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RESEARCH**

APPLICATION NUMBER:

209355Orig1s000

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)	209355
Priority or Standard	Standard
Submit Date(s)	December 5, 2017
Received Date(s)	December 5, 2017
PDUFA Goal Date	October 5, 2018
Division/Office	DDDP/ODE III
Review Completion Date	See DARRTS signature page
Established Name	halobetasol propionate lotion, 0.01%
(Proposed) Trade Name	BRYHALI™
Pharmacologic Class	corticosteroid
Code name	IDP-122 Lotion
Applicant	Dow Pharmaceutical Sciences (DPS)
Formulation(s)	lotion
Dosing Regimen	once daily
Applicant Proposed Indication(s)/Population(s)	topical treatment of plaque psoriasis
Recommendation on Regulatory Action	approval
Recommended Indication(s)/Population(s)	topical treatment of plaque psoriasis in adults

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DISCIPLINE	REVIEWER	OFFICE/ DIVISION	SECTIONS AUTHORED/ ACKNOWLEDGED/ APPROVED	AUTHORED/ ACKNOWLEDGED/ APPROVED
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DB=Division of Biometrics
 DCP=Division of Clinical Pharmacology
 DDDP=Division of Dermatology and Dental Products
 DEPI=Division of Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 DMPP=Division of Medical Policy Programs
 OB=Office of Biostatistics
 OCP=Office of Clinical Pharmacology
 ODE=Office of Drug Evaluation
 OPQ=Office of Pharmaceutical Quality
 OPDP=Office of Prescription Drug Promotion
 OSI=Office of Scientific Investigations
 OSE=Office of Surveillance and Epidemiology
 OTS=Office of Translational Sciences
 QT-IRT=QT Interdisciplinary Review Team
 RBPM=Regulatory Business Project Manager
 SRPM=Safety Regulatory Project Manager

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	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
DLQI	Dermatology Life Quality Index
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IGA	Investigator's 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
MCMC	Markov Chain Monte Carlo
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

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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
SD	standard deviation
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Halobetasol propionate lotion, 0.01% is a corticosteroid that the Applicant proposes for the topical treatment of plaque psoriasis. The proposed dosing regimen is once daily application to affected areas for up to 8 weeks, and the proposed and approved proprietary name is Bryhali™.

The product was developed under the codename “IDP-122 Lotion” and will generally be referenced by that moniker in this review.

Dow Pharmaceutical Sciences (DPS) submitted the application under the 505(b)(2) pathway, with Ultravate Cream (0.05%) named as the listed drug (LD). IDP-122 Lotion contains 0.01% w/w halobetasol propionate, which is a lower concentration than in the listed drug.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant provided substantial evidence of effectiveness from 2 adequate and well-controlled studies of identical design. The studies evaluated IDP-122 Lotion for treatment of adult subjects with moderate-to-severe plaque psoriasis. IDP-122 Lotion was statistically superior to placebo in both studies in the target population for the primary endpoint, “treatment success,” defined as at least a 2-grade improvement from baseline in the Investigator’s Global Assessment (IGA) and an IGA score equating to “clear” or “almost clear.” The treatment response was similar across both studies.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

IDP-122 Lotion is a topical corticosteroid product that the Applicant proposes for the topical treatment of plaque psoriasis in adults. Psoriasis is a common, chronic, immune-mediated skin disorder that is characterized by sharply demarcated scaly, erythematous plaques of localized or generalized distribution. The extent of involvement is one consideration in the approach to patient management. Disease of limited extent may be effectively managed with topical treatment.

The Applicant provided substantial evidence of effectiveness from two identically-designed, randomized, double-blind, vehicle-controlled, Phase 3 trials (301 and 302). The trials enrolled subjects 18 years of age and older who had a clinical diagnosis of psoriasis with an IGA score of 3 (moderate) or 4 (severe) and had an area of plaque psoriasis that covered a BSA of 3% to 12% (excluding the face, scalp, palms, soles, axillae, and intertriginous areas). The pre-specified primary endpoint was the percentage of subjects with treatment success at Week 8, where treatment success was defined as at least a 2-grade improvement from baseline in IGA score and an IGA score equating to “Clear” or “Almost Clear”. In study 301, 37% of subjects in the IDP-122 group achieved treatment success compared to 8% in the vehicle group. In study 302, treatment success was achieved by 38% and 12% of subjects, respectively. IDP-122 was statistically superior (p -value <0.001) to vehicle for the primary endpoint in both Phase 3 trials.

A total of 430 subjects constituted the Safety Population: 217 subjects (50.5%) were randomized to IDP-122 Lotion treatment, and 213 (49.5%) were randomized to Vehicle treatment. The safety database did not raise any new safety concerns. There was only one report of a local adverse reaction suggestive of treatment-related effect (telangiectasia), and it had resolved by Week 12 (4 weeks post-treatment). The pattern of treatment emergent adverse events (TEAEs), including serious adverse events (SAEs) was not worrisome. The overall incidence of SAEs was low in both treatment groups and higher in the Vehicle arm (2.8%) compared to IDP-122 (1.8%). Similarly, the overall incidence of TEAEs was higher in the Vehicle arm (23.9%) compared to IDP-122 (21.5%). “Application dermatitis” and “hyperglycemia” were the only TEAEs that occurred in at least 1% of subjects treated with IDP-122 Lotion and more frequently than in vehicle-treated subjects. Dermal safety studies did not reveal IDP-122 Lotion to be an irritant or contact sensitizer. HPA axis suppression was observed following once daily use of IDP-122 Lotion for 8 weeks. However, the incidence of HPA axis suppression was low: one subject (5.6%) at Day 29 and 3 subjects (15.8%) at Day 57. Adrenal function had returned to normal on follow-up testing. Findings from routine laboratory testing were unremarkable. In summary, the Applicant adequately characterized the safety profile of IDP-122 Lotion, and the product was generally well-tolerated.

Product labeling and routine pharmacovigilance activities should serve as adequate risk mitigation strategies. I conclude that the Applicant has established that the benefits of IDP-122 Lotion for treatment of adult patients with plaque psoriasis outweigh its risks.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> Psoriasis is a common, chronic, multi-system, inflammatory disorder which presents in the skin as scaly, erythematous plaques. The disease may have significant impact on a patient's quality of life. The prevalence of psoriasis in the United States is approximately 2-3 %. 	<p>Plaque psoriasis can be a serious disease because of its chronicity and impact on quality of life.</p>
Current Treatment Options	<ul style="list-style-type: none"> Current topical therapeutic options include synthetic vitamin D3 derivatives, retinoids and corticosteroids. There are several approved topical corticosteroids available for treatment of psoriasis, including other halobetasol propionate products, marketed in a variety of dosage forms. The Applicant's product provides for a lower concentration of halobetasol than is found in any of the marketed products. 	<p>There are a number of FDA-approved products with an acceptable risk-benefit profile for the treatment of plaque psoriasis in adults. None of these treatments provides for cure.</p> <p>Multiple topical corticosteroid products of various potencies and dosage forms are available for treatment of psoriasis. propionate 0.05% products are available in cream, ointment, lotion, and foam dosage forms. The Applicant's product presents a lower concentration of halobetasol than in any of the other products.</p>
Benefit	<ul style="list-style-type: none"> The Applicant provided substantial evidence of effectiveness from two identically-designed, randomized, double-blind, vehicle-controlled, Phase 3 trials (301 and 302). The trials enrolled subjects 18 years of age and older who had a clinical diagnosis of psoriasis with an IGA score of 3 (moderate) or 4 (severe) and had an area of plaque psoriasis that covered a BSA of 3% to 12% (excluding the face, scalp, palms, soles, axillae, and intertriginous areas). The pre-specified primary endpoint was the percentage of subjects with treatment success at Week 8, where treatment success was defined as at least a 2-grade improvement from baseline in IGA score and an 	<p>The Applicant has met the evidentiary standard for provision of substantial evidence of effectiveness under the proposed conditions of use.</p> <p>The Applicant convincingly demonstrated that IDP-122 Lotion is effective for treatment of plaque psoriasis. Some subjects may achieve the "clear" or "almost clear," and these are highly clinically-meaningful outcomes.</p>

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>IGA score equating to “Clear” or “Almost Clear”. In study 301, 37% of subjects in the IDP-122 group achieved treatment success compared to 8% in the vehicle group. In study 302, treatment success was achieved by 38% and 12% of subjects, respectively. IDP-122 was statistically superior (p-value<0.001) to vehicle for the primary endpoint in both Phase 3 trials.</p>	
<p>Risk</p>	<ul style="list-style-type: none"> • The Applicant has met the evidentiary standard for provision of substantial evidence of effectiveness under the proposed conditions of use. • The Applicant convincingly demonstrated that IDP-122 Lotion is effective for treatment of plaque psoriasis. Some subjects may achieve the “clear” or “almost clear,” and these are highly clinically-meaningful outcomes. 	<p>The safety review did not reveal any worrisome types or patterns of events. No new safety concerns were identified. The safety profile appears to be similar to other topical corticosteroids, including other halobetasol dosage forms.</p>
<p>Risk Management</p>	<ul style="list-style-type: none"> • A PREA PMR to characterize the safety of IDP-122 Lotion in adolescents will be issued. The Applicant will be required to conduct a safety pharmacokinetic and HPA axis suppression study under maximal use conditions in subjects 6 to 16 years 11 months of age years of age with psoriasis. 	<p>Product labeling and routine pharmacovigilance are adequate risk mitigation strategies for this product.</p>

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

<input checked="" type="checkbox"/>	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
<input checked="" type="checkbox"/>	Clinical outcome assessment (COA) data, such as	Sec. 7.2
<input checked="" type="checkbox"/>	Patient reported outcome (PRO)	
<input type="checkbox"/>	Observer reported outcome (ObsRO)	
<input checked="" type="checkbox"/>	Clinician reported outcome (ClinRO)	
<input type="checkbox"/>	Performance outcome (PerfO)	
<input type="checkbox"/>	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
<input type="checkbox"/>	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Sec 2.1 Analysis of Condition]
<input type="checkbox"/>	Observational survey studies designed to capture patient experience data	
<input type="checkbox"/>	Natural history studies	
<input type="checkbox"/>	Patient preference studies (e.g., submitted studies or scientific publications)	
<input type="checkbox"/>	Other: (Please specify)	
<input type="checkbox"/>	Patient experience data that were not submitted in the application, but were considered in this review:	
<input type="checkbox"/>	Input informed from participation in meetings with patient stakeholders	
<input type="checkbox"/>	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
<input type="checkbox"/>	Observational survey studies designed to capture patient experience data	
<input type="checkbox"/>	Other: (Please specify)	
<input type="checkbox"/>	Patient experience data was not submitted as part of this application.	

2 Therapeutic Context

2.1. Analysis of Condition

Psoriasis is a common, chronic, multi-system, inflammatory disorder which presents in the skin as scaly, erythematous plaques. These plaques commonly involve the extensor surfaces of the extremities, but may present anywhere from the scalp to the soles of the feet. Extent of body surface area affected may vary from limited to extensive, and the extent of involvement is one consideration in the approach to patient management. Disease of limited extent may be effectively managed with topical treatment, and corticosteroids are among the topical treatment options. There are several approved topical corticosteroids available for treatment of psoriasis, including other halobetasol propionate products. The prevalence of psoriasis in the United States is approximately 2-3%.

2.2. Analysis of Current Treatment Options

Products available for the topical treatment of plaque psoriasis include those listed in Table 1.

Table 1: Summary of Treatment Armamentarium

Product Class	Example
Corticosteroid*	Clobetasol ointment
Synthetic vitamin D ₃ derivative	Calcipotriene cream
Synthetic vitamin D ₃ derivatives/corticosteroid combination product	Calcipotriene and betamethasone dipropionate ointment
Retinoid	Tazarotene gel

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant proposes marketing of halobetasol propionate lotion, 0.01% for the topical treatment of plaque psoriasis. Halobetasol propionate is a corticosteroid, and the moiety was initially approved on 12/17/1990 in an ointment dosage form for topical use for “the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses” (Ultravate® ointment; NDA 19968). A cream dosage form was approved for the same indication on 12/27/1990 (Ultravate® cream; NDA 19967). It has since been approved in other dosage forms, including a lotion, which was approved on 11/06/2015 for the topical treatment of plaque psoriasis in patients eighteen (18) years of age and older and is marketed Ultravate (halobetasol propionate) lotion, 0.05%. Most recently, a foam dosage form was approved (date: 05/24/2018) for the topical treatment of plaque psoriasis in patients 18 years of age and older. However, all other marketed halobetasol propionate products are 0.05%, and these products are ranked as super-potent (Class I).¹ Thus, the Applicant’s product is unique in that it represents a lower concentration halobetasol product, relative to all other currently available products. The potency of IDP-122 Lotion based on the vasoconstrictor assay is between upper mid-strength to super potent (using visual data) and between upper mid-strength to high potent (ChromaMeter data).

3.2. Summary of Presubmission/Submission Regulatory Activity

End of Phase 2 (EOP2) Meeting



subsequent development of halobetasol propionate lotion, 0.01% was under IND 126779 [redacted] (b) (4) The Agency received new IND 126779 on 08/07/2015, and the Applicant opened the IND with 2 identical Phase 3 protocols.

The Agency agreed to a waiver of photosafety studies, and the Agency agreed that a long-term safety study was not needed if the Applicant constructed an adequate clinical bridge to Ultravate cream, 0.05%.

¹ Valencia IC, Kerdel FA. Chapter 216. Topical Corticosteroids. In: Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Wolff K. eds. *Fitzpatrick’s Dermatology in General Medicine*, 8e. New York, NY: McGraw-Hill; 2012.
<http://accessmedicine.mhmedical.com/content.aspx?bookid=392&Sectionid=41138952>. Accessed August 31, 2015.

Pediatric Plan

The Applicant submitted the Agreed Initial Pediatric Study Plan (iPSP) on 05/31/2016. The iPSP proposed the following:

-  (b) (4)
- Partial waiver of study of children birth to 5 years  (b) (4) of age because of the small number of children in this age group the necessary studies are impossible or highly impracticable (e.g., the number of patients in that age group is so small or patients in that age group are geographically dispersed) (FDA Section 505b(a)(4)(B)(i) of the Act).
- Deferral for conduct of a Phase 1 PK/HPA axis suppression study of pediatric subjects 6 – 16 years 11 months because the Phase 3 studies in adults were ongoing, and the Applicant anticipated the marketing application would be submitted prior to completion of the planned pediatric study.

The timeline for the pediatric study:

- Final Protocol Submission: June 2017
- Study Completion: June 2020
- Final Report Submission: Dec 2020

 (b) (4)

Pre-NDA Meeting

The pre-NDA meeting was held on 08/02/2017. The Agency agreed that 425 subjects with psoriasis who were treated with the to-be-marketed formulation of IDP-122 Lotion, approximately 365 of whom were treated for at least 8 weeks (the intended dosing duration for the to-be-marketed product) appeared to be adequate to support a marketing application.

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

4.1. Office of Scientific Investigations (OSI)

Three clinical sites underwent OSI audit. The selected sites, with the rationale for selection are presented below, as per the Clinical Inspection Summary:

1. Site 607 for Trial 301: Brock McConnehey, D.O. (Boise, ID):

This site was selected because of high efficacy effect: 54% in the IDP-122 Lotion group and 1% in the vehicle group.*

2. Site 618 for Trial 301: David Stoll, M.D. (Beverly Hills, CA)

This site had high efficacy effect: 71% in the IDP-122 Lotion group and 0% in vehicle group.*

3. Site 711 for Trial 302: Edward Primka, M.D. (Knoxville, TN)

This site was selected due to:

- High efficacy effect: 88% in the IDP-122 Lotion group and 0% in the vehicle group.*
- High protocol violations (the inspection report summary discusses four subjects with reports of missed doses and extra doses; these violations were infrequent and considered unlikely to have had a major impact on efficacy over the treatment period).
- More subjects discontinued from the vehicle arm (this item was not further addressed in the inspection report summary).

***Source:** Efficacy-by-Site tables by Rebecca Hager, Ph.D. for site-selection meeting.

The inspections identified no deviations from the regulations for any of the sites. The final classification of all three inspections was No Action Indicated (NAI).

4.2. Product Quality

Novel excipients: No.

Any impurity of concern: No

Recommendations and Conclusion on Approvability

The applicant of this NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug substance and drug product.

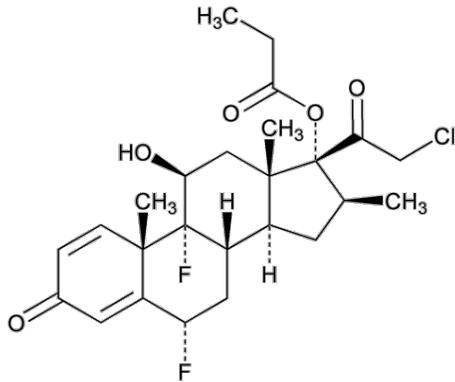
The facility review team from the Office of Process and Facility (OPF) has issued an “Acceptable” recommendation for the facilities involved in this application.

From a quality perspective, this NDA is approvable provided labeling and label comments are adequately addressed by the applicant.

Summary of Quality Assessments

Drug Substance

Bryhali lotion is a product containing 0.01% (w/w) halobetasol propionate. Halobetasol propionate, is a synthetic corticosteroid. The chemical name for halobetasol propionate is 21-chloro-6 α , 9-difluoro-11 β , 17-dihydroxy-16 β -methylpregna-1, 4-diene-3,20-dione 17-propionate. The chemical structure of halobetasol propionate is:



It has a molecular formula of C₂₅H₃₁ClF₂O₅ and a molecular weight of 484.96 g/mol. Halobetasol propionate is a white to off-white crystalline powder. It is practically insoluble in water, freely soluble in dichloromethane and in acetone. The drug substance is manufactured by (b) (4). Detailed CMC information of halobetasol propionate drug substance for this NDA is referred to DMF # (b) (4).

DMF # (b) (4) has been reviewed and found adequate in supporting the approval of this NDA. The NDA is recommended for approval from drug substance perspective

Drug Product

The drug product, Bryhali, is a topical lotion which contains 0.01% (w/w) halobetasol propionate. 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%. All the inactive ingredients are of compendial grade. 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) a (b) (4) cap. The container closure system is deemed acceptable for its intended use in terms of its safety, protection of the drug product, and compatibility with the drug formulation based on information provided.

The final specification for the halobetasol propionate lotion is deemed adequate to ensure the identity, strength, purity, and quality of the drug product during its expiration dating period. The long-term stability data up to 30 months for the three registration batches of the drug product produced at (b) (4) scale are provided in the NDA

submission. The stability data submitted are sufficient to support the proposed expiration dating period of 36 months when stored at room temperature. The results of in-use studies support that the product can be continuously used over the course of 8 weeks with no undesirable trends to physical, chemical or microbial characteristics. The estimated EIC (expected introduction concentration) for the drug substance is well below 1 ppb. The claim of categorical exclusion is acceptable per 21 CFR 25.31 (b).

The recommended expiration dating period of the drug product is 36 months. The NDA is recommended for approval from the drug product perspective.

Labeling and Labels

Pending labeling negotiation with applicant.

Drug Product Manufacturing Process

The bulk drug product is prepared by  (b) (4)



The batch formula, manufacturing process parameters, and in-process controls and tests are deemed adequate to ensure the robustness of the drug product manufacturing process. The NDA is recommended for approval from the perspective of drug product manufacturing process.

Biopharmaceutics

The applicant is seeking approval for halobetasol propionate lotion, 0.01%. The applicant has not submitted any in vitro release test (IVRT) related information for the proposed product. There was a manufacturing site change from Dow Pharmaceutical Sciences facility in Petaluma, CA to Valeant Pharmaceuticals International, Inc. facility at Laval (Canada) prior to Phase 3 clinical trials. However, Phase 3 studies were conducted with batches of the drug product manufactured at the proposed commercial site. Therefore, additional data are not needed to support the manufacturing site change. Additionally, the lack of an IVRT method and in vitro release acceptance criteria will not affect the approvability of this NDA. The Division of Biopharmaceutics defers the approvability decision on this NDA to the other review disciplines.

