) did not have knowledge of treatment location at each site.

Visual Assessments used the following rating scale:
0 = No pallor; no change from surrounding area.
1 = Mild pallor; slight or indistinct outline of application site.
2 = Moderate pallor; discernible outline of application site.
3 = Intense pallor; clean, distinct outline of application site.
Any subject with a visual baseline assessment score greater than zero (0) was not considered eligible for dosing.

For ChromaMeter assessments, one ChromaMeter operator (b) (6)) performed all of the assessments for all subjects using one ChromaMeter (RE# (b) (4)). The instrument was calibrated against the manufacturer's standard calibration plate before each interval reading. Evaluations using the ChromaMeter a-scale reading were performed at each site at pre-dose (in duplicate) (baseline assessments) and at approximately 18 hours after the application of the study drug (2 hours [± 15 minutes] after washing the test sites to remove study drug).

Statistical analyses were performed separately for the visual and ChromaMeter data. A four-point ordinal visual scale ranging from 0 (no pallor) to 3 (intense pallor) was utilized in this study for the primary analysis of potency.

The primary analysis was based on the visual scoring. The data from the ChromaMeter were analyzed and are presented for informational purposes. The postdose ChromaMeter readings at each treated site were corrected for both the average pre-dose (baseline) readings and the average post-dose baseline-adjusted reading for the two untreated sites (on the same arm) at the corresponding post-dose reading time. The relative potency of the test formulations of IDP-118 (halobetasol propionate 0.01% / tazarotene 0.045%) Lotion and IDP-122 (halobetasol propionate) Lotion, 0.01% were estimated by comparing them with the reference products of known potency.

Reviewer comments: *The applicant has submitted validation reports of ChromaMeter. The validation results of ChromaMeters are acceptable.*

Demographics:
Summary of demographics is shown in Table 48.

Results of vasoconstriction analysis: Mean results from visual assessments (primary endpoint) and mean results from ChromaMeter assessments (secondary endpoint) are provided in Table 49 and Table 50, respectively. Comparison of p-values for statistical significance after adjusting for multiple testing (Tukey method) of head-to-head study drugs for the visual (primary) and Chromameter-derived (informational) data are presented in Table 51 and Table 52, respectively.

Reviewer comments: *The results of visual assessment were inconclusive in that the proposed drug was not statistically different from Ultravate Cream, 0.05% (Class 1, supper high), Fluocinonide Cream, 0.05% (Class 2, potent), and Betamethasone dipropionate cream, 0.05% (Class 3, upper mid-strength). Hence the ChromaMeter data was given more consideration. The chromameter results indicated that the potency of the proposed product is upper mid-strength to high. Whether the need of conducting a VCA study as a post-marketing commitment will be decided at resubmission.*

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

Reference
Corticosteroid classes: A quick reference guide including patch test substances and cross-reactivity, Jacob and Steele, *J Am Acad Dermatol, April 2006*; 723-727.

Table 48: Demographics summary of subjects in Study V01-118A-101

SUBJECTS INCLUDED IN STATISTICAL ANALYSIS (N = 30)	
Gender	
Males	19 (63.33%)
Females	11 (36.67%)
Hispanic or Latino Race	
American Indian or Alaskan Native	0 (0.00%)
Asian	0 (0.00%)
Black or African American	0 (0.00%)
Native Hawaiian or Other Pacific Islander	0 (0.00%)
White	2 (6.67%)
Other	0 (0.00%)
Not Hispanic or Latino Race	
American Indian or Alaskan Native	0 (0.00%)
Asian	0 (0.00%)
Black or African American	0 (0.00%)
Native Hawaiian or Other Pacific Islander	0 (0.00%)
White	27 (90.00%)
Other	1 (3.33%)
Age (years)	
Mean ± SD	43.10 ± 11.73
Median	45.00
Range	21 - 61
Age Groups	
< 18	0 (0.00%)
18 – 40	12 (40.00%)
41 – 64	18 (60.00%)
65 – 75	0 (0.00%)
> 75	0 (0.00%)
Weight (lbs)	
Mean ± SD	181.80 ± 37.69
Median	175.50
Range	116 - 247
BMI (kg/m^2)	
Mean ± SD	27.47 ± 4.96
Median	29.40
Range	18.5 – 34.2
Tobacco User[2]	
Yes	0 (0.00%)
No	30 (100.00%)
Fitzpatrick Skin Type	
I	1 (3.33%)
II	14 (46.67%)
III	15 (50.00%)

[1] Determined at screening.
[2] Defined as current tobacco user (having used tobacco or nicotine-containing products within 30 days prior to dosing).

Source: Table 11.2.1 of study report.

Table 49: Mean results from visual assessments in order of most to least potent formulation (primary endpoint) in Study V01-118A-101

Formulations		N	Mean and Standard Deviation	REGWQ Grouping*
Product 3	Ultravate® (halobetasol propionate) Cream, 0.05%; RANBAXY Lot No: 94614; Expiration Date: 06/17	30	1.6833 ± 0.7598	A
Product 2	IDP-122 (halobetasol propionate 0.01%) Lotion; Dow Pharmaceutical Sciences, a division of Valeant Pharmaceuticals North America LLC Lot No: 8083839; Manufacture Date 03/05/15	30	1.5333 ± 0.7303	A
Product 5	BETAMETHASONE DIPROPIONATE CREAM USP, 0.05%; E. FOUGERA & CO., A division of Fougera Pharmaceuticals Inc. Lot No: FU6538; Expiration Date: NOV 18	30	1.5167 ± 0.7484	A
Product 1	IDP-118 (halobetasol propionate 0.01% / tazarotene 0.045%) Lotion; Dow Pharmaceutical Sciences, a division of Valeant Pharmaceuticals North America LLC Lot No: 8083850; Manufacture Date: 03/10/15	30	1.3833± 0.6654	A
Product 4	Fluocinonide Cream USP, 0.05%; Mfd. by: Taro Pharmaceuticals Inc.; Dist. by: Taro Pharmaceuticals U.S.A., Inc. Lot No: K510921749; Expiration Date: APR 2017	30	1.0333 ± 0.7063	B
Product 6	TRIAMCINOLONE ACETONIDE CREAM USP, 0.1%; E FOUGERA & CO., A division of Fougera Pharmaceuticals Inc. Lot No: FR1170; Expiration Date: OCT 18	30	0.8000 ± 0.8052	B
Product 7	Vehicle Lotion; Dow Pharmaceutical Sciences, a division of Valeant Pharmaceuticals North America LLC Lot No: 8083428; Manufacture Date: 02/20/15	30	0.1333 ± 0.3198	C
Untreated	No Treatment	30	0.0750 ± 0.1165	C

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

Source: Table 11.4.1.1 of study report.

Table 50: Mean results from chromameter assessments in order of most to least potent formulation (informational) in Study V01-118A-101

Formulations		N	Mean and Standard Deviation	REGWQ Grouping*
Product 3	Ultravate® (halobetasol propionate) Cream, 0.05%; RANBAXY Lot No: 94614; Expiration Date: 06/17	30	2.2743 ± 0.9760	A
Product 5	BETAMETHASONE DIPROPIONATE CREAM USP, 0.05%; E. FOUGERA & CO., A division of Fougera Pharmaceuticals Inc. Lot No: FU6538; Expiration Date: NOV 18	30	1.8147 ± 0.9760	B
Product 2	IDP-122 (halobetasol propionate 0.01%) Lotion; Dow Pharmaceutical Sciences, a division of Valeant Pharmaceuticals North America LLC Lot No: 8083839; Manufacture Date 03/05/15	30	1.7177 ± 0.9355	B C
Product 1	IDP-118 (halobetasol propionate 0.01% / tazarotene 0.045%) Lotion; Dow Pharmaceutical Sciences, a division of Valeant Pharmaceuticals North America LLC Lot No: 8083850; Manufacture Date: 03/10/15	30	1.5275 ± 0.7537	B C
Product 4	Fluocinonide Cream USP, 0.05%; Mfd. by: Taro Pharmaceuticals Inc.; Dist. by: Taro Pharmaceuticals U.S.A., Inc. Lot No: K510921749; Expiration Date: APR 2017	30	1.3052 ± 0.9494	C D
Product 6	TRIAMCINOLONE ACETONIDE CREAM USP, 0.1%; E FOUGERA & CO., A division of Fougera Pharmaceuticals Inc. Lot No: FR1170; Expiration Date: OCT 18	30	0.9092 ± 0.8186	D
Product 7	Vehicle Lotion; Dow Pharmaceutical Sciences, a division of Valeant Pharmaceuticals North America LLC Lot No: 8083428; Manufacture Date: 02/20/15	30	0.0263 ± 0.5661	E
Untreated	No Treatment	30	0.0013 ± 0.0027	E