Quality Microbiology

The drug product is a non-sterile lotion containing 0.01%/ halobetasol propionate.

(b) (4)
Microbial limit tests per USP <61> and <62> for Total Aerobic Microbial Count and Total Combined Yeast/Mold Count, and specified organisms (*P. aeruginosa* and *S. aureus*) are included in the drug product specification. Test for *Bulkholderia Cepacia Complex* (Bcc) (b) (4) are also included in the drug product specification. The test methods have been properly validated.

The results of stability studies indicated that proposed 36-month expiration dating period is acceptable (b) (4)

The drug product's microbiological quality throughout its expiration dating period can be assured by the stability testing program. The NDA is recommended for approval from the perspective of quality microbiology.

Facilities

Table 2: Facilities Related to Drug Substance Manufacture and Testing

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Final Recommendation
(b) (4)			Approve based on profile
			Approve based on profile
			Approve based on profile
			Approve based on profile
			Approve based on profile
			Approve based on profile
			Approve based on profile

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Final Recommendation
(b) (4)			Approve based on profile
			Approve based on profile
			No Further Evaluation (NFE)

Facilities Related to Drug Product Manufacture and Testing

All the facilities are deemed acceptable in their identified functions and responsibilities to support the approval of NDA 209355.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The applicant has developed BRYHALI (halobetasol propionate) Lotion, 0.01%, for the topical treatment of plaque psoriasis. Halobetasol propionate has been marketed for the treatment of plaque psoriasis for more than 20 years. All excipients used in BRYHALI Lotion are commonly used in topical products and are listed in the FDA's Inactive Ingredient Guide.

The applicant is seeking approval of BRYHALI Lotion 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 has established an adequate clinical bridge to the Listed Drug, Ultravate (halobetasol propionate) Cream, 0.05%. Refer to Clinical Pharmacology section of this review for the details. The applicant is relying on the Agency's finding of safety for the Listed Drug. The nonclinical information from the approved label for the Listed Drug that the applicant intends to rely on includes fertility and reproduction, embryofetal development and genotoxicity. The toxicities of halobetasol propionate are well characterized and typical for the drug class.

The applicant conducted a pivotal repeat dose dermal toxicity study with a fixed dose combination drug product containing halobetasol propionate and tazarotene in a lotion vehicle and halobetasol and tazarotene monads in a lotion vehicle. The lotion vehicle composition used in this study is the same as used in BRYHALI Lotion. The applicant used the toxicity data from the halobetasol portion of this repeat dose dermal toxicity study to support the safety of BRYHALI Lotion.

The pivotal 3-month repeat dose dermal toxicity study in minipigs was conducted with five treatment groups that included 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%) of the combination product and monad groups containing halobetasol propionate (0.02%) or tazarotene (0.090%) in the lotion vehicle. The mid dose group is equivalent to the halobetasol propionate concentration used in BRYHALI lotion. Topical administration of the three doses of the fixed dose combination drug product as well as halobetasol propionate and tazarotene monads once daily for 90 days was well tolerated in minipigs. Treatment related effects included 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. Decreased organ weights and/or microscopic changes observed in target organs showed partial or full reversibility following a 1-month recovery period. The halobetasol propionate lotion monad used in this study contains 0.02% halobetasol propionate

which is 2-fold higher than the concentration used in BRYHALI Lotion. The toxicity profile for the halobetasol propionate lotion monad was consistent with that of topical corticosteroids.

BRYHALI 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

The applicant intends to rely on the Agency's findings of safety for Ultravate Cream (NDA 19967) as the Listed Drug.

The following nonclinical pharmacology and toxicology studies were reviewed under IND (b) (4) 126779. A summary of these studies is provided below.

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.

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. This review will focus on the data available for halobetasol propionate from this study. An $IC_{50} > 10 \mu M$ (the highest concentration tested) was established for halobetasol propionate. Therefore, halobetasol propionate has no hERG inhibition potential based on the results from this in vitro study.

No standalone safety pharmacology studies have been conducted with the drug substance or the drug product. The effects of halobetasol propionate on ECG measurements were evaluated in the 3-month repeat dose minipig dermal toxicity study. There were no test article-related ECG abnormalities noted in this study.

5.4. ADME/PK

The applicant has not conducted nonclinical pharmacokinetic studies with the drug substance or drug product. However, the toxicokinetics (TK) of halobetasol propionate were determined in the 3-month repeat dose toxicity study in minipigs conducted with three doses of the fixed dose combination product containing halobetasol propionate and tazarotene in a lotion vehicle and the monad halobetasol propionate in a lotion vehicle. A summary of the halobetasol propionate 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. The concentration of halobetasol propionate in the low strength, clinical strength, enhanced strength and HP lotion monad in the following table are 0.002%, 0.01%, 0.02% and 0.02%, respectively. The low strength, clinical strength and enhanced strength products also contained tazarotene at concentrations of 0.01%, 0.045% and 0.09%. It appears that the presence of tazarotene in the low, clinical and enhanced strength products increased the systemic exposure to halobetasol propionate compared to the halobetasol propionate lotion monad.

Type of Study	Major Findings
<p>TK data from a repeat dose toxicology study</p> <p>A 3-month Study of IDP-118-A by Dermal Administration in Minipigs with a 1-month Recovery Period, Study # V01-118A-605^a</p>	<p><u>Halobetasol propionate TK data for male minipigs</u></p> <p><i>T_{max}</i>:</p> <p>Low strength: 4 hrs Clinical strength: 4 hrs Enhanced strength: 4 hrs HP lotion monad: 8 hrs</p> <p><i>AUC₀₋₂₄</i>:</p> <p>Low strength: 1.3 ng·hr/mL Clinical strength: 2.8 ng·hr/mL Enhanced strength: 4.0 ng·hr/mL HP lotion monad: 1.4 ng·hr/mL</p> <p><i>C_{max}</i>:</p> <p>Low strength: 0.14 ng/mL Clinical strength: 0.23 ng/mL Enhanced strength: 0.31 ng/mL HP lotion monad: 0.08 ng/mL</p> <p><i>Accumulation</i>: No evidence of systemic accumulation from Day 28 to Day 90, indicating steady-state had been achieved by Day 28.</p> <p><i>Dose proportionality</i>: Systemic exposure increased in a roughly dose-</p>

Type of Study	Major Findings
	<p>proportional manner</p> <p><u>Halobetasol propionate TK data for female minipigs</u></p> <p><i>T_{max}</i>:</p> <p>Low strength: 4 hrs Clinical strength: 3 hrs Enhanced strength: 4 hrs HP lotion monad: 4 hrs</p> <p><i>AUC₀₋₂₄</i>:</p> <p>Low strength: 1.0 ng·hr/mL Clinical strength: 2.1 ng·hr/mL Enhanced strength: 4.9 ng·hr/mL HP lotion monad: 0.92 ng·hr/mL</p> <p><i>C_{max}</i>:</p> <p>Low strength: 0.10 ng/mL Clinical strength: 0.23 ng/mL Enhanced strength: 0.35 ng/mL HP lotion monad: 0.07 ng/mL</p> <p><i>Accumulation</i>: No evidence of systemic accumulation from Day 28 to Day 90, indicating steady-state had been achieved by Day 28.</p> <p><i>Dose proportionality</i>: Systemic exposure increased in a roughly dose-proportional manner</p>

^a – IDP-118A is the code name for the fixed dose combination product containing halobetasol propionate and tazarotene in a lotion vehicle

The applicant conducted a human maximal use pharmacokinetic/hypothalamic-pituitary-adrenal (HPA) axis suppression study to determine biocomparability between BRYHALI Lotion and the Listed Drug to establish an adequate clinical bridge to the Listed Drug. It is determined that the applicant has established an adequate clinical bridge to the Listed Drug, Ultravate Cream. Refer to Clinical Pharmacology section of this review for the details.

5.5. Toxicology

5.5.1. General Toxicology

Study 1: 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 conducted with five treatment groups that included 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%) of the fixed dose combination product, as well as monad groups containing halobetasol propionate (0.02%) or tazarotene (0.090%) in the lotion vehicle. The lotion vehicle used in this study contains the same excipient composition as BRYHALI Lotion. The mid dose group is equivalent to the halobetasol propionate concentration used in BRYHALI Lotion. The halobetasol propionate monad group contained 0.02% halobetasol propionate, which is 2-fold higher than the halobetasol propionate concentration used in BRYHALI Lotion.

Administration of the three doses of the fixed dose combination product as well as halobetasol propionate and tazarotene monads by once daily dermal application for 90 days was well tolerated in minipigs.

Treatment related effects included 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. The toxicity profile of the halobetasol propionate lotion monad group was consistent with that of topical corticosteroids.

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.

Halobetasol propionate was detected in plasma following dermal administration of the three doses of the fixed dose combination product and the halobetasol propionate lotion monad group. 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 AUC, were observed in the high dose of the fixed dose combination product on Day 28 for halobetasol propionate. There was no evidence of drug systemic accumulation between Days 28 and 90, and steady state appeared to be reached by Day 28. Systemic exposure to halobetasol propionate appeared to increase after treatment with the fixed dose combination product as compared to the halobetasol propionate lotion monad. Refer to Section 5.4 ADME/PK for toxicokinetic details for this study.

5.5.2. Genetic Toxicology

The applicant is relying on the Agency's finding of safety for the Listed Drug, Ultravate Cream, and references the Listed Drug's label for genetic toxicology information to support the NDA for BRYHALI Lotion. The following genetic toxicology information is included in the Listed Drug label.

Positive mutagenicity effects were observed in two genotoxicity assays. Halobetasol propionate was positive in a Chinese hamster micronucleus test, and in a mouse lymphoma gene mutation assay in vitro.

In other genotoxicity testing, halobetasol propionate was not found to be genotoxic in the Ames/Salmonella assay, in the sister chromatid exchange test in somatic cells of the Chinese hamster, in chromosome aberration studies of germinal and somatic cells of rodents, and in a mammalian spot test to determine point mutations.

5.5.3. Carcinogenicity

The applicant is relying on the Agency's finding of safety for the Listed Drug, Ultravate Cream. The Ultravate Cream label indicates that long-term animal studies have not been performed to evaluate the carcinogenic potential of halobetasol propionate. Therefore, no carcinogenicity information is included in the Ultravate Cream label.

5.5.4. Reproductive and Developmental Toxicology

The applicant is relying on the Agency's finding of safety for the Listed Drug, Ultravate Cream, and references the Listed Drug label for reproductive and developmental toxicology information to support the NDA for BRYHALI Lotion. The following reproductive and developmental toxicology information is included in the Listed Drug label.

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.

5.5.5. Other Toxicology Studies

Study 1: 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 two lotion formulations of the fixed dose combination of halobetasol propionate and tazarotene, the halobetasol propionate lotion monad and the tazarotene lotion monad. The results from the halobetasol propionate monad lotion will be provided in this review.

Halobetasol propionate was predicted to be minimally-irritating to non-irritating to the eye based on the results from this study.

Study 2: A Reduced Local Lymph Node Assay with IDP-118 Lotion (Study # 7001-U6HP-02-10, GLP)

This study was conducted to determine if two lotion formulations of the fixed dose combination of halobetasol propionate and tazarotene 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. Treatment with either of the two lotion formulations of the fixed dose combination of halobetasol propionate and tazarotene did not result in a SI of greater than or equal to 3 relative to appropriate controls. Therefore, these findings suggest that the two lotion formulations of the fixed dose combination of halobetasol propionate and tazarotene are not sensitizers.

5.6. Labeling

Revisions to the applicant's proposed wording for the nonclinical and related sections of the label are provided below. Refer to the clinical review for recommended revisions for the clinical information contained in Section 8 of the labeling. With the exception of the Section 8 subheading "Pregnancy Exposure Registry", "Risk Summary" and "Data" which the applicant underlined per PLLR specifications, it is recommended that the underlined wording be inserted into and the ~~strike through~~ wording be deleted from the

BRYHALI Lotion label text. A clean copy of these revised labeling sections is provided in Section 13.3 Appendices.

(b) (4)

HIGHLIGHTS OF PRESCRIBING INFORMATION INDICATIONS AND USAGE

(b) (4) BRYHALI Lotion is a corticosteroid indicated for the topical treatment of plaque psoriasis.

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available (b) (4) data on (b) (4) BRYHALI Lotion use in (b) (4) pregnant (b) (4) to inform (b) (4) a drug-associated risks (b) (4) of major-birth defects, (b) (4) miscarriage, or adverse maternal or fetal outcomes.

(b) (4)

In animal reproduction studies, increased malformations, including cleft palate and omphalocele, were observed after oral administration of halobetasol propionate during organogenesis to pregnant rats and rabbits. The available data do not support relevant comparisons of systemic halobetasol propionate exposures achieved in the animal studies to exposures observed in humans after topical use of BRYHALI Lotion.

Data

Animal Data

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

(b) (4)
Halobetasol propionate was embryotoxic in rabbits but not in rats. Cleft palate was observed in both rats and rabbits. Omphalocele was seen in rats but not in rabbits.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

(b) (4)
Corticosteroids play a role in cellular signaling, immune function, inflammation, and protein regulation; however, the precise mechanism of action in plaque psoriasis is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

(b) (4)
Halobetasol propionate was not found to be genotoxic in the Ames assay, in the sister chromatid exchange test in Chinese hamster somatic cells, in chromosome aberration studies of germinal and somatic cells of rodents, or in a mammalian spot test. Positive mutagenicity effects were observed (b) (4) in (b) (4) a mouse lymphoma gene mutation assay in vitro and in a Chinese hamster micronucleus test.

NDA/BLA Multi-disciplinary Review and Evaluation – NDA 209355
BRYHALI™ (halobetasol propionate) lotion, 0.01%

Studies in rats following oral administration of halobetasol propionate at dose levels up to 0.05 mg/kg/day, [REDACTED] (b) (4) indicated no impairment of fertility or general reproductive performance.

6 Clinical Pharmacology

6.1. Executive Summary

The clinical pharmacology program consisted of a Maximal Use Pharmacokinetic (PK) Study (MUsT) that evaluated PK of IDP-122 Lotion in adult subjects with moderate or severe psoriasis under maximal use conditions, and a vasoconstrictor study that evaluated vasoconstrictor potency of IDP-122 Lotion. Because the applicant followed a 505(b)(2) regulatory pathway, relative bioavailability and comparative HPA axis suppression between IDP-122 Lotion and the Listed Drug, Ultravate® (halobetasol propionate) Cream, 0.05% were assessed in the MUsT. The key review findings with specific recommendations and comments are summarized below:

Evidence of effectiveness	Efficacy was not evaluated in the PK study. See section 7 for further information on evidence of effectiveness from the two Phase 3 trials.
General dosing instruction	The proposed dosing regimen (apply once daily) is acceptable and supported primarily by the data from two Phase 3 trials and the MUsT.
Pharmacokinetics	PK of halobetasol propionate (HP) was assessed under maximal use conditions following application of IDP-122 Lotion for 14 days and the systemic exposure was at or near steady state by Day 14.
HPA Axis Suppression	Following administration of IDP-122 Lotion once daily, the incidence of HPA axis suppression was 5.6% on Day 29 and 15.8% on Day 57.
Vasoconstrictor Potency	The potency of IDP-122 Lotion is between potent to superpotent
Clinical Bridge between IDP-122 and the Listed Drug	Clinical bridge between IDP-122 and Ultravate® Cream was established by demonstrating that the systemic exposure of IDP-122 under maximal use conditions was not greater than Ultravate® cream.
Recommendation	From a clinical pharmacology standpoint, this NDA is acceptable provided labeling comments are adequately addressed by the applicant.
Post Marketing Requirement	Conduct a maximal use PK and HPA axis suppression in subjects 6 years to less than 17 years if age with plaque psoriasis.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Pharmacokinetics	
PK parameters	The majority of the plasma concentrations of HP following IDP-122 treatment were below the lower limit of quantification (LLOQ) of 50 pg/mL. By Day 14, the systemic concentrations of IDP-122 were at or near steady state and were quantifiable only in 5 out of 20 subjects. On Day 14 the Mean C _{max} (SD) was 31.2 (62.2) pg/mL and Median T _{max} was 2.15 hr. AUC _(0-t) could be estimated only in two subjects and the values were 437 pg*hr/mL, and 3890 pg*hr/mL. Mean AUC _(0-t) , t _{1/2} and K _{el} were not reliably estimated due to insufficient number of quantifiable timepoints.
Relative Bioavailability	Following administration of IDP-122 Lotion or Ultravate Cream, mean C _{max} for 14 days were 31.2 pg/mL and 58.2 pg/mL, respectively. The ratio of arithmetic means was 0.536. This is supportive of establishing clinical bridge between IDP-122 and Ultravate Cream. AUC values were not used due to insufficient data to permit any statistical analysis due to quantifiable values only in 2 subjects in the IDP-122 arm.
Pharmacodynamics	
HPA Axis Suppression	IDP-122 caused reversible HPA axis suppression when applied once daily for 8 weeks. Specifically, HPA axis suppression was observed in 1 subject (5.6%) on Day 29 and 3 subjects (15.8%) on Day 57.
Vasoconstrictor Potency	IDP-122 Lotion is in the range of potent to superpotent topical corticosteroid.
Bioanalytical Assays	
The validation reports for quantification of plasma concentration of HP and cortisol assay were submitted and bioanalytical methods were adequately validated.	

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed a dosing regimen of application of a thin layer of IDP-122, once daily to affected areas for up to 8 weeks is supported by safety from the maximal use study and efficacy and safety data from the two Phase 3 trials. Refer to Section 7 of this review for

efficacy and safety findings from the Phase 3 trials. It should be noted that the applicant is seeking a longer duration of treatment (i.e. 8 weeks) compared to the listed drug which is approved for a 2 week treatment duration.

Therapeutic Individualization

Therapeutic individualization was not evaluated.

Outstanding Issues

There are no outstanding issues that would preclude the approval of IDP-122 (halobetasol, 0.01%) Lotion from a Clinical Pharmacology perspective.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Study V01-118A-501 (MUSt) was a multicenter, open-label, randomized study designed to assess the safety, plasma PK profile, and HPA axis suppression potential of topically applied IDP-122 (halobetasol propionate [HP] 0.01%) Lotion compared with Ultravate® Cream (HP 0.05%) in subjects at least 18 years of age with moderate to severe plaque psoriasis.

A total of 46 subjects were randomized to the treatment with either IDP-122 Lotion (24 subjects) or Ultravate Cream (22 subjects). Twenty subjects (83.3%) in the IDP-122 Lotion group and 22 subjects (100%) in Ultravate® group completed the study. Reasons for discontinuation in the IDP-122 group included subject request (8.3%), adverse event (4.2%) [i.e. cerebrovascular event (see details under summary of safety below)] and other (4.2%). It is noted that two subjects received a different treatment than to which the subject was originally randomized. These subjects were accounted for and included in the correct treatment group such that there were 23 subjects in the IDP-122 Lotion and Ultravate® Cream arms. The analyses using PK and Safety populations was performed based on the actual treatment received. The PK population further excluded two subjects in the IDP-122 Lotion group due to having no PK data on Days 1-2, 14-15, or 28-29. Therefore, PK analyses was performed in 21 subjects in IDP-122 group (excluding the 2 subjects that discontinued) and 23 subjects in Ultravate Cream group. Demographic data by PK population are summarized in Table 3. The mean age was 47.8 years for IDP-122 group and 49.2 years in Ultravate group and majority of subjects were White and male.