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

Source: Table 11.4.1.3 of study report.

Table 51: Comparison of p-values for statistical significance - visual assessment (primary) in Study V01-118A-101

	Product 1	Product 2	Product 3	Product 4	Product 5	Product 6	Product 7	Untreated
Product 1	—	0.9446	0.2985	0.1336	0.9706	0.0003	<.0001	<.0001
Product 2	0.9446	—	0.9446	0.0041	1.0000	<.0001	<.0001	<.0001
Product 3	0.2985	0.9446	—	<.0001	0.9060	<.0001	<.0001	<.0001
Product 4	0.1336	0.0041	<.0001	—	0.0065	0.6281	<.0001	<.0001
Product 5	0.9706	1.0000	0.9060	0.0065	—	<.0001	<.0001	<.0001
Product 6	0.0003	<.0001	<.0001	0.6281	<.0001	—	<.0001	<.0001
Product 7	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	—	0.9998
Untreated	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	0.9998	—

Source: Table 11.4.1.2 of study report.

Table 52: Comparison of p-values for statistical significance - chromameter assessments (informational) in Study V01-118A-101

	Product 1	Product 2	Product 3	Product 4	Product 5	Product 6	Product 7	Untreated
Product 1	—	0.9431	0.0003	0.8775	0.6570	0.0054	<.0001	<.0001
Product 2	0.9431	—	0.0190	0.1980	0.9990	<.0001	<.0001	<.0001
Product 3	0.0003	0.0190	—	<.0001	0.1020	<.0001	<.0001	<.0001
Product 4	0.8775	0.1980	<.0001	—	0.0453	0.2432	<.0001	<.0001
Product 5	0.6570	0.9990	0.1020	0.0453	—	<.0001	<.0001	<.0001
Product 6	0.0054	<.0001	<.0001	0.2432	<.0001	—	<.0001	<.0001
Product 7	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	—	1.0000
Untreated	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	1.0000	—

Source: Table 11.4.1.4 of study report.

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/s/

DAWN WILLIAMS
06/15/2018

SNEZANA TRAJKOVIC
06/15/2018

JILL A LINDSTROM
06/15/2018

OFFICE OF CLINICAL PHARMACOLOGY MEMORANDUM

NDA: 209354	**Submission Date:** 08/18/2017; 12/19/2017; 1/18/2018
Brand Name	DUOBRII
Generic Name	Halobetasol propionate and tazarotene lotion, 0.01%/0.045%
Primary Reviewer	Yanhui Lu, Ph.D.
Secondary Reviewer	Chinmay Shukla, Ph.D.
Tertiary Reviewer	Chandrahas G. Sahajwalla, Ph.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Dermatology and Dental Products
Submission Type	Original NDA
Applicant	Dow Pharmaceutical Sciences
Indication	Treatment of plaque psoriasis

Summary: The applicant is seeking approval of a new combination product of halobetasol propionate (HBP) and tazarotene, 0.01%/0.045%, in a lotion formulation for the treatment of plaque psoriasis. The proposed dosing regimen is to be applied once daily topically. The applicant is following a 505(b)(2) regulatory pathway for this application and has identified Ultravate (halobetasol propionate) Cream, 0.05% (NDA 019967) and Tazorac (tazarotene) Cream, 0.05% (NDA 021184) as listed drugs for HBP and tazarotene, respectively. The applicant conducted 11 clinical studies that included two identically designed Phase 3 pivotal trials, a long-term safety study, a maximal use pharmacokinetic (PK)/ hypothalamic-pituitary-adrenal (HPA) axis suppression study, and a vasoconstrictor assay (VCA) study. Relative bioavailability to the listed drugs was assessed in the maximal use PK study to support a clinical bridge.