Table 3: Summary of Subject Demographic Characteristics (PK Population)

		IDP-122 Lotion (N=21)	Ultravate Cream (N=23)
Age	Mean (SD)	47.8 (13.20)	49.2 (14.39)
	Median (Min, Max)	51.0 (25, 74)	47.0 (27, 77)
Sex	Male	15 (71.4%)	18 (78.3%)
	Female	6 (28.6%)	5 (21.7%)
Ethnicity	Hispanic or Latino	10 (47.6%)	13 (56.5%)
	Not Hispanic or Latino	11 (52.4%)	10 (43.5%)
Race	American Indian or Alaska Native	0 (0.0%)	0 (0.0%)
	Asian	0 (0.0%)	0 (0.0%)
	Black or African American	2 (9.5%)	1 (4.3%)
	Native Hawaiian or Other Pacific Islander	0 (0.0%)	0 (0.0%)
	White	18 (85.7%)	21 (91.3%)
	Other/Multiple	1 (4.8%)	1 (4.3%)

Source: Adapted from Table 12 in in CSR for Study V01-118A-501.

Baseline disease characteristics are summarized in Table 4. All subjects had at least 20% of treatable body surface area (BSA) involvement of psoriasis and scores of moderate (3) or severe (4) of Investigator's Global Assessment (IGA). Mean % BSA affected by psoriasis in the allowed treatment areas was comparable between IDP-122 group (27.3%) and Ultravate group (30.8%). There were a greater percentage of subjects (38.1%) who had a severe (4) Baseline IGA score in the IDP-122 Lotion group compared with the Ultravate Cream group (21.7%).

Table 4: Summary of Baseline Disease Characteristics (PK Population)

		IDP-122 Lotion (N=21)	Ultravate Cream (N=23)
%BSA affected by psoriasis in allowed treatment area	Mean (SD)	27.3 (11.76)	30.8 (13.29)
	Median (min, max)	24 (20, 74)	25 (20, 68)
Investigator's Global Assessment	0 - Clear	0 (0%)	0 (0%)
	1 - Almost Clear	0 (0%)	0 (0%)
	2 - Mild	0 (0%)	0 (0%)
	3 - Moderate	13 (61.9%)	18 (78.3%)
	4 - Severe	8 (38.1%)	5 (21.7%)

Source: Adapted from Table 14.1.2.3 in CSR for Study V01-118A-501.

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The subjects were instructed to use the study medication from the supplied dosing cup to apply approximately 7 g (a cupful) of the study drug per day on the identified minimum 20% BSA. The amount of drug used during the treatment period is summarized in Table 33 in Section 13.4. OCP Appendices. Mean amount of formulation used over the treatment period was 409 g for IDP-122 (4 weeks) and 117g for Ultravate cream (2 weeks). Mean daily usage was approximately 7.3 g for IDP-122 Lotion and 8.4 g for Ultravate cream. The subjects in Ultravate Cream group used greater amount of study drug than the Ultravate Cream labeling recommended dose of less than 50 g/week.

Plasma samples of IDP-122 Lotion were collected on Days 1-2, Days 14-15, and Days 28-29 at predose, and at 1, 2, 4, 8 (\pm 15 minutes), 12 (\pm 30 minutes), and 24 hours (\pm 60 minutes) postdose. Table 5 summarizes the PK parameters of HP. By Day 14, the systemic concentrations of HP appear to be at or near steady-state after administration of IDP-122 Lotion once daily for 2 weeks. On Day 14, mean C_{max} (SD) was 31.2 (62.2) pg/mL and due to lack of sufficient number of quantifiable points, the $AUC_{(0-t)}$ was calculated for only for two subjects and the values were 437 pg*hr/mL and 3890 pg*hr/mL. Median T_{max} values were 4.95 hours, and 2.15 hours for Days 1-2, and Days 14-15, respectively. Values for $t_{1/2}$ and K_{el} were calculated from one subject, hence mean values were not reliably estimated. PK parameters were comparable between Day 14-15 and Day 28-29.

Table 5: Summary of HP Pharmacokinetic Parameters for IDP-122 Lotion

		Day 1-2	Day 14-15	Day 28-29	AR ^a
C_{max} (pg/mL)	N	21	20	19	1
	Mean (SD)	8.6 (28.5)	31.2 (62.2)	28.7 (71.2)	1.22 (NA)
	Median	0	0	0	
	(min, max)	(0, 117)	(0, 220)	(0, 303)	
AUC_(0-t) (pg·hr/mL)	N	1	2	2	0
	Mean (SD)	678 (NA)	2160 (2440)	2060 (2760)	NA
	Median		2160	2060	
	(min, max)		(437, 3890)	(110, 4010)	
AUC₍₀₋₂₄₎ (pg·hr/mL)	N	0	1	0	
	Mean		3890 (NA)		
T_{max}	N	2	5	5	
	Mean (SD)	4.95 (4.17)	4.83 (5.01)	5.55 (4.36)	
	Median	4.95	2.15	3.82	
	(min, max)	(2.00, 7.90)	(0.883, 12.1)	(1.95, 12.0)	
K_{el} (h⁻¹)	N		1		
	Mean (SD)		0.0212 (NA)		
t_{1/2} (h)	N		1		
	Mean (SD)		32.7 (NA)		

^aAccumulation Ratio Day 28 vs. Day 1

Note: Plasma concentrations below the lower limit of quantification are included as 0 pg/mL in summary statistic computations. The mean (SD) values calculated in 2 subjects and less, cannot be used for any statistical tests.

Source: Adapted from Table 14.3.0.1.2.1 in CSR for Study V01-118A-501.

The majority of the plasma concentrations of HP following IDP-122 treatment were BLQ (LLOQ of 50 pg/mL). On Day 14, systemic concentrations were quantifiable only in 5 out of 20 subjects and statistical inference for AUC at steady state was not possible as AUC_(0-t) were calculable in 2 subjects. Dose accumulation appears to be minimal as most plasma concentrations of HP remained unquantifiable for most of subjects at Day 14-15. The accumulation ratio (AR) for C_{max} was calculable for 1 subject between Days 28-29 and Days 1-2.

Systemic Exposure of IDP-122 Lotion vs. Ultravate Cream

Table 6 summarizes the comparison of steady-state PK between IDP-122 and Ultravate Cream. As the mean AUC values was not reliably estimated, the summary statistics of C_{max} were used to compare the systemic exposure between IDP-122 Lotion and Ultravate Cream. Mean C_{max} following administration of IDP-122 Lotion or Ultravate Cream for 14 days were 31.2 pg/mL and 58.2 pg/mL, respectively. The ratio of arithmetic means was 0.536. Geometric means for C_{max} were calculated by imputing BLQ values with ½ LLOQ value (25 pg/mL). The ratio of geometric means was 0.715

(90% CI: 48.8 % to 105%). Geometric mean and 90% CI for the ratio of AUC was not estimated due to insufficient data. Also, individual plasma concentration profiles (see 13.4 OCP Appendices) revealed that there were greater number of quantifiable plasma concentrations in the subjects in Ultravate Cream group compared to IDP-122 Lotion group, such that it was possible to estimate steady state AUC values in 8 subjects in the Ultravate Cream arm versus only 2 subjects in the IDP-122 arm. Furthermore, 12(52%) of 23 subjects in Ultravate group had at least one quantifiable plasma concentration on Day 14-15, compared to only 5 (25%) of 20 subjects in IDP-122 group. Integrated PK results reveals that the systemic exposure of HP following IDP-122 under maximal use conditions was not greater than Ultravate Cream. In conclusion, totality of this evidence supports establishment of a clinical bridge between IDP-122 Lotion and the Listed drug (Ultravate Cream).

Table 6: Comparison of Systemic Exposure (Day 14) of IDP-122 Lotion to Ultravate Cream

	IDP-122 Lotion (N=21)	Ultravate Cream (N=23)	Ratio (IDP-122 vs Ultravate)
C_{max} (pg/mL)			
N	20	23	
Arithmetic Mean (SD)	31.2 (62.2)	58.2 (72.6)	0.536
Geometric Mean (90% CI) ^a	36.5 (27.8, 48.0)	51.0 (38.5, 67.6)	0.715 (0.488, 1.050)
AUC_(0-t) (pg*h/mL)			
N	2	8	
Arithmetic Mean (SD)	2160	1910	1.13
Geometric Mean (90% CI)	1300 (1.31, 1300000)	1550 (925, 2600)	0.841 (0.222, 3.18)
AUC_(0-24h) (pg*h/mL)			
N	1	0	
Arithmetic Mean (SD)	3890 (NA)		NA
Geometric Mean (90% CI)	3890 (NA)		NA

^aGeometric means were calculated by imputing BLQ values with ½ LLOQ values (25 pg/mL).
 Source: Reviewer's analysis and adapted from Table 23 in CSR for Study V01-118A-501.

HPA Axis Suppression Evaluation

HPA axis suppression potential of IDP-122 Lotion was evaluated on Day 29 and Day 57 and for Ultravate Cream, it was evaluated on Day 15. Table 7 summarized the HPA axis suppression results. The HPA axis suppression test was normal at Screening for all subjects. In the IDP-122 Lotion group, an abnormal HPA axis suppression test was reported for 1 (5.6%) subject on Day 29 and for 3 (15.8%) subjects on Day 57; while in the Ultravate group abnormal HPA axis suppression was reported only in 1 (5%) subject on Day 15. Per applicant, the subject with the abnormal HPA axis suppression test at Day 29 also had an abnormal result at Day 57 and all 3 subjects had normal HPA axis

suppression test results at the unscheduled follow-up visits. Hence the results suggest that IDP-122 caused reversible HPA axis suppression after stopping the 8 week treatment. Although the HPA axis suppression rate for IDP-122 Lotion is three times higher than Ultravate Cream, in general the incidence of HPA axis suppression is considered as low and this will not preclude further assessment in pediatric subjects which will be requested as a post marketing requirement (PMR).

Table 7: Summary of HPA Axis Suppression Tests by Visit (Safety Population)

	Screening	Day 15	Day 29	Day 57
IDP-122 Lotion				
N	23	-	18	19
Normal	23 (100%)	-	17 (94.4%)	16 (84.2%)
Abnormal	0 (0%)	-	1 (5.6%)	3 (15.8%)
Ultravate® Cream				
N	23	20	-	-
Normal	23 (100%)	19 (95%)	-	-
Abnormal	0 (0%)	1 (5%)	-	-

Note: Poststimulation cortisol levels ≤ 18 $\mu\text{g/dL}$ considered abnormal.

Source: Adapted from Table 14.3.1.1.2 in CSR for Study V01-118A-501

In Table 7, it was noted that in the IDP-122 Lotion cohort, there were 23 subjects at screening and on Day 29 and Day 57 there were only 18 and 19 subjects, respectively. This is because HPA tests on Day 29 and Day 57 were not performed in four subjects who discontinued treatment. One subject was tested on screening and Day 57 without being tested on Day 29.

Summary of Safety

No deaths were reported in the study. In the IDP-122 Lotion group, a serious adverse event (SAE) which was a cerebrovascular incident was reported for 1 subject (4.3%) on Day 23 and this subject was withdrawn from the study. The applicant noted that this SAE was not considered related to the study drug. TEAEs were reported for 26.1% of subjects. Most frequently reported TEAEs were the nervous system disorders MedDRA System Organ Class (13.0%), which included headache (8.7%) and cerebrovascular accident (4.3%). A treatment-emergent adverse events (TEAEs) leading to discontinuation of study drug was reported for 1 subject (4.3%). 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.

Methods and Validation for Bioanalytical Assays

Halobetasol propionate in human plasma samples obtained from Study V01-118A-501 was quantified using LC-MS/MS. Full validation report was submitted and bioanalytical method was adequately validated. Summary of the validation parameters is presented in Table 34 in Section 13.4. under OCP Appendices. All PK samples were analyzed within the established long-term stability window (448 days). The assay was linear over

the range of 50.0 to 12800 pg/mL. The linearity range was adequate as none of the plasma concentrations exceeded the upper limit of the quantifiable concentration range. The applicant reported that approximately 10 % (121 out of 1204 samples) were analyzed for incurred sample repeat analysis (ISR) and 97% of ISR samples met the criteria of assay reproducibility, which was the percent difference must be within 20% of the mean of the original and repeated values.

Serum samples for HPA axis suppression evaluation were analyzed for cortisol concentration using commercially available cortisol assay kit. The validation report for cortisol assay kit was submitted and bioanalytical method was adequately validated. The applicant noted that all samples were analyzed within the manufacturer's recommended storage limit.

Vasoconstrictor Potential of IDP-122 Lotion

Vasoconstrictor properties of IDP-122 (HP, 0.01%) Lotion was evaluated in a single-point, randomized, evaluator-blinded, within-subject, single-center study (V01-118A-101). Detailed review is available in Section 13.4. under OCP Appendices. The relative potency of IDP-122 Lotion was estimated by comparing it with the reference products of known potency and a vehicle lotion formulation, using Stoughton-McKenzie bioassay system. Thirty (30) healthy, nontobacco-using adult subjects were enrolled in the study. 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. Also, two untreated control sites were designated on each forearm as a ChromaMeter reference site. The degree of vasoconstriction was measured using visual scoring (primary) and a ChromaMeter (informational) at pre-dose and at approximately 18 hours after the application of the formulations (i.e. after 2 hours [± 15 minutes] after washing of the test sites to remove study drug following 16 hours of application). The results are summarized in Table 8 which indicate that the potency of IDP-122 is between potent to super-potent.

Table 8: Vasoconstrictor Potential in Order of Most to Least Potent

Visual Assessment (Primary)	Rank	ChromaMeter Assessment
Ultravate® (HP, 0.05%) Cream (super potent)	1	Ultravate® (HP, 0.05%) Cream (super potent)
IDP-122 (HP, 0.01%) Lotion	2	Betamethasone Dipropionate Cream, 0.05% (upper mid-strength potent)
Betamethasone Dipropionate Cream, 0.05% (upper mid-strength potent)	3	IDP-122 (HP, 0.01%) Lotion
Fluocinonide Cream, 0.05% (potent)	4	Fluocinonide Cream, 0.05% (potent)
Triamcinolone Acetonide Cream (mid-strength potent)	5	Triamcinolone Acetonide Cream (mid-strength potent)
Vehicle Lotion	6	Vehicle Lotion
Untreated	7	Untreated

Source: Adapted from Table 11.4.1.1 and Table 11.4.1.3 in CSR for Study V01-118A-101.

Formulations

The to-be-marketed formulation was used in two Phase 3 trials and in a maximal use PK study. Hence, PK bridge between to-be-marketed and clinical formulations is not necessary for approval of this NDA.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The efficacy evaluated in the two Phase 3 trials and was not evaluated in the Phase 1 Pharmacokinetic Study (V01-118A-501). See Section 7 of this multi-disciplinary review for efficacy results.

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

Based on the safety results from the maximal use and Phase 3 trials and efficacy and safety results from the Phase 3 trials, the proposed dosing regimen is appropriate.

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

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No. A dose adjustment is not necessary based on the available efficacy and safety data in Phase 3 trials. The effect of intrinsic and extrinsic factors on the PK of IDP-122 Lotion was not evaluated.

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

Food-drug interaction studies are not needed for topical products. Drug-drug interaction potential was not needed for approval of this product, as the applicant followed 505(b)(2) pathway and a clinical bridge was established with the listed drug.

7 Statistical and Clinical Evaluation

7.1. Sources of Clinical Data and Review Strategy

7.1.1. Table of Clinical Studies

The clinical development program consisted of 8 studies:

- Two Phase 3, vehicle-controlled, double-blind, randomized (pivotal) studies in adult subjects with moderate to severe plaque psoriasis:
 - V01-122A-301 (301)
 - V01-122A-302 (302)
- Two Phase 2 controlled studies in adult subjects with moderate to severe plaque psoriasis:
 - V01-118A-201 (Phase 2, effect size, 201)
 - V01-122A-203 (Phase 2, clinical bridging to Ultravate Cream, 0.05%, 203)
- One Phase 1 PK study conducted in adult subjects with moderate to severe plaque psoriasis:
 - IDP-118A-501 (Phase 1 PK/clinical Bridging to Ultravate Cream, 0.05%, 501)
- Three Phase 1 studies conducted in adult healthy volunteers:
 - V01-118A-101 (steroid potency, 101)
 - V01-118A-102 (21-day cumulative irritation, 102)
 - V01-118A-103 (repeat insult patch test [RIPT], 103)

Table 9 provides additional details of these studies.

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Table 9: Listing of Clinical Trials Relevant to this NDA*

Study Type, ID, Sites, Location	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Duration of Treatment	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Primary Efficacy and Other Variables
Efficacy (Pivotal) V01-122A-301 20 sites in the US	The objective of the study was to evaluate the safety and efficacy of topical IDP-122 Lotion in comparison with vehicle when applied once daily to adult subjects with moderate to severe plaque psoriasis (defined as an IGA score of 3 or 4).	A Phase 3, Multicenter, Double-Blind, Randomized, Vehicle Controlled Clinical Study to Assess the Safety and Efficacy of IDP-122 in the Treatment of Plaque Psoriasis	Test Product: •IDP-122 (HP 0.01%) Lotion Reference Therapy: •IDP-122 Vehicle Lotion Test product and reference therapy were applied topically, once daily for 8 weeks.	8 weeks	Planned: approximately 210 randomized in a 2:1 ratio •140 subjects to IDP-122 Lotion •70 subjects to IDP-122 Vehicle Lotion Analyzed: 217 subjects were randomized •143 subjects to IDP-122 Lotion •74 subjects to IDP-122 Vehicle Lotion	Moderate to severe plaque psoriasis, covering 3% to 12% BSA	•Primary efficacy: Percentage of subjects with treatment success, defined as at least a 2-grade improvement from Baseline in IGA score and an IGA score equating to Clear or Almost Clear at Week 8 •Secondary efficacy: Percentage of subjects with treatment success in IGA score at each of Weeks 12, 6, 4, and 2 •Tertiary efficacy: Percentage of subjects with at least a 2-grade improvement from Baseline in psoriasis signs (erythema, plaque elevation, and scaling) of the selected target lesion •Other: BSA affected by psoriasis, DLQI •Safety: AEs; local skin reactions; abbreviated physical examinations; vital signs; and safety laboratory tests

Study Type, ID, Sites, Location	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Duration of Treatment	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Primary Efficacy and Other Variables
Efficacy (Pivotal) V01-122A-302 17 sites in the US	The objective of the study was to evaluate the safety and efficacy of topical IDP-122 Lotion in comparison with vehicle when applied once daily to adult subjects with moderate to severe plaque psoriasis (defined as an IGA score of 3 or 4).	A Phase 3, Multicenter, Double-Blind, Randomized, Vehicle Controlled Clinical Study to Assess the Safety and Efficacy of IDP-122 in the Treatment of Plaque Psoriasis	Test Product: •IDP-122 (HP 0.01%) Lotion Reference Therapy: •IDP-122 Vehicle Lotion Test product and reference therapy were applied topically, once daily for 8 weeks.	8 weeks	Planned: approximately 210 randomized in a 2:1 ratio •140 subjects to IDP-122 Lotion •70 subjects to IDP-122 Vehicle Lotion Analyzed: 213 subjects were randomized •142 subjects to IDP-122 Lotion •71 subjects to IDP-122 Vehicle Lotion	Moderate to severe plaque psoriasis, covering 3% to 12% BSA	•Primary efficacy: Percentage of subjects with treatment success, defined as at least a 2-grade improvement from Baseline in IGA score and an IGA score equating to Clear or Almost Clear at Week 8 •Secondary efficacy: Percentage of subjects with treatment success in IGA score at each of Weeks 12, 6, 4, and 2 •Tertiary efficacy: Percentage of subjects with at least a 2-grade improvement from Baseline in psoriasis signs (erythema, plaque elevation, and scaling) of the selected target lesion •Other: BSA affected by psoriasis, DLQI •Safety: AEs; local skin reactions; abbreviated physical examinations; vital signs; and safety laboratory tests

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Study Type, ID, Sites, Location	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Duration of Treatment	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Primary Efficacy and Other Variables
PK V01-118A-501 12 sites in the US	The objectives of this study were to evaluate the following in adult subjects with moderate to severe plaque psoriasis: •Safety of IDP-118 (halobetasol propionate [HP] 0.01% and tazarotene [Taz] 0.045%) Lotion and IDP-122 (HP Monad 0.01%) Lotion administered topically once daily for 8 weeks •Systemic exposure of HP, Taz, and tazarotenic acid from IDP-118 Lotion when applied once daily for 4 weeks compared with that from 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 from IDP-122 Lotion when applied once daily for 4 weeks compared with that from Ultravate Cream applied for 2 weeks •Comparison of the hypothalamic-pituitary-adrenal (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.	A Phase 1b Open-Label, Randomized Study Evaluating the Absorption and Systemic PK and HPA Axis Suppression Potential of Topically Applied IDP-118 Lotion and HP Monad (IDP-122) Lotion in Subjects with Moderate to Severe Plaque Psoriasis	Test Products: •IDP-118 Lotion (HP 0.01%, Taz 0.045%) administered topically once daily in the morning for 8 weeks (approximately 7 g/day) •IDP-122 Lotion (HP 0.01%) administered topically once daily in the morning for 8 weeks (approximately 7 g/day) Reference Therapy: •Ultravate Cream (HP 0.05%) administered topically once daily in the morning for 2 weeks (approximately 7 g/day) •Tazorac Cream (Taz 0.05%) administered topically once daily in the morning for 4 weeks (approximately 7 g/day)	2, 4, or 8 weeks	Planned: approximately 90 subjects, with a 1:1:1:1 randomization ratio in order to obtain 20 evaluable subjects in each treatment group Analyzed: 94 subjects randomized •23 subjects to IDP-118 Lotion •24 subjects to IDP-122 Lotion •22 subjects to Ultravate Cream •25 subjects to Tazorac Cream	Moderate to severe plaque psoriasis with at least 20% treatable BSA	•PK: Plasma concentrations and pharmacokinetic (PK) parameters of HP, Taz, and tazarotenic acid (as appropriate) on Days 1-2 (all treatment groups), Days 14-15 (all treatment groups), and Days 28-29 (all treatment groups except Ultravate Cream) •PD/Safety: Percentage of subjects manifesting HPA axis suppression defined as a cortisol level of ≤18 µg/dL measured at 30 minutes after stimulation with cosyntropin •Other safety: AEs, local skin reactions; abbreviated physical examinations; vital signs; and safety laboratory tests •Efficacy: IGA scores

Study Type, ID, Sites, Location	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Duration of Treatment	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Primary Efficacy and Other Variables
Efficacy (Effect Size) V01-118A-201 18 sites in the US	The objective of the study was to evaluate the safety and efficacy of topical IDP-118 Lotion in comparison with its monads and vehicle when applied once daily to adult subjects with moderate to severe plaque psoriasis (defined as an IGA score of 3 or 4).	A Phase 2, Multicenter, Double-Blind, Randomized, Vehicle Controlled Clinical Study to Assess the Safety and Efficacy of IDP-118 in the Treatment of Plaque Psoriasis	Test Products: •IDP-118 (HP 0.01%, Taz 0.045%) Lotion •IDP-118 Monad (HP 0.01%) Lotion (“HP Monad [IDP-122]”) •IDP-118 Monad (Taz 0.045%) Lotion Reference Therapy: •IDP-118 Vehicle Lotion The test products and the reference therapy were applied topically, once daily for 8 weeks.	8 weeks	Planned: approximately 210 subjects randomized in a 2:2:2:1 ratio •60 subjects to IDP-118 (HP 0.01%, Taz 0.045%) Lotion •60 subjects to IDP-118 Monad (HP 0.01%) Lotion (IDP-122) •60 subjects to IDP-118 Monad (Taz 0.045%) Lotion Analyzed: 212 subjects were randomized •59 subjects to IDP-118 (HP 0.01%, Taz 0.045%) Lotion •63 subjects to IDP-118 Monad (HP 0.01%) Lotion (IDP-122) •59 subjects to IDP-118 Monad (Taz 0.045%) Lotion •31 subjects to IDP-118 Vehicle Lotion	Moderate to severe plaque psoriasis, covering 3% to 12% BSA	•Efficacy: Percentage of subjects with treatment success, defined as at least a 2-grade improvement from Baseline in IGA score and an IGA score equating to Clear or Almost Clear, at Week 8; IGA scores and percentage of subjects with treatment success at Weeks 12, 6, 4, and 2; percentage of subjects with treatment success at Week 8 cross-tabulated with Week 12 (4-week follow-up); percentage of subjects with at least a 2-grade improvement from Baseline in the IGA; percentage of subjects with at least a 2-grade improvement in each of the psoriasis signs (erythema, plaque elevation, and scaling) of the selected target lesion •Safety: AEs; local skin reactions; abbreviated physical examinations; vital signs; and safety laboratory tests

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Study Type, ID, Sites, Location	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Duration of Treatment	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Primary Efficacy and Other Variables
Efficacy (Clinical Bridge) V01-122A-203 15 sites in the US	The objective of the study was to establish a clinical bridge for IDP-122 (HP 0.01%) Lotion when applied topically once daily to subjects with moderate to severe plaque psoriasis (defined as an IGA score of 3 or 4) to that of the comparator drug Ultravate (HP) Cream, 0.05%.	A Phase 2, Multi-Center, Double-Blind, Randomized, Vehicle-Controlled Study to Compare the Safety and Efficacy of IDP-122 Lotion to Ultravate® (HP) Cream, 0.05% in the Treatment of Plaque Psoriasis	Test Product: •IDP-122 (HP 0.01%) Lotion Reference Therapy: •Ultravate (HP) Cream, 0.05% •Vehicle Lotion •Vehicle Cream The test product and reference therapy were applied topically, once daily for 2 weeks.	2 weeks	Planned: approximately 150 subjects randomized in a 4:4:1:1 ratio •60 subjects to IDP-122 Lotion •60 subjects to Ultravate Cream •15 subjects to Vehicle Lotion •15 subjects to Vehicle Cream Analyzed: 150 subjects were randomized •60 subjects to IDP-122 Lotion •57 subjects to Ultravate Cream •17 subjects to Vehicle Lotion •16 subjects to Vehicle Cream	Moderate to severe plaque psoriasis, covering 3% to 12% BSA	•Efficacy: Percentage of subjects with treatment success, defined as at least a 2-grade improvement from Baseline in IGA score and an IGA score equating to Clear or Almost Clear, at Week 2; percentage of subjects with at least a 2-grade improvement from Baseline in IGA score at Week 2; percentage of subjects with at least a 2-grade improvement from Baseline for each of the psoriasis signs (erythema, plaque elevation, and scaling) of the selected target lesion at Week 2; and BSA affected by psoriasis •Safety: AEs, local skin reactions; abbreviated physical examinations; vital signs; and safety laboratory tests

Study Type, ID, Sites, Location	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Duration of Treatment	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Primary Efficacy and Other Variables
PD (Steroid Potency) V01-118A-101 1 site in the US	The objective of this study was to use the vasoconstrictor response to determine the potency of IDP-118 (halobetasol propionate [HP] 0.01% / tazarotene [Taz] 0.045%) Lotion and IDP-122 (HP 0.01%) Lotion compared to four currently marketed topical corticosteroid formulations of known potency and a vehicle lotion in healthy adult male and female subjects.	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	Test Products: •IDP-118 Lotion (HP 0.01%, Taz 0.045%) •IDP-122 Lotion (HP 0.01%) Reference Therapy: •Ultravate Cream (HP 0.05%) •Betamethasone Dipropionate Cream 0.05% •Fluocinonide Cream 0.05% •Triamcinolone Acetonide Cream 0.1% •Vehicle Lotion •No Treatment Test products and reference therapy were administered topically as a single dose that remained on the skin for 16 hours.	16 hours	30	Healthy subjects	•PD: Vasoconstriction, assessed as skin blanching and measured using visual scoring (primary) and a ChromaMeter (informational) •Safety: AEs

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Study Type, ID, Sites, Location	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Duration of Treatment	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Primary Efficacy and Other Variables
Other (Safety; 21-Day Cumulative Irritancy) V01-118A-102 1 site in the US	The primary objective of this study was to determine the potential of IDP-118 and IDP-122 to cause skin irritation after repeated topical application to the healthy skin of humans under controlled conditions. In addition, safety was assessed by evaluation of any AEs reported during the study.	A 21-Day, Randomized, Controlled Study to Evaluate the Skin Irritation Potential of IDP-118 Lotion (halobetasol propionate 0.01% and tazarotene 0.045%) and IDP-122 Lotion (halobetasol propionate 0.01%) in Healthy Volunteers Using a Cumulative Irritant Patch Test Design (Within-Subject Control)	Test Products: •IDP-118 Lotion (HP 0.01%, Taz 0.045%) •IDP-122 Lotion (HP 0.01%) •Vehicle Lotion Reference Therapy: •Tazorac Cream (Taz 0.05%) • Sodium lauryl sulfate 0.5% aqueous solution for topical administration •Saline 0.9% for topical administration Test products and reference therapy were administered topically as semi-occlusive patches at approximately 0.2 mL per patch once daily for 21 days to the infrascapular area of the back.	21 days	40	Healthy subjects	*Safety: Skin irritation, assessed as a mean cumulative irritation score, calculated from the total observed scores for each subject on Days 2 through 22; and AEs
Other (Safety; Repeat Insult Patch Testing) V01-118A-103 1 site in the US	The primary objective of this study was to determine the potential of IDP-118 Lotion and IDP-122 Lotion to induce sensitization by repeated topical application to the healthy skin of humans under controlled conditions. Safety was assessed by evaluation of any AEs reported during the study.	A Randomized, Controlled Study to Evaluate the Sensitizing Potential of IDP-118 Lotion (halobetasol propionate 0.01% and tazarotene 0.045%) and IDP-122 Lotion (halobetasol propionate 0.01%) in Healthy Volunteers Using a Repeat Insult Patch Test Design (Within-Subject Control)	Test Products: •IDP-118 Lotion (HP 0.01%, Taz 0.045%) •IDP-122 Lotion (HP 0.01%) •Vehicle Lotion Reference Therapy: •Saline 0.9% for topical administration Test products and reference therapy were administered topically as semi-occlusive patches at approximately 0.2 mL per patch 9 times over 3 weeks during the induction phase to individual sites on the infrascapular area of the back, followed by a 10 to 14-day rest phase, followed by a 48-hour challenge phase to naïve sites on the infrascapular area of the back	3 weeks during the induction phase, followed by a 10 to 14-day rest phase, followed by a 48-hour challenge phase	244	Healthy subjects	*Safety: Sensitization, assessed at approximately 30 minutes and at approximately 24, 48, and 72 hours after patch removal from the challenge phase; cumulative irritation scores during the induction phase; and AEs

*Source: Table 1 from Tabular Listing, Module 5.2

7.1.2. Review Strategy

Data Sources

The sources of data used for the evaluation of the efficacy and safety of halobetasol propionate lotion, 0.01% for the proposed indication included final study reports submitted by the applicant, datasets [Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM)], and literature references.

This application was submitted in eCTD format and entirely electronic. The electronic submission including the protocols, statistical analysis plans (SAPs), clinical study

reports, and SAS transport datasets in Study Data Tabulation Modal (SDTM) and Analysis Data Model (ADaM) format were in the following network path:

- Original submission: <\\cdsesub1\evsprod\nda209355\0001\m5\datasets>

Data and Analysis Quality

In general, the data submitted by the applicant to support the efficacy and safety of halobetasol propionate lotion, 0.01% for the proposed indication appeared adequate. A final statistical analysis plan (SAP) was submitted and most relevant analysis decisions (e.g., pooling of sites, analysis population membership, etc.) were made prior to unblinding.

7.2. Review of Relevant Individual Trials Used to Support Efficacy

7.2.1. Study Design and Endpoints

The applicant conducted two identically-designed, randomized, double-blind, vehicle-controlled, Phase 3 trials (V01-122A-301 and V01-122A-302, hereinafter referred to as Trials 301 and 302) to evaluate the efficacy of IDP-122 (halobetasol propionate) Lotion, 0.01% for the topical treatment of plaque psoriasis. Subjects who met the following key inclusion criteria were eligible to be enrolled in the trials:

- Male or female at least 18 years of age
- Had an area of plaque psoriasis appropriate for topical treatment that covers a body surface area (BSA) between 3% and 12% excluding the face, scalp, palms, soles, axillae, and intertriginous areas
- Had a clinical diagnosis of psoriasis at the baseline visit with an Investigator's Global Assessment (IGA) score of 3 or 4 (the face, scalp, palms, soles, axillae, and intertriginous areas were to be excluded from this assessment if psoriasis was present)
- Had a target lesion that met the following criteria:
 - Measured between 16-100 cm² inclusive
 - Had a score of at least 3 for at least 2 of the 3 psoriasis signs (erythema, plaque elevation, and scaling) with a sum of at least 8 for the 3 scores, and could not have a score of 0 or 1 for any one of the signs
 - Target lesions could not be on excluded areas or areas covering bony prominences (i.e., elbows and knees)

The Investigator's Global Assessment (IGA) scale is presented in Table 10.

Table 10: Investigator’s Global Assessment 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 plaques 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 coarse 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: Applicant’s Table 2 in protocol 301

The protocols specify that eligible subjects were randomized in a 2:1 ratio to receive IDP-122 lotion or vehicle lotion respectively. The protocols state, “the study drug kits will be numbered sequentially and dispensed randomly to the subjects entering the study within each investigational center. Study drug supplies will be distributed to the investigational centers to maintain the randomization ratio within each investigational center.” The randomization lists and dates provided by the applicant indicate that randomization was stratified by investigational center.

The protocols state that the study drug was dispensed to subjects at the baseline visit and was to be applied topically to the affected areas (as determined by the investigator at baseline) once daily for 8 weeks, with the initial application made by the subject per instruction from the study staff. All areas affected by psoriasis were to be treated with the study drug excluding the face, scalp, palms, soles, groin, axillae, and intertriginous areas.

According to the protocols, subjects received two 45-gram containers of study drug from the investigational center at baseline, Week 2, Week 4, and Week 6, and subjects were asked to return their containers so that drug usage compliance could be evaluated.

The protocols specify that after completion of the 8-week treatment period, subjects were asked to return to the investigational center at Week 12 for a post-treatment follow-up visit. Subjects who terminated the study early were to be asked to complete all Week 8 assessments prior to starting any alternative therapy for psoriasis.

If signs or symptoms developed in the selected treatment areas during the treatment period that would restrict daily activities or make continued application of the study drug difficult due to discomfort, the protocols state that the investigator could instruct the subject to temporarily interrupt use of the study drug and resume application of the study drug once the signs/symptoms subsided. If the study drug was interrupted, discontinued, or a concomitant medication was used to treat a sign/symptom, then an adverse event was to be recorded.

The primary endpoint specified in the SAPs is the percentage of subjects with treatment success at Week 8, where treatment success is defined as at least a 2-grade improvement from baseline in IGA score and an IGA score equating to “Clear” or “Almost Clear”.

The SAPs specify the following secondary endpoints:

- Percentage of subjects with treatment success at Week 12
- Percentage of subjects with treatment success at Week 6
- Percentage of subjects with treatment success at Week 4
- Percentage of subjects with treatment success at Week 2

7.2.2. Statistical Methodologies

The SAPs state that except where noted, all statistical tests are two-sided and performed at the 0.05 level of significance. The intent-to-treat (ITT) population is defined as all subjects who were randomized and dispensed study drug, and it is the primary population for the evaluation of efficacy. The SAPs state that subjects in the ITT population who complete the Week 8 visit without any major protocol violations are included in the per protocol (PP) analysis set; specifically, the Week 8 PP population includes subjects in the ITT population who did not meet any of the following criteria:

- Violated the inclusion/exclusion criteria
- Used an interfering concomitant medication
- Did not attend the Week 8 visit
- Missed more than 1 post-baseline study visit prior to Week 8
- Was not compliant with the dosing regimen (i.e., not apply 80%-120% of the expected applications of study medication during participation in the study)
- Had a Week 8 visit outside of the visit window by more than ± 5 days

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The SAPs state that subjects who discontinued from the study due to an adverse event related to study treatment or documented lack of treatment effect are included in the Week 8 PP population. The SAPs define the Week 12 PP population as subjects in the Week 8 PP population who did not meet any of the following criteria:

- Used an interfering concomitant medication between Week 8 and Week 12
- Did not attend the Week 12 visit
- Had a Week 12 visit outside of the visit window by more than ± 7 days

The SAPs state that subjects that discontinued from the study due to an adverse event related to study treatment or documented lack of treatment effect are included in the Week 12 PP population.

The SAPs state that the studies were intended to be conducted in a manner such that a minimum of 15 subjects (i.e., approximately 10 subjects in the IDP-122 arm and 5 subjects in the vehicle arm) were randomized at each investigational site. If there were too few subjects in a treatment arm at a given site, then the data were combined to achieve the desired minimum sample size per treatment arm. For each trial, the SAPs specify combining the data from the site with the smallest enrollment with the data from the site with the largest enrollment, restricted to sites that did not meet minimum enrollment. If there was a further need to combine data, the SAPs specify combining the data of the site with the second smallest enrollment with the data from the site with the second largest enrollment, and so on. The combined sites and sites large enough to not be combined are referred to as "analysis centers".

The SAPs specify analyzing the primary and secondary endpoints using a Cochran-Mantel-Haenszel (CMH) test stratified by analysis center. The primary method for handling missing data specified in the SAPs is Markov Chain Monte Carlo (MCMC) multiple imputation (MI). The SAPs state that missing data was imputed for each treatment group separately by the following procedure:

- Calculate the number of missing Week 8 values to be estimated by MCMC in each treatment group. Define "nmiss" be the maximum number of missing Week 8 values among the treatment groups.
- Impute the missing efficacy data using MCMC method 5 x "nmiss" times to generate 5 x "nmiss" datasets.
- The imputed data is dichotomized into success/failure endpoints.
- Each dataset is analyzed using the CMH test stratified by analysis center.
- CMH test statistics are normalized using the Wilson-Hilferty transformation.
- The results are combined using PROC MIANALYZE in SAS.

Seeds for the MCMC MI procedure are specified in the SAPs for each assessment (i.e., IGA, erythema, plaque elevation, and scaling) and treatment group (i.e., IDP-122 and vehicle). Neither the protocols nor the SAPs pre-specified the variables that would be used in the MCMC imputation; the applicant's provided SAS code indicates that only measurements of the variable of interest at each visit (e.g., IGA score at baseline and Weeks 2, 4, 6, 8, and 12) were included in the imputation model.

The SAPs specify using a gated sequential procedure for testing the secondary endpoints in the order they are listed in Section 7.2.1, and that the process will terminate if a non-statistically significant p-value is observed.

Two sensitivity analyses of the ITT population for the primary endpoint were specified in the SAPs. The first sensitivity analysis imputes missing IGA values using Last Observation Carried Forward (LOCF). For the second sensitivity analysis, the primary endpoint is analyzed using “a repeated measures logistic regression model (generalized estimating equations), with treatment success as the dependent variable and treatment, analysis center and visit (Weeks 2, 4, 6 and 8) as independent factors.” The SAPs specify that the efficacy analyses will also be conducted on the Week 8 and Week 12 PP populations using LOCF to impute missing values.

The SAPs state that the consistency of treatment response for the primary efficacy variable would be investigated across the analysis centers. The SAPs specify analyzing the percentage of subjects with treatment success at Week 8 with a logistic regression model with factors for treatment group, analysis center, and the interaction term of treatment group by analysis center. If the interaction p-value is less than or equal to 0.10, the SAPs state that a sensitivity analysis that excludes analysis centers with the extreme efficacy result will be performed to determine the robustness of the treatment effect. If the analysis results in an interaction terms with p-value greater than 0.10, then the SAPs state that the conclusions from the pooled data will be considered to be free of the impact of extreme analysis centers.

To identify the analysis center(s) with extreme efficacy results, the SAPs state that first all subsets that can be created by excluding 1 analysis center will be analyzed. If 1 or more of the subsets result in an interaction p-value greater than or equal to 0.10, then the analysis center excluded from the subset with the largest interaction p-value is deemed the extreme analysis center. If all subset interaction p-values are less than or equal to 0.10, then the applicant will repeat the analysis for all subsets that can be created by excluding 2 analysis centers, and so on until the logistic regression interaction p-value exceeds 0.10. Once the extreme analysis center(s) have been identified, then the treatment p-value of the remaining analysis centers will be computed.