In the maximal use PK study, adult subjects with moderate to severe plaque psoriasis with at least 20% body surface area involved were treated with the proposed combination product once daily for 8 weeks. HBP and tazarotene (a prodrug) were not measurable (below the lower limit of quantitation) in many of the PK samples; however, tazarotenic acid (an active metabolite of tazarotene) was measurable (> 5 pg/mL) in all subjects. For HBP, mean (SD) C_{max} and AUC_{last} values were 87.2 (96.6) pg/mL and 1145 (1501) pg*hr/mL on Day 14 and 101.9 (135.4) pg/mL and 1300 (1959) pg*hr/mL on Day 28, respectively. For tazarotenic acid, mean (SD) C_{max} and AUC_{last} values were 466.1 (390.0) pg/mL and 8513 (7096) pg*hr/mL on Day 14 and 523.4 (523.3) pg/mL and 9954 (10091) pg*hr/mL on Day 28, respectively.

The mean (SD) C_{max} and AUC_{last} values of HBP on Day 14 following once daily application of Ultravate Cream, 0.05% for 2 weeks were 58.8 (72.8) pg/mL and 708 (1099) pg*hr/mL, respectively. Following once daily application of Tazorac Cream, 0.05% for 4 weeks, the mean (SD) C_{max} and AUC_{last} values of tazarotenic acid were 288.8 (327.5) pg/mL and 5331 (5932) pg*hr/mL on Day 14 and 340.3 (351.8) pg/mL and 6419 (6842) pg*hr/mL on Day 28, respectively. Relative bioavailability assessment results suggested that the systemic exposure of the proposed combination product was higher when compared to each of the monads in the corresponding listed drugs. The 90% confidence interval on the ratio of geometric means of C_{max} and AUC for both HBP and tazarotenic acid were outside (in fact higher) the no effect boundary of 80% to 125%.

With the 8-week's once daily treatment with the halobetasol propionate and tazarotene lotion, 0.01%/0.045% under maximal use conditions, 15% (3 of 20) and 0% (0 of 20) subjects had HPA axis suppression on Days 29 and 57, respectively. The incidence of HPA axis suppression was sufficiently low to allow for further assessment in pediatric subjects, which will be requested as a post-marketing requirement (PMR).

Results of the VCA study indicated that the potency of the proposed drug is upper mid-strength to high.

Outstanding issue: The relative bioavailability assessment showed that the bioavailability of the proposed combination product, halobetasol propionate and tazarotene lotion, 0.01%/0.045%, was higher than each of the listed drugs for the individual monads. This indicates that the clinical bridge was not established. The applicant has provided clinical safety data from the Phase 3 trials and the long-term safety study to support the safety of the higher systemic exposure with the combination product; however, the non-establishment of the clinical bridge may impact the applicant's ability to provide animal toxicity data from the listed drugs.

From a Clinical Pharmacology standpoint, this application is acceptable because although the PK bridge was not established, the applicant has provided safety data for the proposed combination product from the two Phase 3 trials and long-term safety study.

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: Although the PK bridge was not established, the applicant has submitted safety data for the proposed combination product from the two Phase 3 trials and long-term safety study which are being evaluated by the clinical team. Therefore, from the clinical pharmacology standpoint, data submitted in NDA 209354 are acceptable.

Reviewer comments: *Labeling discussion did not take place in this review cycle.*

Post Marketing Requirement (PMR): Conduct a maximal use PK/HPA axis suppression study in pediatric subjects (b)(4) to less than 17 years of age with moderate to severe plaque psoriasis.

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/s/

YANHUI LU
04/13/2018

CHINMAY SHUKLA
04/13/2018

CHANDRAHAS G SAHAJWALLA
04/13/2018