The SAPs also state that site-to-site variability (prior to pooling into analysis centers) will be investigated. Similarly to the analysis of analysis centers, the primary endpoint will be analyzed with a logistic regression with factors of treatment group, site, and the interaction term of treatment group by site. The SAPs specify that 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 217 subjects, 143 to IDP-122 and 74 to vehicle, from 20 centers in the United States (US). Trial 302 enrolled and randomized 213 subjects, 142 to IDP-122 and 71 to vehicle, from 17 sites in the US. Table 11 presents the reasons for subject discontinuation from the studies as classified by the applicant. In both trials, there was a greater proportion of subjects who discontinued the trial in the vehicle arm compared to the IDP-122 arm, with a greater discontinuation rates overall in Trial 301. There was no apparent difference between treatment arms in the reasons that subjects discontinued.

Table 11: Disposition of Subjects Enrolled in Trials 301 and 302

ITT Population	Trial 301		Trial 302	
	IDP-122 N=143	Vehicle N=74	IDP-122 N=142	Vehicle N=71
Discontinued	14 (9.8%)	13 (17.6%)	7 (4.9%)	6 (8.5%)
Adverse event	1 (0.7%)	1 (1.4%)	2 (1.4%)	1 (1.4%)
Lost to follow-up	6 (4.2%)	6 (8.1%)	4 (2.8%)	2 (2.8%)
Protocol violation	1 (0.7%)	0	0	0
Subject request ⁽¹⁾	6 (4.2%)	6 (8.1%)	1 (0.7%)	3 (4.2%)

Source: Reviewer's analysis (same as applicant's analysis).

(1) Two subjects in the IDP-122 arm and 1 subject in the vehicle arm of Trial 301 seemingly discontinued due to lack of efficacy.

In Trial 301, the applicant classified 3 subjects, 2 in the IDP-122 arm and 1 in the vehicle group, as discontinued due to subject request; however, the applicant's listing of discontinued subjects indicates that these subjects dropped out due to lack of efficacy. The listing states that subject (b) (6) (IDP-122) requested to be withdrawn "due to worsening of her psoriasis", subject (b) (6) (IDP-122) withdrew consent "to seek treatment for psoriasis", and subject (b) (6) (vehicle) "said medication not working".

Table 12 presents the demographic characteristics for the subjects enrolled in Trials 301 and 302. In Trial 301, the IDP-122 arm had a greater proportion of male subjects and lower proportion of White subjects compared to the vehicle arm. Trial 302 had a slightly older subject population than Trial 301 as reflected in both the mean and median subject age at baseline. Otherwise, the demographics were generally balanced across the treatment arms within each trial and across both trials. The majority of subjects were White (approximately 87%), and the median age of subjects was in the low to mid-50s. Approximately 60% of subjects were males.

Table 12: Demographic Characteristics of Subjects Enrolled in Trials 301 and 302

ITT Population	Trial 301		Trial 302	
	IDP-122 N=143	Vehicle N=74	IDP-122 N=142	Vehicle N=71
Age				
Mean (SD)	51.6 (14.8)	51.0 (15.4)	54.1 (13.3)	53.4 (12.7)
Median	51	51	56	54
Range	20, 88	20, 85	19, 83	22, 80
Sex				
Male	85 (59.4%)	39 (52.7%)	87 (61.3%)	42 (59.2%)
Female	58 (40.6%)	35 (47.3%)	55 (38.7%)	29 (40.8%)
Race				
White	121 (84.6%)	68 (91.9%)	122 (85.9%)	61 (85.9%)
Black or African American	13 (9.1%)	3 (4.1%)	12 (8.5%)	2 (2.8%)
Asian	5 (3.5%)	2 (2.7%)	4 (2.8%)	2 (2.8%)
Native Hawaiian or Other Pacific Islander	2 (1.4%)	1 (1.4%)	0	1 (1.4%)
Multiple or Other	2 (1.4%)	0	4 (2.8%)	5 (7.0%)
Ethnicity				
Hispanic or Latino	41 (28.7%)	20 (27.0%)	35 (24.6%)	23 (32.4%)
Not Hispanic or Latino	102 (71.3%)	54 (73.0%)	107 (75.4%)	48 (67.6%)

Source: Reviewer's analysis (similar to applicant's analysis).

Table 13 presents the baseline disease characteristics of the trial subjects. Approximately 86% of subjects had moderate disease (IGA score of 3) at baseline and a median BSA of 5%. These baseline disease attributes were similar across treatment arms in each trial. However, Trial 301 had a higher proportion of subjects with severe disease (IGA score of 4) compared to Trial 302.

Table 13: Baseline Disease Characteristics of Subjects Enrolled in Trials 301 and 302

ITT Population	Trial 301		Trial 302	
	IDP-122 N=143	Vehicle N=74	IDP-122 N=142	Vehicle N=71
IGA				
Moderate (3)	121 (84.6%)	61 (82.4%)	124 (87.3%)	65 (91.5%)
Severe (4)	22 (15.4%)	13 (17.6%)	18 (12.7%)	6 (8.5%)
BSA (%)				
Mean (SD)	6.1 (2.8)	6.1 (2.9)	6.1 (2.9)	5.8 (2.7)
Median	5	5	5	5
Range	3, 12	3, 12	3, 12	3, 12

Source: Reviewer's analysis (same as applicant's analysis).

7.2.4. Results for the Primary and Secondary Efficacy Endpoints

Table 14 presents the proportion of subjects with missing IGA assessment data at each study visit. There was generally more missing data in the vehicle group compared to the IDP-122 group in both trials, and the amount of missing data increased over time. There was a greater amount of missing data in Trial 301 compared to Trial 302.

Table 14: Missing IGA Assessment Data by Visit for Trials 301 and 302

ITT Population	Trial 301		Trial 302	
	IDP-122 N=143	Vehicle N=74	IDP-122 N=142	Vehicle N=71
Week 2	6 (4.2%)	3 (4.1%)	1 (0.7%)	2 (2.8%)
Week 4	6 (4.2%)	7 (9.5%)	5 (3.5%)	4 (5.6%)
Week 6	10 (7.0%)	12 (16.2%)	4 (2.8%)	3 (4.2%)
Week 8	12 (8.4%)	9 (12.2%)	7 (4.9%)	5 (7.0%)
Week 12	12 ⁽¹⁾ (8.4%)	13 (17.6%)	7 (4.9%)	6 (8.5%)

Source: Reviewer's analysis.

(1) Two additional subjects (b) (6) were discontinued at a visit on study days 65 and 64 (after the Week 8 visit) due to subject request to be withdrawn, seemingly due to lack of efficacy.

The pre-specified primary endpoint in the protocols and SAPs was the percentage of subjects with treatment success at Week 8, where treatment success is defined as at least a 2-grade improvement from baseline in IGA score and an IGA score of 0 or 1 equating to “Clear” or “Almost Clear”. The secondary endpoints evaluated treatment success at Week 12 (i.e., 4 weeks after the end of treatment), Week 6, Week 4, and Week 2. The results for the primary and secondary endpoints are presented in Table 15. All endpoints were analyzed with a CMH test stratified by analysis center, and the primary method for handling missing data was MCMC multiple imputation (MI). The results are combined from 60 MI datasets for Trial 301 and 35 MI datasets for Trial 302 according to the pre-specified procedure in the SAPs. All primary and secondary endpoints were statistically significant, except for treatment success at Week 2 in Trial 302 (p-value=0.053). Figure 1 depicts the proportion of subjects with treatment success over time.

Table 15: Results of the Primary and Secondary Endpoints for Trials 301 and 302

ITT Population	Trial 301			Trial 302		
	IDP-122 N=143	Vehicle N=74	p-value ⁽¹⁾	IDP-122 N=142	Vehicle N=71	p-value ⁽¹⁾
Primary endpoint						
Treatment success ⁽²⁾ at Week 8	36.5%	8.1%	<0.001	38.4%	12.0%	<0.001
Secondary endpoints						
Treatment success ⁽²⁾ at:						
Week 12 ⁽³⁾	19.5%	6.7%	0.018	23.0%	9.3%	0.014
Week 6	30.1%	7.9%	<0.001	27.7%	4.3%	<0.001
Week 4	19.8%	2.8%	<0.001	19.3%	0.2%	<0.001
Week 2	7.1%	0%	0.020	4.9%	0%	0.053

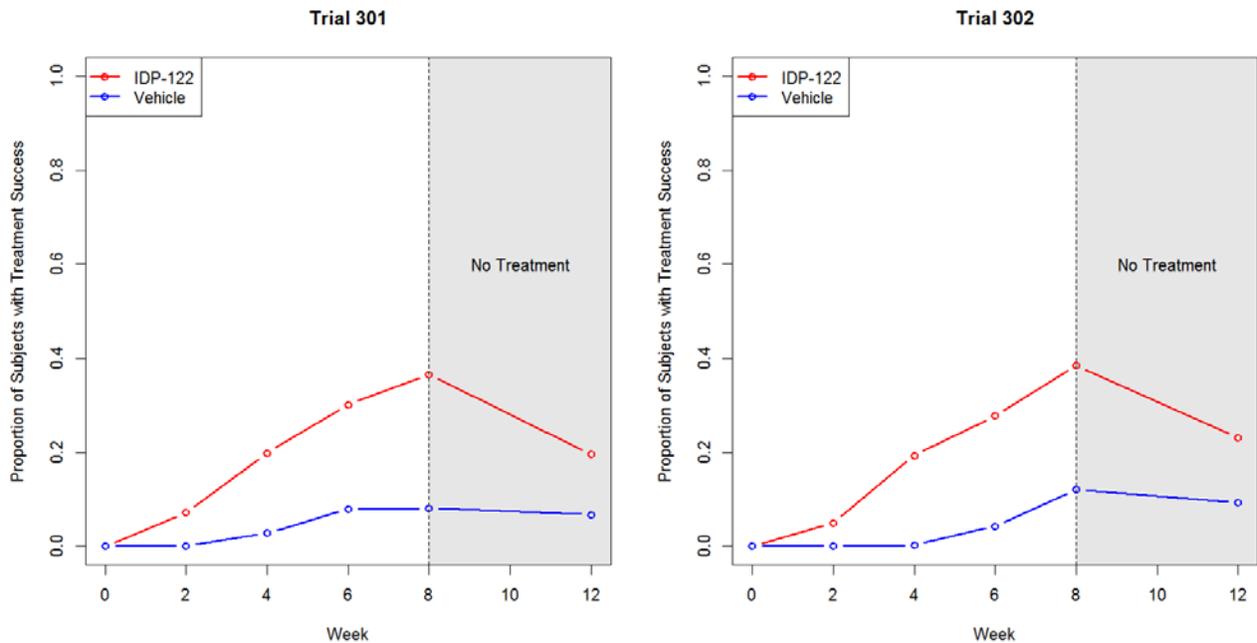
Source: Reviewer's analysis (same as applicant's analysis). Multiple imputation (MI) was used to handle missing data. Results are combined from 60 MI datasets for Trial 301 and 35 MI datasets for Trial 302.

(1) P-values were calculated from a CMH test stratified by analysis center.

(2) Treatment success was defined as at least a 2-grade improvement in IGA score from baseline and an IGA score equating to clear or almost clear.

(3) The Week 12 evaluation is 4 weeks after the end of treatment.

Figure 1: Proportion of Subjects with Treatment Success by Week for Trials 301 and 302



Source: Reviewer's analysis (same as applicant's analysis).

The treatment difference at Week 2 in Trial 302 is not statistically significant. Treatment success was defined as at least a 2-grade improvement in IGA score from baseline and an IGA score equating to clear or almost clear.

The SAPs specify imputing missing values for the ITT population using LOCF and analyzing the Week 8 PP population imputing missing values using LOCF as sensitivity analyses. As there was a high amount of missing data in the vehicle arm in Trial 301, this reviewer conducted sensitivity analyses using both non-responder and worst-case imputation to handle missing data. In non-responder imputation, all subjects with missing data are imputed as non-responders (i.e., not achieving treatment success). In worst-case imputation, subjects in the IDP-122 arm with missing data are imputed as non-responders, and subjects in the vehicle arm with missing data are imputed as responders. Table 16 presents the results of these sensitivity analyses. The sensitivity analyses support the conclusion of the primary analysis that IDP-122 is superior to vehicle for the primary endpoint. While worst-case imputation may not be based on a reasonable or scientifically-justified assumption, the results from this imputation provide confidence that the superiority of IDP-122 was not driven by the method chosen to handle missing data.

Table 16: Sensitivity Analyses of the Primary Endpoint at Week 8 for Trials 301 and 302

	Trial 301			Trial 302		
	IDP-122	Vehicle	p-value ⁽¹⁾	IDP-122	Vehicle	p-value ⁽¹⁾
ITT Population	N=143	N=74		N=142	N=71	
MI (primary analysis)	36.5%	8.1%	<0.001	38.4%	12.0%	<0.001
LOCF ⁽²⁾	51 (35.7%)	6 (8.1%)	<0.001	53 (37.3%)	8 (11.3%)	<0.001
Non-responder ⁽³⁾	51 (35.7%)	5 (6.8%)	<0.001	53 (37.3%)	8 (11.3%)	<0.001
Worst-case ⁽⁴⁾	51 (35.7%)	14 (18.9%)	0.013	53 (37.3%)	13 (18.3%)	0.003
Week 8 PP Population	N=120	N=60		N=134	N=60	
LOCF ⁽²⁾	49 (40.8%)	5 (8.3%)	<0.001	51 (38.1%)	6 (10.0%)	<0.001

Source: Reviewer's analysis. The primary endpoint was the percentage of subjects with treatment success at Week 8, where treatment success was defined as at least a 2-grade improvement in IGA score from baseline and an IGA score equating to clear or almost clear.

- (1) P-values were calculated from a CMH test stratified by analysis center.
- (2) Missing data was handled using last observation carried forward (LOCF).
- (3) Subjects with missing data are imputed as non-responders.
- (4) Subjects in the IDP-122 arm with missing data are imputed as non-responders, and subjects in the vehicle arm with missing data are imputed as responders.

As another sensitivity analysis, the SAPs specify analyzing the primary endpoint using “a repeated measures logistic regression model (generalized estimating equations), with treatment success as the dependent variable and treatment, analysis center and visit (Weeks 2, 4, 6 and 8) as independent factors.” The applicant’s study reports indicate that this model resulted in analysis issues that caused the applicant to omit variables from the analysis (Week 2 and analysis center in Trial 301; Week 2, Week 4, and analysis center in Trial 302). The conclusions from these analyses are consistent with those of the primary analysis, though the results are excluded from this review due to the post-hoc changes.

7.2.5. Patient Reported Outcomes (PROs)

The protocols for Trials 301 and 302 included the assessment of the Dermatology Life Quality Index (DLQI) which is a patient reported outcome (PRO). The endpoints based on the DLQI were designated as “other” endpoints to be summarized descriptively; as these endpoints were not included in the multiplicity testing strategy, the results for these endpoints are not presented in this review.

7.2.6. Findings in Special/Subgroup Populations

7.2.6.1. Sex, Race, Age, and Geographic Region

Table 17 presents the efficacy results for the primary endpoint (i.e., the percentage of subject with an IGA score of 0 or 1 and at least a 2-grade improvement from baseline at Week 8) by sex, race (White, Black or African American, and other), ethnicity (Hispanic or Latino and not Hispanic or Latino), age (<median age and ≥median age, <65 years old and ≥65 years old), and baseline disease severity (moderate and severe as defined by the IGA scale). Female subjects had higher response rates than male subjects, but the treatment effect size (i.e., the difference in response rates between the IDP-122 and vehicle arms) for the two sexes was similar. Younger subjects (as categorized in Table

17) had a higher treatment success rate than older subjects in both trials. Efficacy across the other subgroups appeared consistent or the sample sizes were too small to make conclusions.

Table 17: Results of the Primary Endpoint at Week 8 by Sex, Race, Ethnicity, Age, and Baseline Disease Severity for Trials 301 and 302

ITT Population	Trial 301			Trial 302		
	(N _I , N _V) ⁽¹⁾ (143, 74)	IDP-122	Vehicle	(N _I , N _V) ⁽¹⁾ (142, 71)	IDP-122	Vehicle
Sex						
Male	85, 39	33.9%	5.3%	87, 42	34.0%	7.5%
Female	58, 35	40.3%	11.2%	55, 29	45.4%	18.5%
Race						
White	121, 68	38.0%	8.0%	122, 61	37.2%	9.0%
Black or African American	13, 3	23.2%	18.9%	12, 2	42.9%	50.0%
Other ⁽²⁾	9, 3	35.0%	0%	8, 8	50.0%	25.0%
Ethnicity						
Hispanic or Latino	41, 20	32.2%	6.8%	35, 23	46.2%	13.2%
Not Hispanic or Latino	102, 54	38.2%	8.6%	107, 48	35.9%	11.4%
Age⁽³⁾						
<Median age	67, 36	43.7%	8.1%	64, 38	41.1%	13.6%
≥ Median age	76, 38	30.1%	8.2%	78, 33	36.2%	10.1%
<65 years old	110, 56	38.0%	8.9%	114, 57	42.5%	12.6%
≥65 years old	33, 18	31.5%	5.7%	28, 14	21.8%	9.6%
Baseline Disease Severity						
IGA score of 3 (moderate)	121, 61	36.5%	9.9%	124, 65	41.4%	13.1%
IGA score of 4 (severe)	22, 13	36.4%	0%	18, 6	17.6%	0%

Source: Reviewer's analysis (similar to applicant's analysis). Multiple imputation (MI) was used to handle missing data. Results are combined from 60 MI datasets for Trial 301 and 35 MI datasets for Trial 302. The primary endpoint was the percentage of subjects with treatment success at Week 8, where treatment success was defined as at least a 2-grade improvement in IGA score from baseline and an IGA score equating to clear or almost clear.

(1) N_I = subgroup sample size in the IDP-122 arm and N_V = subgroup sample size in the vehicle arm.

(2) Includes those classified as American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, or Other/Multiple.

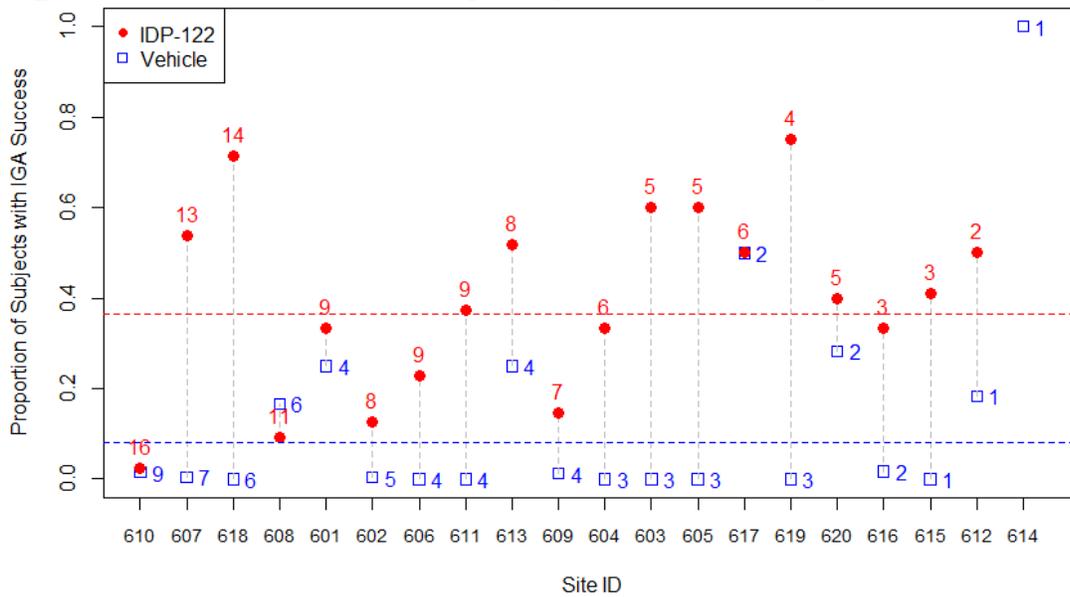
(3) The median age in Trial 301 was 51 years old and the median age in Trial 302 was 55 years old.

7.2.6.2. Center

Trial 301 enrolled 217 subjects from 20 sites in the US, and Trial 302 enrolled 213 subjects from 17 sites in the US. Figure 2 and Figure 3 present the results of the primary endpoint (i.e., the proportion of subjects with an IGA score of 0 or 1 with at least a 2-grade improvement from baseline at Week 8) by site for Trials 301 and 302 respectively. The figures depict the sites ordered by the number of subjects enrolled and randomized at each site, with the largest sites appearing on the left.

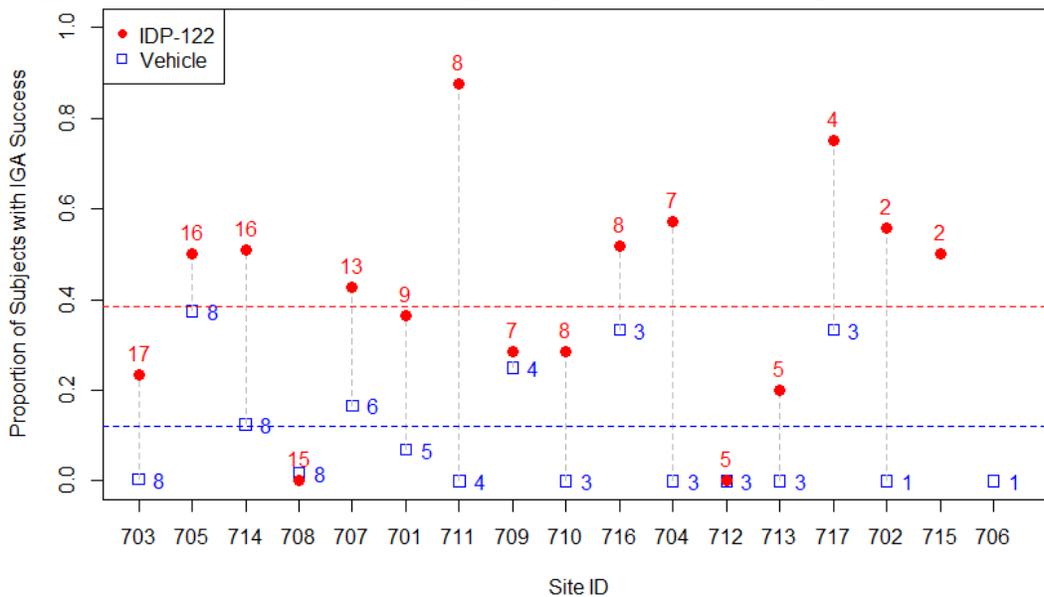
In Trial 301, sites 607 and 618 are two of the largest sites, and both have large treatment effects; however, it does not appear that any single site drove the efficacy results. In Trial 302, site 711 has a large treatment difference compared to the other sites. Of note, site 608 in Trial 301 and site 708 in Trial 302 both have efficacy trending in the opposite direction (i.e., results from the vehicle arm are more favorable) and several other sites had small treatment differences (e.g., site 610 in Trial 301).

Figure 2: Results of the Primary Endpoint at Week 8 by Site for Trial 301



Source: Reviewer's analysis. Multiple imputation (MI) was used to handle missing data, and results are combined from 60 MI datasets for Trial 301. The primary endpoint was the percentage of subjects with treatment success at Week 8, where treatment success was defined as at least a 2-grade improvement in IGA score from baseline and an IGA score equating to clear or almost clear. The numbers on the plot denote the sample sizes of each treatment arm within each site.

Figure 3: Results of the Primary Endpoint at Week 8 by Site for Trial 302



Source: Reviewer's analysis. Multiple imputation (MI) was used to handle missing data, and results are combined from 35 MI datasets for Trial 302. The primary endpoint was the percentage of subjects with treatment success at Week 8, where treatment success was defined as at least a 2-grade improvement in IGA score from baseline and an IGA score equating to clear or almost clear. The numbers on the plot denote the sample sizes of each treatment arm within each site.

The SAPs specify investigating the consistency of the treatment effect for the primary endpoint across the analysis centers and the sites prior to pooling. The percentage of subjects with treatment success at Week 8 was analyzed according to the SAPs with a logistic regression with factors for treatment group, analysis center, and the interaction

term of treatment group by analysis center. The applicant's study report states that the analysis was conducted using a logistic regression model with Firth's penalized likelihood. For the analysis investigating the treatment effect across analysis centers, the interaction term had a p-value greater than 0.10 in both trials.

For the investigation of the treatment effect across sites, the applicant removed sites 612, 614, and 615 from the analysis of Trial 301 and removed sites 702, 706, and 715 from the analysis of Trial 302 so that each site in the analyses had at least 2 subjects per treatment arm. Including the deleted sites in the analysis results in computational issues, and the SAPs allowed for the deletion of sites from the analysis for this reason. The interaction terms in the analysis across sites had p-values greater than 0.10 in both trials.

7.3. Review of Safety

Safety Review Approach

The safety review will focus on the integrated safety database, which consists of data combined from the 2 Phase 3 studies, 301 and 302. The Applicant pooled data from these studies as the studies were of identical design; all other studies differed in design.

The Applicant defined the safety analysis set as including all subjects who were randomized, received at least one confirmed dose of study drug, and had at least one post-baseline safety assessment

The Applicant's pooling strategy and definition of the safety analysis set are acceptable. I conclude that the safety database is adequate in size and extent of exposure of study subjects to permit a reasonable assessment of the safety of IDP-122 Lotion.

7.3.2. Review of the Safety Database

Overall Exposure

A total of 746 subjects were exposed to IDP-122 Lotion in the clinical development program. The Applicant excluded four subjects from the safety population (one from the IDP-122 Lotion group; three from the Vehicle group), as they did not have any post-baseline safety evaluation. Exclusion of these subjects is consistent with the definition of the safety analysis set (see Section 7.3.1).

The treatment duration in the psoriasis studies was 8 weeks, except for study 203, where the treatment duration was 2 weeks.

Treatment compliance was defined as application of at least 80% but no more than 120% of the expected applications while enrolled in the study. Most subjects were compliant with treatment: 98.2% in the IDP-122 group and 97.8% in the Vehicle group.

Table 18: Number of Subjects Randomized /Treated in the IDP-122 Lotion Program (All Clinical Studies)*

Clinical Trial Groups	IDP-122 Lotion (HP 0.01%)	Vehicle	Total
Healthy volunteers	314	314	314**
Controlled trials conducted for this indication (excluding studies in healthy volunteers)	408	209	617
All other trials conducted for this indication	24	-	46
Total	746		977

*Source: Table 4 Summary of Clinical Safety

***70 subjects had all treatments applied in 2 Phase 1 dermal safety studies and are only counted once in the total number for the safety database.

For the safety population, the median amount of IDP-122 Lotion used was ~182 g and ~156 g for the Vehicle group. The median number of days of exposure to study treatment was 56 for both treatment groups.

Table 19: Summary of Extent of Exposure (Safety Population, Studies 301 and 302 Combined)*

	Total Amount of Study Drug Used (g)	Total Number of Days of Exposure	Total Number of Applications
IDP-122 Lotion (N=284)			
N	258	276	276
Mean	181.90	55.8	55.2
SD	92.307	6.60	6.75
Median	182.15	56.0	56.0
Min. to Max.	5.2 to 349.9	3 to 86	3 to 86
Vehicle Lotion (N=142)			
N	131	139	139
Mean	162.35	55.3	54.4
SD	90.267	7.70	8.46
Median	156.20	56.0	56.0
Min. to Max.	22.4 to 370.9	12 to 67	12 to 67

*Source: Table 5 of Summary of Clinical Safety

Relevant characteristics of the safety population:

Demographic and baseline disease characteristics of the safety population have been previously discussed, as the Safety Population consists of the pooled data from the 2 Phase 3 trials. Demographic and baseline disease characteristics were similar between

treatment groups and across the 2 studies. See Table 20.

Table 20: Summary of Subject Demographic Characteristics (Safety Population, Studies 301 and 302 Combined)*

	IDP-122 Lotion (N=284)	Vehicle Lotion (N=142)	Total (N=426)
Age (years)			
N	284	142	426
Mean	52.8	52.5	52.7
SD	14.15	14.11	14.12
Median	54.0	53.0	53.5
Min. to Max.	19 to 88	20 to 85	19 to 88
Sex			
N	284	142	426
Male	172 (60.6%)	80 (56.3%)	252 (59.2%)
Female	112 (39.4%)	62 (43.7%)	174 (40.8%)
Ethnicity			
N	284	142	426
Hispanic or Latino	76 (26.8%)	42 (29.6%)	118 (27.7%)
Not Hispanic or Latino	208 (73.2%)	100 (70.4%)	308 (72.3%)
Race			
N	284	142	426
American Indian or Alaska Native	0 (0.0%)	0 (0.0%)	0 (0.0%)
Asian	9 (3.2%)	4 (2.8%)	13 (3.1%)
Black or African American	25 (8.8%)	5 (3.5%)	30 (7.0%)
Native Hawaiian or Other Pacific Islander	2 (0.7%)	2 (1.4%)	4 (0.9%)
White	242 (85.2%)	126 (88.7%)	368 (86.4%)
Other	6 (2.1%)	5 (3.5%)	11 (2.6%)

*Source: Table 6 of Summary of Clinical Safety

Adequacy of the safety database:

The safety database was adequate in size and extent of drug exposures (concentrations and duration) to assess the safety of IDP-122 Lotion in the target population of adults with plaque psoriasis.

7.3.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

No issues were identified regarding data integrity. The submission quality was adequate. Some hyperlinks led to the wrong destination, and some differently-named links led to the same destination. Some study reports had missing information e.g., missing tables in the body of the study report for study 103 (contact sensitization).

Categorization of Adverse Events

The Applicant defined an adverse event (AE) as any untoward medical occurrence in a subject administered a medicinal product and which did not necessarily have a causal relationship with the study drug.

Investigators were to report all AEs occurring after the subject signed the informed consent through the last study visit were to be reported. Cutaneous tolerability signs and symptoms that resulted in the subject's requiring a concomitant therapy or discontinuation from the study were reported as AEs.

Routine Clinical Tests

The Applicant performed clinical laboratory testing as presented in Table 21. The schedule of testing varied according to the study.

The safety assessments appear reasonable and adequate for the study population and indication.

Table 21: Key Safety Variables Assessed in Each Study (All Clinical Studies)*

Study	AEs	Chemistry /	Physical Examination	Vital Sign	LSRs	HPA Axis Evaluation	Other
PHASE 3 CONTROLLED STUDIES							
Study 301	x	X	x	x	x		
Study 302	x	X	x	x	x		
PHASE 1/2 PSORIASIS STUDIES							
Study 201	x	X	x	x	x		
Study 203	x	X	x	x	x		
Study 501	x	X	x	x	x	x	
HEALTHY VOLUNTEER STUDIES							
Study 101	x			x ^a			
Study 102	x						x ^b
Study 103	x						x ^c

*Source: Table 3 of Summary of Clinical Safety

^a During screening for all patients and at the discretion of the investigator after screening

^b Skin irritation, assessed as a mean cumulative irritation score and a mean total irritation score

^c Sensitization and skin irritation, assessed as a mean irritation score

AE = adverse event; **LSR** = local skin reaction (generally included evaluations of the severity of itching, dryness, and burning/stinging, as well as the presence of skin atrophy, striae, telangiectasia, and folliculitis); **HPA** = hypothalamus-pituitary-adrenal

7.3.4. Safety Results

Deaths

Two deaths were reported in the clinical development program:

- A 76 y/o White female in in the IDP-122 Lotion group in study 302 experienced a severe myocardial infarction on Day 38 of study treatment. Study treatment was discontinued the same day. She underwent cardiac stent placement on Day 43. She expired on Day 53. She had a history diabetes and acid reflux.
- A 64 y/o male (race not found) in the vehicle group in study 201 experienced a serious (unspecified) infection on Day 48 and was hospitalized. He experienced

severe congestive heart failure during the hospitalization. Study drug was discontinued on an unspecified date. On Day 75, his wife reported that the CHF was “fatal” (date of death is unclear). He had a history of diabetes, hypertension, hyperlipidemia, atrial fibrillation, and pacemaker placement.

Both deaths were related to cardiac events in subjects at increased risk for such events. I conclude that these deaths were not likely related to study treatment.

Serious Adverse Events

In the Safety Population, 5 of 284 subjects (1.8%) in the IDP-122 Lotion group and 4 of 142 subjects (2.8%) in the Vehicle group experienced SAEs. No pattern was apparent to occurrence of SAEs.

IDP-122 Lotion group:

- One subject died, and this subject has been previously discussed (Section 8.4.1)
- A 60-year-old White female experienced “severe chronic heart failure” on Day 50 and was hospitalized. No action was taken regarding the study medication. She recovered. Her past medical history included placement of an automatic implantable cardiac defibrillator and cardiac stents, myocardial infarction, hypercholesterolemia, hypertension, and diabetes.
- A 24-year-old White male experienced severe diverticulitis with perforation on Day 68 (following completion of study treatment). He recovered. He had a history of diverticulitis, hypercholesterolemia, and hypertension.
- A 47-year-old White male experienced severe Staphylococcal infection and severe sepsis on Day 37. No action was taken regarding the study medication. He was considered recovered from the events on Day 45.
- A 45-year-old White male experienced a hypertensive crisis on Day 89 and was hospitalized. He recovered on Day 93.

Vehicle group

- A 59-year-old White male experienced a severe lobar pneumonia on Day 6. He was hospitalized. No action was taken regarding the study medication. He recovered.
- A 53-year-old White male was reported with an anal fissure in on Day 14 and was hospitalized. No action was taken regarding the study. The subject recovered.
- An 82-year-old White male experienced cellulitis on Day 37 and was hospitalized. No action was taken regarding study medication. He recovered. During the posttreatment follow-up period, the subject also experienced the following SAEs: severe diverticulitis (Day 85) and severe chronic heart failure (Day 93).
- A 65-year-old White female underwent a cholecystectomy on Day 55.

Table 22: Summary of Treatment-Emergent Serious Adverse Events by MedDRA System Organ Class and Preferred Term (Safety Population) (V01-122A-301 and V01-122A-302 Combined)*

System Organ Class ^a Preferred Term	IDP-122 Lotion (N=284)	IDP-122 Vehicle Lotion (N=142)
Subjects Reporting Any Serious Adverse Event	5 (1.8%)	4 (2.8%)
Total Number of Serious Adverse Events	6	6
Cardiac disorders	2 (0.7%)	1 (0.7%)
Cardiac failure chronic	1 (0.4%)	1 (0.7%)
Myocardial infarction	1 (0.4%)	0
Infections and infestations	1 (.4%)	2 (1.4%)
Sepsis	1 (0.4%)	0
Staphylococcal infection	1 (0.4%)	0
Application site cellulitis	0	1 (0.7%)
Diverticulitis	0	1 (0.7%)
Lobar pneumonia	0	1 (0.7%)
Gastrointestinal disorders	1 (0.4%)	1 (0.7%)
Diverticular perforation	1 (0.4%)	0
Anal fissure	0	1 (0.7%)
Vascular disorders	1 (0.4%)	0
Hypertensive crisis	1 (0.4%)	0
Surgical and medical procedures	0	1 (0.7%)
Cholecystectomy	0	1 (0.7%)

*Sources: ISS Tables 14.3.1.4.1 and 14.3.1.4.2

Phase 1 and 2 Psoriasis Studies

The death that occurred in study 201 has been previously discussed (see above).

The following other SAEs were reported from study 201:

- IDP-122 Lotion group: a subject experienced an acute myocardial infarction and coronary artery disease.
- Vehicle Lotion group: a subject experienced a “hernia obstructive.”

One SAE was reported from study 501: a subject in the IDP-122 Lotion group experienced a severe cerebrovascular accident with right side upper limb hemiplegia.

No SAEs were reported from study 203.

Phase 1 Healthy Volunteer Studies

In Study 103 (contact sensitization study), 3 of 244 subjects (1.2%) experienced the following 5 SAEs: lower abdominal pain, dehydration, and vomiting; pyelonephritis; colitis.

No SAEs were reported in studies 101 and 102.

Dropouts and/or Discontinuations Due to Adverse Effects

Pertaining, to the Safety Population, the same proportion of subjects in each treatment group discontinued the study (1.4%). “Application site dermatitis” was the only TEAE that was reported in more than one subject as the basis for discontinuation: it was reported in 2 subjects, and both subjects were in the IDP-122 Lotion group.

Table 23: Summary of TEAEs Leading to Permanent Withdrawal of Study Drug and/or Early Discontinuation from the Study (Safety Population, Studies 301 and 302 Combined)*

System Organ Class ^a Preferred Term	IDP-122 Lotion	Vehicle Lotion
Subjects Who Discontinued Study Drug Due to TEAE	4 (1.4%)	2 (1.4%)
Cardiac disorders	1 (0.4%)	0
Myocardial infarction	1 (0.4%)	0
General disorders and administration site conditions	2 (0.7%)	0
Application site dermatitis	2 (0.7%)	0
Hepatobiliary disorders	0	1 (0.7%)
Cholecystitis	0	1 (0.7%)
Infections and infestations	1 (0.4%)	0
Application site infection	1 (0.4%)	0
Skin and subcutaneous tissue disorders	1 (0.4%)	1 (0.7%)
Psoriasis	1 (0.4%)	1 (0.7%)
Surgical and medical procedures	0	1 (0.7%)
Cholecystectomy	0	1 (0.7%)

^a Counts reflect numbers of subjects reporting one or more adverse events that map to MedDRA. At each level of summarization (System Organ Class or Preferred Term) subjects are counted once.

Note: MedDRA Version 18.0.

Note: Treatment-emergent adverse events are those with an onset after the first application of study drug.

*Source: Table 13 Summary of Clinical Safety

Significant Adverse Events

A higher proportion of TEAEs was reported as severe in the Vehicle Lotion group (2.8%) compared to the IDP-122 Lotion group (2.1%). No type of TEAE was reported as severe multiple times.

Table 24: Summary of Severe TEAEs – Through Week 8 Visit (Safety Population, Studies 301 and 302 Combined)*

System Organ Class ^a Preferred Term	IDP-122 Lotion (N=284)	Vehicle Lotion
Subjects Reporting Any Severe TEAE	6 (2.1%)	4 (2.8%)
Infections and infestations	2 (0.7%)	2 (1.4%)
Application site infection	1 (0.4%)	0
Sepsis	1 (0.4%)	0
Application site cellulitis	0	1 (0.7%)
Lobar pneumonia	0	1 (0.7%)
General disorders and administration site conditions	1 (0.4%)	1 (0.7%)
Application site pain	0	1 (0.7%)
Application site pruritus	1 (0.4%)	1 (0.7%)
Investigations	1 (0.4%)	0
Neutrophil count increased	1 (0.4%)	0
White blood cell count increased	1 (0.4%)	0
Vascular disorders	1 (0.4%)	0
Hypertension	1 (0.4%)	0
Skin and subcutaneous tissue disorders	0	1 (0.7%)
Psoriasis	0	1 (0.7%)
Cardiac disorders	2 (0.7%)	0
Cardiac failure chronic	1 (0.4%)	0
Myocardial infarction	1 (0.4%)	0

^a Counts reflect numbers of subjects reporting one or more adverse events that map to MedDRA. At each level of summarization (System Organ Class or Preferred Term) subjects are only counted once under the greatest reported severity.

Note: MedDRA Version 18.0.

Note: Treatment-emergent adverse events are those with an onset after the first application of study drug.

*Source: Table 9 SCS

Treatment Emergent Adverse Events and Adverse Reactions

Table 25: Summary of the TEAEs Occurring in ≥1% of the Subjects in Either Treatment Group Through Week 8 (Safety Population, Studies 301 and 302 Combined)*

System Organ Class ^a Preferred Term	IDP-122 Lotion (N=284)	Vehicle Lotion (N=142)
Subjects Reporting Any TEAE	61 (21.5%)	34 (23.9%)
Infections and infestations	28 (9.9%)	15 (10.6%)
Nasopharyngitis	7 (2.5%)	6 (4.2%)
Upper respiratory tract infection	7 (2.5%)	2 (1.4%)
Gastroenteritis	3 (1.1%)	1 (0.7%)
Urinary tract infection	1 (0.4%)	2 (1.4%)
Application site cellulitis	0	3 (2.1%)
General disorders and administration site conditions	8 (2.8%)	5 (3.5%)
Application site pain	1 (0.4%)	2 (1.4%)
Investigations	7 (2.5%)	5 (3.5%)
Metabolism and nutrition disorders	7 (2.5%)	3 (2.1%)
Injury, poisoning and procedural complications	5 (1.8%)	4 (2.8%)
Muscle strain	1 (0.4%)	2 (1.4%)
Respiratory, thoracic and mediastinal disorders	4 (1.5%)	2 (1.4%)
Cough	3 (1.1%)	1 (0.7%)
Musculoskeletal and connective tissue disorders	5 (1.8%)	1 (0.7%)
Vascular disorders	4 (1.4%)	1 (0.7%)
Hypertension	4 (1.4%)	1 (0.7%)
Nervous system disorders	3 (1.1%)	3 (2.1%)
Gastrointestinal disorders	3 (1.1%)	2 (1.4%)
Skin and subcutaneous tissue disorders	2 (0.7%)	2 (1.4%)
Psoriasis	0	2 (1.4%)
Psychiatric disorders	0	2 (1.4%)

*Source: Table 7 of Summary of Clinical Safety

^a Counts reflect numbers of subjects reporting one or more adverse events that map to MedDRA. At each level

Laboratory Findings

There were no clinically-meaningful differences in the median change between the IDP-122 and Vehicle groups for any laboratory parameter in the psoriasis studies (laboratory testing was not done in the healthy volunteer studies). The proportion of subjects with laboratory shifts from the normal range was generally similar between treatment groups, except for hematocrit at Week 8: 6.8% of subjects in the IDP-122 group shifted from normal to low by the end of treatment. However, the shift in hematocrit was considered to have been clinically significant only for one subject: A 38 y/o female's hematocrit was 0.314 (L/L) at Screening, 0.286 at Week 4, and 0.294 at Week 8 (no post-treatment values were reported). The event was reported as TEAE of anemia. She completed the study. For all other laboratory parameters, the differences between treatment groups in the proportion of subjects who shifted outside of the normal range was < 5%.

Vital Signs

There were no clinically-meaningful differences in vital signs between treatment groups across the development program.

Electrocardiograms (ECGs)

Electrocardiograms were not done.

QT

From the QT Interdisciplinary Review Team consult: “In the sponsor’s maximal use PK study in patients, the steady state C_{max} for halobetasol propionate was lower for IDP-122 lotion compared to the listed drug Ultravate cream (31.2 vs. 58.2 pg/mL).” Thus, the Applicant was not required to conduct a thorough QT study.

Immunogenicity

This section is not applicable.

7.3.5. Analysis of Submission-Specific Safety Issues

Local Skin Reactions (LSRs) and Local Tolerability Assessments

Local Skin Reactions (LSRs) were assessed at each visit by the following: Itching, dryness, and burning/stinging and were graded on a 4-point scale: none (0), mild (1), moderate (2), or severe (3). Atrophy, striae, telangiectasia, and folliculitis were recorded as absent or present. In the Safety Population, severe LSRs were reported in a higher proportion of subjects in the Vehicle group. No subjects were reported to have developed new atrophy or striae i.e., subjects who had those skin changes, had them at baseline (2 and 6 subjects, respectively). Telangiectasias were reported for one subject in the IDP-122 Lotion group, which had resolved by Week 12.

Table 26: Summary of Subjects with Treatment-Emergent Grade 3 Local Skin Reactions (Safety Population, Studies 301 and 302 Combined)*

Grade 3 (Severe) Reported	IDP-122 Lotion	Vehicle Lotion
Itching		
N	283	142
Yes	43 (15.2%)	39 (27.5%)
No	240 (84.8%)	103 (72.5%)
Dryness		
N	283	142
Yes	20 (7.1%)	22 (15.5%)
No	263 (92.9%)	120 (84.5%)
Burning/Stinging		
N	283	142
Yes	12 (4.2%)	10 (7.0%)
No	271 (95.8%)	132 (93.0%)

Note: Treatment-emergent assessments are those performed after the first application of study drug.

*Source: Table 15 SCS

7.3.6. Safety Analyses by Demographic Subgroups

The Applicant presented adverse events by age according to the following categories: < 53 years and ≥ 53 years. The age of 53 years does not seem a reasonable cut-point to mark the beginning of the geriatric category. The Applicant provided no rationale for this approach. The International Council for Harmonisation (ICH)-E7 guideline defines the geriatric population as comprising individuals aged 65 years or older (although stating this is arbitrary and for purposes of the document). A total of 93 subjects in the Safety Population were ≥ 65 years old (21.8%), 61 of whom were exposed to IDP-122 Lotion.

A total of 252 subjects (59.2%) in the Safety Population were male, and 174 (40.8%) were female.

Of 426 subjects in the Safety Population, 368 (86%) were White, 30 (7%) were Black, 13 (3%) were Asian, 11(3%) were “Other,” and, 4 (1%) were “Native Hawaiian or Other Pacific Islander.”

No safety signals were identified in age, gender, or race demographic subgroups. There were no apparent differences in the occurrence of adverse events in demographic subgroups, although the limited number of subjects in certain demographic subgroups limits conclusions. Given the long marketing history of the halobetasol propionate moiety (initially approved in 1990) and the lower concentration in the Applicant’s product relative to all other approved halobetasol products, new safety issues would not appear to be likely.

7.3.7. Specific Safety Studies/Clinical Trials

The Applicant conducted two dermal safety studies:

- Cumulative irritancy
- Contact sensitization

1. Cumulative irritancy

Generally, I will not discuss the results from the IDP-118 Lotion or Tazorac® Cream sites, as they are not relevant to the application that is under review.

Title (Study Number): “A 21-Day, Randomized, Controlled Study to Evaluate the Skin Irritation Potential of IDP-118 Lotion (Halobetasol propionate 0.01% and tazarotene 0.045%) and IDP-122 Lotion (Halobetasol propionate 0.01%) in Healthy Volunteers Using a Cumulative Irritant Patch Test Design” (V01-118A-102)

OBJECTIVES: The objective of this study was to determine the irritation potential of IDP-118 Lotion (Halobetasol propionate 0.01% and tazarotene 0.045%) and IDP-122 Lotion (Halobetasol propionate 0.01%) on normal skin.

METHODOLOGY: This was a randomized, single-center, controlled, evaluator-blinded, within-subject comparison study of the following six investigational products (IPs):

- IDP-118 Lotion (a combination product containing HP and tazarotene),
- IDP-122 Lotion, and
- Vehicle Lotion for the IDP-118 and IDP-122 (identical vehicle),
- Tazorac® Cream,
- positive control (sodium lauryl sulfate or SLS), and
- negative control (saline).

Patches were applied to six randomly-assigned, adjacent sites (Sites 1-6) on one side of the infrascapular area of the back, under semi-occlusive conditions. Patches were applied once daily and were removed 24 ± 2 hours after applications. The same study material was applied to the same test site throughout the study. A total of 21 applications of each product were made over 22 days. Patch sites were assessed at Baseline (Day 1) and immediately following patch removal i.e., 21 times post-baseline. Dermal reactions at the application sites were clinically assessed using the scoring system presented in Tables 27; 28 and 29 below.

The number of subjects enrolled was intended to provide for 30 completed subjects.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: healthy males or females 18 years of age or older, of any skin type or race, providing the skin pigmentation allowed for discernment of erythema

CRITERIA FOR EVALUATION:

Cumulative Irritancy

The scoring system presented in Table 27 and Table 28 below was used to assess patch test sites. The symbols and their respective numerical equivalent grades were used to express dermal reactions. Notations in Table 29 could be recorded in place of a grade if circumstances precluded assignment of a grade or in addition to a grade to document damage to the epidermis and/or spreading of a reaction beyond the patch site.

Table 27: Response Symbols and Numerical Equivalents*

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

*Source: Table 1 SAP

Table 28: Effects on Superficial Layers of the Skin

Symbol	Grade	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: Table 2 SAP

Table 29: Other Notations

Not	Definition
X	Subject absent
B	Burning or stinging sensation
PD	Patch dislodged
NA	Patch not applied
NP	No patch due to limiting irritation
I	Itching
D	Damage to epidermis: oozing, crusting, and/or superficial erosions
P	Papular response
pv	Papulovesicular response
S	Spreading of reaction beyond patch site (i.e., reaction where study material did not come in contact with skin)
T	Tape related reaction

*Source: Table 3 SAP

The grades from Table 27 and Table 28 were summed daily at each evaluation and for each product. A sum of “three” was set for the determination of irritancy.

The primary variable of interest was the mean cumulative irritation score (the mean of the observed scores on Days 2 through 22).

RESULTS:

Forty subjects were randomized, and 36 completed the study. The study population included 8 (20%) males and 32 (80%) females; 26 (65%) were Black or African American and 14 (35%) were White. Subjects ranged in age from 22 to 74 (mean age was 51.2 years). Most subjects had Fitzpatrick skin type IV (n=18, 45%), V (n=13, 32.5%), III (n=7, 17.5%), II (n=1, 2.5%) and VI (n=1, 2.5%).

Mean cumulative irritation scores were as follows (also see Table 30 below):

- IDP-122 Lotion: 0.01,
- Vehicle Lotion: 0.03,
- 0.9% saline: 0.04, and
- 0.5% SLS: 0.23.

Mean total irritation scores were as follows (see Table 30)

- IDP-122 Lotion: 0.30,
- Vehicle Lotion: 0.63,
- 0.9% saline: 0.88, and
- 0.5% SLS: 4.73.

Two subjects experienced four AEs:

- One subject had a cough.
- The other subject had dental surgeries, which result in three AE reports.

Table 30: Summary of Mean and Total Irritation Score– Safety Population: IDP 122 Lotion*

	Number of Subjects	Mean (SD)	P values			
			Normalized Total Score[1]	C. Vehicle Lotion	D. 0.5% SLS	E. 0.9% Saline
Mean Irritation Score						
IDP-122 Lotion	40	0.01 (0.04)		0.6039	<.0001	0.3811
Vehicle Lotion	40	0.03 (0.07)			<.0001	0.7203
0.5% SLS	40	0.23 (0.26)				<.0001
0.9% Saline	40	0.04 (0.12)				
Overall P value		<.0001				
	Number of Subjects	Mean (SD)	P values			
			Normalized Total Score[1]	C. Vehicle Lotion	D. 0.5% SLS	E. 0.9% Saline
Total Irritation Score						
IDP-122 Lotion	40	0.30 (0.76)	3/No significant irritation	0.6162	<.0001	0.3758
Vehicle Lotion	40	0.63 (1.41)	6/No significant irritation		<.0001	0.6998
0.5% SLS	40	4.73 (5.49)	47/No significant irritation			<.0001
0.9% Saline	40	0.88 (2.62)	9/No significant irritation			
Overall P value		<.0001				

*Source: Table 12-2 of study report for study 102

[1] A normalized total score for each patch was calculated by summing the total irritation scores for each subject, dividing by the number of subjects and multiplying by a factor of 10: 0-49 = No significant irritation; 50-199 = Slightly irritating; 200- 449 = Moderately irritating; 450-630 = Highly irritating
 P values are from pairwise comparisons of products from the analysis of variance with main effects of subject and product using Fisher's Least Significant Differences.

Note: Baseline scores were not included in mean or total calculations. Scores greater than 3 were included in mean and total calculations as a maximum score of 3. If patch was discontinued due to severe irritation, the last observed score (=3) was carried forward.

[1] A normalized total score for each patch was calculated by summing the total irritation scores for each subject, dividing by the number of subjects and multiplying by a factor of 10: 0-49 = No significant irritation; 50-199 = Slightly irritating; 200- 449 = Moderately irritating; 450-630 = Highly irritating

CONCLUSION: The study was of standard design for assessment of cumulative irritancy. There was no evidence of significant irritation identified with IDP-122 or Vehicle Lotion under the conditions of study.

2. Contact Sensitization

Title (Study Number): “A Randomized, Controlled Study to Evaluate the Sensitizing Potential of IDP-118 Lotion (Halobetasol propionate 0.01% and tazarotene 0.045%) and IDP-122 Lotion (Halobetasol propionate 0.01%) in Healthy Volunteers Using a Repeat Insult Patch Test Design” (V01-118A-103)

Generally, I will not discuss the results from the IDP-118 Lotions sites, as they are not relevant to the application that is under review.

OBJECTIVES: The objective of this study was to determine the sensitization potential of IDP-118 Lotion (Halobetasol propionate 0.01% and tazarotene 0.045%) and IDP-122 Lotion (Halobetasol propionate 0.01%) on normal skin.

METHODOLOGY: This was a randomized, single-center, controlled, evaluator-blinded, within-subject comparison study of the following investigational products (IPs): IDP-118 Lotion, IDP-122 Lotion, Vehicle Lotion, and 0.9% saline (negative control), conducted in healthy volunteers. Patch test sites were randomly assigned and adjacent and on the back. Patches were applied under semi-occlusive conditions. The study consisted of Induction, Rest, Challenge, and Rechallenge phases (rechallenge was not a required phase of the study, as discussed below).

The Induction Phase consisted of a total of nine patch applications over three weeks. Patches were applied on Mondays, Wednesdays, and Fridays. Approximately 48 hours after patch placement, subjects returned to have the patches removed (patches placed on Fridays remained in place until Monday i.e., for 72 hours). Test sites were evaluated immediately after patch removal, and the same scoring system was used as per the cumulative irritancy study (see Tables 27; 28; 29 above)

The Rest Period followed the Induction Period and consisted of a 10 to 14 day period during which no patches were applied.

During the Challenge Phase, subjects who completed the Induction Phase and the Rest Period had identical patches applied to naïve sites. Patches remained in place for 48 hours. After removal, application sites were evaluated at 30 minutes and approximately 24, 48, and 72 hours using the previously-referenced scoring system.

A subject was to be rechallenged to any of the study materials if the investigator identified any sign suggestive of contact sensitization (i.e., definite erythema with papules and or edema) at any of the four challenge evaluations. Rechallenge patches were to be applied to a new naïve sites, left in place for 48 hours, then removed followed by evaluation of test sites at the same timepoints as was done in the Challenge Phase.

The number of subjects enrolled was intended to provide for 200 completed subjects.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: healthy males or females 18 years of age or older, of any skin type or race, providing the skin pigmentation allowed for discernment of erythema

RESULTS:

A total of 244 subjects were randomized in the study, and 208 completed the study.

Thirty-six (36) subjects were discontinued from the study; 21 due to protocol violations, 7 due to subject withdrawal, 6 were lost to follow-up, 1 was the physician's decision, and 1 due to an AE.

Table 31: Summary of Subject Enrollment and Disposition – All Subjects

Number of Subjects Randomized	244
Number of Subjects Completing Study, n (%)	208 (85.2)
Subjects Included in Analysis of Safety Population (Safety Analysis), n	244 (100.0)
Subjects Included in Analysis of Cumulative Irritancy (Irritancy Analysis),	220 (90.2)
Subjects Included in Analysis of Sensitization (Sensitization Analysis), n	208 (85.2)
Number of Subjects Discontinued, n (%)	36 (14.8)
Reason for Discontinuation, n (%)	
Adverse Event	1 (0.4)
Protocol Violation	21 (8.6)
Physician Decision	1 (0.4)
Lost to Follow-up	6 (2.5)
Withdrawal by Subject	7 (2.9)

*Source: Table 10-1 of study report for study 103

The study population included 165 (67.6%) females and 79 (32.4%) males; 175 (71.7%) were Black or African American, 68 (27.9%) were White, and 1 (0.4%) was Other. Subjects ranged in age from 18 to 75 (mean age: 50.2 years). Most subjects had Fitzpatrick skin type V (n=124, 50.8%), IV (n=43, 17.6%), III (n=37, 15.2%), VI (n=30, 12.3%) and II (n=10, 4.1%).

Sensitization Potential

Dermal sensitization was defined by the recurrence of a cutaneous response at Rechallenge that was equivalent to or more severe than the reaction observed at Challenge.

Per the Statistical Analysis Plan, the Sensitization Population was defined as “all subjects who complete the 3-week Induction Phase and are evaluable for response to the Challenge patch. A subject must have had 9 applications of the study material (or patch discontinuation due to limiting reactions) and no fewer than 8 subsequent readings during Induction and one application followed by 4 subsequent readings during Challenge.” The Sensitization Population was used to estimate of incidence of sensitization.

Of the 244 subjects randomized, 208 were included in the Sensitization Population.

Table 32: Summary of Sensitization Potential– Challenge Readings –Sensitization Population*

	Number of Subjects (N = 208)			
	IDP-118 Lotion	IDP-122 Lotion	Vehicle Lotion	Saline (0.9%)
Subjects with Score of 1, n (%)	5 (2.4)	1 (0.5)	3 (1.4)	1 (0.5)
95% Confidence Limit	0.79, 5.52	0.01, 2.65	0.30, 4.16	0.01, 2.65
Subjects with Sensitization, n (%)	0	0	0	0
95% Confidence Limit	0.00, 1.76	0.00, 1.76	0.00, 1.76	0.00, 1.76

*Source: Table 12-1 of study report for study 103

Based on the assessment in the Challenge Phase, no subjects in any group had a score higher than 1. No subjects were considered to have shown evidence of sensitization. No subjects received rechallenge patch testing.

CONCLUSION: The study design was standard for assessment of contact sensitization. No test products showed evidence of the potential to cause contact sensitization.

7.3.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The following three events were reported in the “Neoplasms benign, malignant and unspecified (including cysts and polyps)” SOC in the Safety Population:

- IDP-122 Lotion group: keratoacanthoma and seborrheic keratosis
- Vehicle Lotion group: skin papilloma

No malignancies were reported in the Safety Population.

Pediatrics and Assessment of Effects on Growth

The Applicant has not conducted a pediatric assessment. The Pediatric Study Plan is discussed in Section 9.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There is no data (clinical or nonclinical) to indicate potential for addiction, abuse, withdrawal, rebound, or physical dependency with IDP-122 Lotion.

7.3.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

IDP-122 Lotion has not been marketed anywhere.

Expectations on Safety in the Postmarket Setting

The halobetasol moiety was initially approved in 1990. The postmarketing experience for IDP-122 Lotion is expected to be similar to other topical halobetasol products.

7.3.10. Integrated Assessment of Safety

A total of 430 subjects constituted the Safety Population: 217 subjects (50.5%) were randomized to IDP-122 Lotion treatment, and 213 (49.5%) were randomized to vehicle treatment. The safety database did not raise any new safety concerns. There was only one report of a local adverse reaction suggestive of corticosteroid effect (telangiectasia), and it had resolved by Week 12 (4 weeks post-treatment). The pattern of TEAEs, including SAEs was not worrisome. The overall incidence of SAEs was low in both treatment groups and higher in the Vehicle arm (2.8%) compared to IDP-122 (1.8%). Similarly, the overall incidence of TEAEs was higher in the Vehicle arm (23.9%) compared to IDP-122 (21.5%). The most commonly reported event was upper respiratory tract infection. TEAEs were most commonly reported in the Infections and infestations SOC, and nasopharyngitis was the most commonly reported TEAE in that SOC. “Upper respiratory tract infection,” “application dermatitis” and “hyperglycemia” were the only TEAEs that occurred in at least 1% of subjects treated with IDP-122 Lotion and more frequently than in vehicle-treated subjects. Dermal safety studies did not reveal IDP-122 Lotion to be an irritant or contact sensitizer.

HPA axis was observed following once daily use of IDP-122 Lotion for 8 weeks. However, the incidence of HPA axis suppression was low: one subject (5.6%) at Day 29 and 3 subjects (15.8%) at Day 57. Adrenal function had returned to normal on follow-up testing. Findings from routine laboratory testing were unremarkable.

In summary, IDP-122 Lotion was generally well-tolerated.

7.4. Summary and Conclusions

7.4.1. Statistical Issues

There were no major statistical issues in this application affecting the overall conclusions. While there was not an inconsequential amount of missing data, sensitivity analyses exploring other methods of handling missing data resulted in similar conclusions to those of the primary analysis (see Table 16 in Section 7.2.4).

There was a small number of subjects in most of the subgroups, and therefore, any treatment differences observed for these subgroups may not be meaningful. The treatment effects for the various subgroups were comparable across the two trials.

7.4.2. Conclusions and Recommendations

To establish the efficacy of IDP-122, the applicant submitted data from two identically-designed, randomized, double-blind, vehicle-controlled, Phase 3 trials (301 and 302). The trials enrolled subjects 18 years of age and older who had a clinical diagnosis of psoriasis with an IGA score of 3 (moderate) or 4 (severe) and had an area of plaque psoriasis that covered a BSA of 3% to 12% (excluding the face, scalp, palms, soles, axillae, and intertriginous areas). The pre-specified primary endpoint was the percentage of subjects with treatment success at Week 8, where treatment success was defined as at least a 2-grade improvement from baseline in IGA score and an IGA score equating to “Clear” or “Almost Clear”. IDP-122 was statistically superior (p -value <0.001) to vehicle for the primary endpoint in both Phase 3 trials (see Table 15 in Section 7.2.4 for full results).

The size of the safety database and the nature of the safety assessments were adequate to characterize the safety of IDP-122 Lotion. The safety evaluation revealed no concerning signals or concerns. The submitted data support approval of the marketing application.

8 Advisory Committee Meeting and Other External Consultations

This application was not discussed at an Advisory Committee Meeting.

9 Pediatrics

On 06/13/2016, the Agency issued a letter of agreement with the Applicant's Initial Pediatric Study Plan (iPSP). The Applicant requested a partial waiver of required studies for the age group of birth to 5 years 11 months of age, as the necessary studies are impossible or highly impracticable because of the small number of children in this category with the disease.

The Applicant requested a deferral of the evaluation of pediatric subjects between 6 years and 16 years, 11 months of age. The basis for the deferral request was that the Phase 3 studies in subjects 18 years of age and older were ongoing at the time of the iPSP, and the Applicant anticipated that the marketing application would be submitted prior to completion of the planned pediatric study.

The Applicant plans to conduct a (b) (6) study in subjects 6 years of age to 16 years 11 months. The study that will evaluate (b) (6), pharmacokinetics (PK), and HPA axis suppression of halobetasol propionate after topical application of IDP-122 Lotion once daily 8 weeks.

(b) (6)

Protocol Submitted: June 26, 2017
Study Completion: June 2020
Study Submission: Dec 2020

The Pediatric Review Committee (PeRC) reviewed the Applicant's pediatric plan on 06/27/2016. The PeRC agreed with the request of partial waiver and deferral of pediatric studies as outlined in the Agreed iPSP.

10 Labeling Recommendations

10.1. Prescribing Information

Labeling negotiations were pending as this review closed.

10.2. Patient Labeling

Patient labeling has been reviewed. Labeling negotiations were pending as this review closed.

11 Risk Evaluation and Mitigation Strategies (REMS)

Product labeling and routine pharmacovigilance activities should be adequate risk evaluation and mitigation strategies for this product. are recommended as methods for postmarket risk evaluation and mitigation.

12 Postmarketing Requirements and Commitments

A PREA PMR will be issued to conduct the study outlined in the agreed iPSP: a (b) (6) study evaluating (b) (6) pharmacokinetics and HPA axis suppression potential of topically applied IDP-122 lotion in pediatric subjects (6 -16 years 11 months of age) with moderate to severe plaque psoriasis.

13 Appendices

13.1. References

A literature review was not conducted for this application.

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): 301 and 302

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>20 for study 301; 17 for study 302</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>2</u>		
<p>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)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p>Significant payments of other sorts: <u>1</u></p> <p>Proprietary interest in the product tested held by investigator: _____</p> <p>Significant equity interest held by investigator in S</p> <p>Sponsor of covered study: <u>1</u></p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

13.3. Nonclinical Pharmacology/Toxicology

13.3.1. Clean version of the recommended labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION INDICATIONS AND USAGE

BRYHALI Lotion is a corticosteroid indicated for the topical treatment of plaque psoriasis.

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on BRYHALI Lotion use in pregnant women to inform a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.

In animal reproduction studies, increased malformations, including cleft palate and omphalocele, were observed after oral administration of halobetasol propionate during organogenesis to pregnant rats and rabbits. The available data do not support relevant comparisons of systemic halobetasol propionate exposures achieved in the animal studies to exposures observed in humans after topical use of BRYHALI Lotion.

Data

Animal Data

Halobetasol propionate has been shown to cause malformations in rats and rabbits when given orally during organogenesis at doses of 0.04 to 0.1 mg/kg/day in rats and 0.01 mg/kg/day in rabbits. Halobetasol propionate was embryotoxic in rabbits but not in rats. Cleft palate was observed in both rats and rabbits. Omphalocele was seen in rats but not in rabbits.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Halobetasol propionate was not found to be genotoxic in the Ames assay, in the sister chromatid exchange test in Chinese hamster somatic cells, in chromosome aberration studies of germinal and somatic cells of rodents, or in a mammalian spot test. Positive mutagenicity effects were observed in a mouse lymphoma gene mutation assay in vitro and in a Chinese hamster micronucleus test.

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

13.4. OCP Appendices (Technical documents supporting OCP recommendations)

Table 33: Summary of Dose Application (PK Population)

		IDP-122 Lotion (N=21)	Ultravate® Cream (N=23)
Amount of Study Drug Used (g)^a	N	10	14
	Mean (SD)	450 (115)	115(37)
	Median (min, max)	443 (173, 573.7)	112 (64.7 to 207.0)
Minimum Amount of Study Drug Used (g)^b	N	21	23
	Mean (SD)	409 (131)	117 (35)
	Median (min, max)	436 (90.8, 573.7)	121 (40.5, 207.0)
Number of Applications	N	21	23
	Mean (SD)	51.9 (12.27)	14.4 (0.66)
	Median (min, max)	56.0 (13 to 58)	14.0 (14, 16)

^aSummary is restricted to subjects with an initial dispense weight and final return weight for all dispensed tubes of study drug.

^bSummary includes all subjects with at least one tube of study drug with two or more recorded weights.
 Source: Adapted from Table 14.3.0.2.3 from Study Report.

Figure 4: Individual Plasma Concentration Profiles on Day 14 for IDP-122 and Ultravate (Red boxes indicate subjects with at least 3 quantifiable points to permit estimation of AUC)

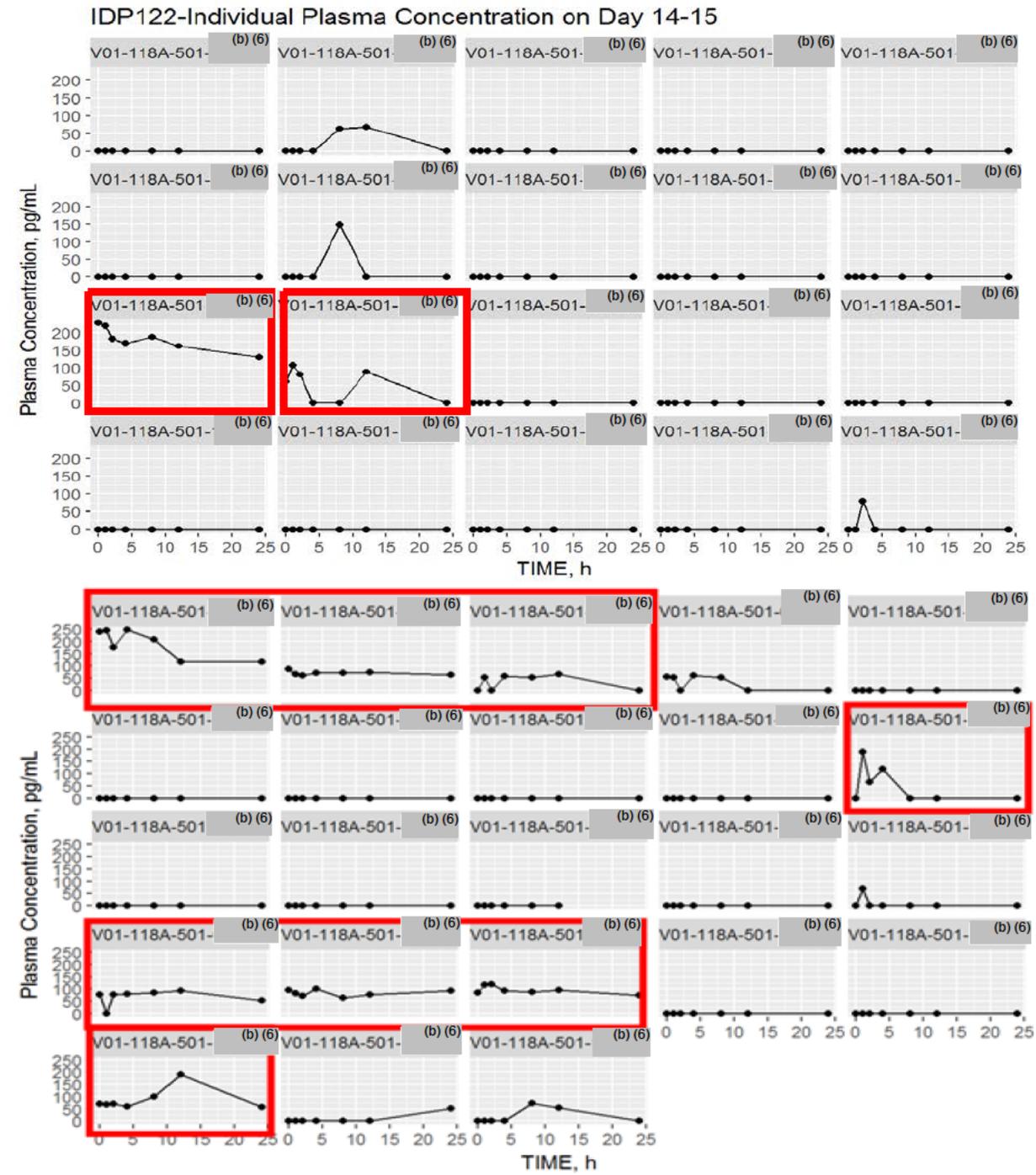


Table 34: Summary of Method Validation Results

Validation Report / Bioanalytical Report	VVALN1404P1P2 VALN1403P2	
Relevant Clinical Trial	V01-118A-501	
Matrix	Human plasma	
Analytes	Halobetasol propionate (HP)	
Linearity	0.0500 to 12.8 ng/mL	
LLOQ	0.0500 ng/mL	
Precision (% CV)	Intra-assay	Inter-assay
	11.6 to 18.6% (LLOQ) 1.3 to 6.3% (above LLOQ)	15.1% (LLOQ) 3.0 to 5.2% (above LLOQ)
Accuracy (% Bias)	Intra-assay	Inter-assay
	8.0 to 6.7% (LLOQ) 0.4 to 6.5% (above LLOQ)	-0.2% (LLOQ) 1.1 to 4.8% (above LLOQ)
Extraction Recovery	Halobetasol Propionate: 91% Halobetasol-d ₃ Propionate (IS): 101%	
Matrix Stability		
Freeze-thaw Stability	HP was stable in K ₂ EDTA human plasma over four cycles of freeze (-70 °C or -20 °C) and thaw (RT).	
Bench-top Stability	HP was stable in K ₂ EDTA human plasma at room temperature under normal laboratory lighting over a period of 9.25 hours	
Long Term Stability	HP was stable in K ₂ EDTA human plasma for at least 448 days, when stored at -20 °C. The established duration of long term stability supported the storage stability of the PK samples.	
Selectivity	Complies following acceptance criteria	
Analyte - HP	Interferences at ≤ 20% LLOQ (at least 5 of 6 screened)	
IS - HP	Interferences at ≤ 5% mean Internal Standard (at least 5 of 6 screened)	
Matrix Effect - HP	% CV for IS Normalized Matrix Factor (MF) must be ≤ 15% over all 6 lots out of 6 spiked matrix lots	
Incurred sample reanalysis (ISR)	Approximately 10% of the samples are re-analyzed. These include samples approximating the C _{max} , provided they did not require dilution, as well as samples near the elimination phase.	
Number of Samples	121	
Total % ISR Samples Pass the acceptance criteria	97%	

Study No. 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

Objective: To determine the potency of IDP-122 (halobetasol propionate) Lotion, 0.01% compared to four currently marketed topical corticosteroid formulations of known potency and a vehicle lotion formulation

- Ultravate® (halobetasol propionate) Cream, 0.05%, super potent
- Fluocinonide Cream USP, 0.05%, potent
- Betamethasone Dipropionate Cream USP, 0.05%, upper mid-strength potent
- Triamcinolone Acetonide Cream USP, 0.1%, mid-strength potent

Reviewer comments: The bracketing using products of known potency class was adequate.

Study Design: A single-point, randomized, evaluator-blinded, within-subject, single-center study was conducted to evaluate the vasoconstrictor properties of IDP-118 (halobetasol propionate 0.01% / tazarotene 0.045%) Lotion and IDP-122 (halobetasol propionate) Lotion, 0.01%, four currently marketed topical corticosteroid formulations of known potency. The study was designed based on the Stoughton-McKenzie bioassay system for formulations of topically applied glucocorticosteroids.

Treatment: 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.

Assessment: The visual evaluator and ChromaMeter operator were blinded as to the location of application of specific study drugs

Visual assessment (primary): The degree of skin blanching was visually evaluated at each site pre-dose (baseline assessments) and at about 18 hours after the application of the study drug (about 2 hours (±15 minutes) after washing the test sites to remove study drug) by a trained evaluator according to 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.

ChromaMeter Assessments: A Minolta ChromaMeter was used in this study to measure the reflective colors from the skin surface. 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 [\pm 15 minutes] after washing the test sites to remove study drug following 16 hour of application).

Reviewer comments: *The applicant has not submitted validation reports of ChromaMeter. As visual assessment was the primary endpoint and ChromaMeter assesment was only informational, the results of visual assessment is mainly considered in the review.*

Study Population: Thirty (30) subjects were enrolled in the study, and all subjects were healthy, nontobacco-using adults. All study participants were screened to determine blanching response to triamcinolone acetonide cream USP, 0.1%. A 10 μ L application of the cream was applied to the upper arm above the forearm. The cream was left in place for 2 hours (\pm 15 minutes). The cream was removed gently wiping with three consecutive cotton balls, 1 damp cotton ball (soaked in a mild, room temperature hypo-allergenic soap solution), 1 damp cotton ball (soaked in room temperature water), and lastly 1 dry cotton ball. About 6-9 hours after application, the site was visually evaluated for blanching. Responders must have had a visual assessment of at least 1 on the 0-3 rating scale. All subjects had an assessment of skin type using the “Fitzpatrick Skin Type Chart” at screening and had a Fitzpatrick score of 3 or less.

Results: Thirty (30) subjects completed the study and were included in the statistical analyses. As the ITT and PP populations were identical, only the PP population analyses were conducted. Mean results from visual assessments (primary) and mean results from ChromaMeter assessments (informational), in order of most to least potent formulation, are presented in Table 35 and Table 37, respectively. The mean of the two values (one per arm) for the all products, and the vehicle lotion formulation, and the mean of the four values (two per arm) for the untreated (control) sites were calculated for each subject and the values pooled across subjects to obtain the overall mean. 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 36 and Table 38, respectively.

Reviewer comments: *The rank order of the mean visual scores of the reference products generally follows their rank order of potency classification. However, it is noted that Betamethasone Dipropionate Cream USP, 0.05% (upper mid-strength) was observed to be more potent than the Fluocinonide Cream USP, 0.05% (high potency). This was also observed with ChromaMeter assesment.*

Using visual data (primary), IDP-122 ranked between Ultravate (super potent) and Betamethasone Dipropionate Cream USP, 0.05% (upper mid-strength) and the mean values of IDP-122 and Betamethasone Dipropionate Cream USP, 0.05% were not significantly different ($p=1.000$). However, IDP-122 ranked higher than Fluocinonide Cream USP, 0.05% (high potency) and the difference in their mean values were statistically significant ($p=0.0041$). The study data supports classification of IDP-122 Lotion as potent to super potent. Using ChromaMeter (informational), IDP-122 also ranked higher than Fluocinonide Cream USP, 0.05% (high potency), though the difference in the mean values were not statistically significant.

Table 35: Mean Results from Visual Assessments in Order of Most to Least Potent Formulation (Primary endpoint) (Note: IDP-118 was another investigational product that was included in the VCA study)

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%; (b) (4) 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%; (b) (4) Lot No: K510921749; Expiration Date: APR 2017	30	1.0333 ± 0.7063	B
Product 6	TRIAMCINOLONE ACETONIDE CREAM USP, 0.1%; (b) (4) 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.

Table 36: Comparison of p-values for statistical significance - Visual Assessment (Primary endpoint)

	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	—

Table 37: Mean Results from ChromaMeter Assessments in Order of Most to Least Potent Formulation (Informational) (Note: IDP-118 was another investigational product that was included in the VCA study)

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%; (b) (4) 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%; (b) (4) Lot No: K510921749; Expiration Date: APR 2017	30	1.3052 ± 0.9494	C D
Product 6	TRIAMCINOLONE ACETONIDE CREAM USP, 0.1%; (b) (4) 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.

Table 38: Comparison of p-values for statistical significance - ChromaMeter Assessment (Informational)

	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	—

Safety: No adverse events were reported by any subjects in this study.

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/

MATTHEW E WHITE
10/01/2018

YICHUN SUN
10/01/2018

Renqin DUAN
10/01/2018

BARBARA A HILL
10/01/2018

JIHYE AHN
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CHINMAY SHUKLA
10/02/2018

REBECCA S HAGER
10/02/2018

MOHAMED A ALOSH
10/02/2018

LAURA L JOHNSON
10/03/2018

BRENDA CARR
10/03/2018

SNEZANA TRAJKOVIC
10/04/2018

JILL A LINDSTROM
10/04/2018

Memorandum

To: NDA 209355
From: Renqin Duan, Ph.D., Pharmacology/Toxicology Reviewer
Through: Barbara Hill, Ph.D., Pharmacology/Toxicology Supervisor

Re:

SDN: 1
Submission date: 12-05-2017
Submission type: Original 505(b)(2) NDA
Drug: BRYHALI (halobetasol propionate) Lotion, 0.01%
Indication: Treatment of plaque psoriasis
Route: Topical
Applicant: Dow Pharmaceutical Sciences, Inc.

The applicant is seeking approval of BRYHALI (halobetasol propionate) Lotion, 0.01%, for the treatment of plaque psoriasis in patients 18 years of age and older via a 505(b)(2) regulatory pathway.

The nonclinical Pharmacology/Toxicology review is complete and has been added to the 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.

The applicant has established an adequate clinical bridge to the Listed Drug, Ultravate (halobetasol propionate) Cream, 0.05%. Refer to Clinical Pharmacology section of the Multi-Disciplinary Review and Evaluation for the details. The applicant is relying on the Agency's finding of safety for the Listed Drug. The nonclinical information from the approved label for the Listed Drug that the applicant intends to rely on includes fertility and reproduction, embryofetal development and genotoxicity. The toxicities of halobetasol propionate are well characterized and typical for the drug class. The toxicity profile for the halobetasol propionate lotion demonstrated in a pivotal 3-month repeat dose dermal toxicity study in minipigs was consistent with that of topical corticosteroids.

BRYHALI 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.

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/s/

Renqin DUAN
07/26/2018

BARBARA A HILL
07/26/2018