CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215309Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number	215309
Priority or Standard	Priority
Submit Date	21 December 2021
Received Date	21 December 2021
PDUFA Goal Date	21 September 2021
Division/Office	Division of Dermatology and Dentistry (DDD)/ Office of Immunology and Inflammation (OII)
Review Completion Date	20 September 2021
Established/Proper Name	Ruxolitinib
(Proposed) Trade Name	OPZELURA
Pharmacologic Class	Janus kinase (JAK) inhibitor
Code name	Not Applicable
Applicant	Incyte Corporation
Dosage form	Cream, 1.5%
Applicant proposed Dosing Regimen	Apply a thin layer of OPZELURA cream, 1.5% twice daily to affected areas of up to 20% of body surface area
Applicant Proposed Indication(s)/Population(s)	OPZELURA cream, 1.5% is indicated for the topical treatment of atopic dermatitis in patients 12 years of age and older.
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	24079001 | Atopic dermatitis (disorder)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	OPZELURA is indicated for the topical short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. <u>Limitation of Use:</u> Use of OPZELURA in combination with therapeutic biologics, other JAK inhibitors or potent immunosuppressants such as azathioprine or cyclosporine is not recommended.
Recommended SNOMED CT Indication Disease Term for each Indication	24079001 | Atopic dermatitis (disorder)

Recommended Dosing Regimen	Apply a thin layer of OPZELURA twice daily to affected areas of up to 20% body surface area. Do not use more than 60 grams per week.

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Matthew White
Nonclinical Reviewer	Jianyong Wang, PhD
Nonclinical Supervisor	Barbara Hill, PhD
Office of Clinical Pharmacology Reviewer	Luke Oh, PhD
Office of Clinical Pharmacology Team Leader	Chinmay Shukla, PhD
Clinical Reviewer	Brenda Carr, MD
Clinical Team Leader	Snezana Trajkovic, MD
Statistical Reviewer	Kathleen Fritsch, PhD
Statistical Team Leader	Mohamed Alosh, PhD
Cross-Disciplinary Team Leader	Snezana Trajkovic, MD
Deputy Division Director	Shari L. Targum, MD, MPH

Additional Reviewers of Application

Division Director	Kendall A. Marcus, MD
Deputy Director for Safety	Tatiana Oussova, MD, MPH
Associate Director for Labeling (Acting)	Strother D. Dixon
OPQ-ATL	Hamid Shafiei, PhD
OPQ – Regulatory Business Process Manager	Melinda Bauerlien, MS
OPQ - Drug Substance (DS)	Jeff Medwid, PhD/Donna Christner, PhD
OPQ - Biopharmaceutics	Kalpana Paudel, PhD/Tapash Ghosh, PhD
OPQ – Drug Product (DP), Environmental Assessment	Caroline Stasinger, PhD/Wendy Wilson-Lee, PhD
OPQ – Process/Facilities	Raeann Wu, PhD/Frank Wackes, PhD
OPQ - Microbiology	Dustin Thomas, PhD/Jesse Wells, PhD
OSE/DMEPA	Madhuri Patel, PharmD/Sevan Kolejian, PharmD, MBA, BCPPS
OSE/DRISK	Joel L. Wessfeld, MD, MPH/Sukhminder K. Sandhu, PhD, MPH, MS
OSE SRPM	Tri Bui-Nguyen, PhD
OCP/PM	Da Zhang, PhD/ Jiang Liu, PhD
DMPP	Susan Redwood, MPH, BSN, RN/LaShawn Griffiths, MSHS-PH, BSN, RN/Shawna Hutchins, MPH, BSN, RN
OPDP	Laurie Bounaccorsi, PharmD/Matthew Falter
COA	Yasmin Choudhry, MD/Selena Daniels, PharmD, MS/Elektra Papadopoulos, MD, MPH
MHT	Jean Limpert, MD/Miriam Dinatale, DO/Lynne P. Yao, MD

OSI	Phuc Nguyen, MD/Karen Bleich, MD/Kassa Ayalew, MD, MPH

OCP/PM = Office of Clinical Pharmacology/Pharmacometrics
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DMPP = Division of Medical Policy Programs
DRISK=Division of Risk Management
COA = Clinical Outcome Assessment
SRPM = Safety Regulatory Project Manager
MHT = Maternal Health Team

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Office of Pharmaceutical Quality Technical Lead	Hamid Shafiei, PhD	OPQ/DNDP II/NDPB V	Sections: 4.2	**Select one:** _X_ Authored _X_ Approved
	Signature: See DARRTS signature page			
Nonclinical Reviewer	Jianyong Wang, PhD	OII/DPT-II	Sections: 5, 14.3	**Select one:** _X_ Authored ___ Approved
	Signature: See DARRTS signature page			
Nonclinical Supervisor	Barbara Hill, PhD	OII/DPT-II	Sections: 5, 14.3	**Select one:** ___ Authored _X_ Approved
	Signature: See DARRTS signature page			
Clinical Pharmacology Reviewer	Luke Oh, PhD	OCP/DIIP	Sections: 6, 14.1	**Select one:** _X_ Authored ___ Approved
	Signature: See DARRTS signature page			
Clinical Pharmacology Team Leader	Chinmay Shukla, PhD	OCP/DIIP	Section: 6, 14.1	**Select one:** ___ Authored X Approved
	Signature: See DARRTS signature page			
Pharmacometrics Reviewer	Da Zhang, PhD	OCP/DPM	Section: 6, 14.1	**Select one:** _X_ Authored ___ Approved
	Signature: See DARRTS signature page			
Pharmacometrics Team Leader	Jiang Liu, PhD	OCP/DPM	Section: 6, 14.1	**Select one:** ___ Authored _X_ Approved
	Signature: See DARRTS signature page			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Division Director	Suresh Doddapaneni, PhD	OCP/DIIP	Section: 6, 14.1	**Select one:** ___ Authored _X _ Approved
	Signature: See DARRTS signature page			
Biostatistics Reviewer	Kathleen Fritsch, PhD	OTS/OB/DB III	Section: 8.1, 8.3	**Select one:** _X_ Authored ___ Approved
	Signature: See DARRTS signature page			
Biostatistics Team Leader	Mohamed Alosh, PhD	OTS/OB/DB III	Section: 8.1, 8.3	**Select one:** ___ Authored _X _ Approved
	Signature: See DARRTS signature page			
Clinical Outcome Assessment Reviewer	Yasmin Choudhry, MD	ODES/DCOA	Section: 8.1.4, 14.5	**Select one:** _X_ Authored ___ Approved
	Signature: See DARRTS signature page			
Clinical Outcome Assessment Team Leader	Selena Daniels, PharmD, MS	ODES/DCOA	Section: 8.1.4, 14.5	**Select one:** ___ Authored _X _ Approved
	Signature: See DARRTS signature page			
Clinical Outcome Assessment Associate Director	Elektra Papadopoulos, MD	ODES/DCOA	Section: 8.1.4, 14.5	**Select one:** ___ Authored _X _ Approved
	Signature: See DARRTS signature page			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Brenda Carr, MD	OII/DDD	Section: 1, 2, 3, 4.1, 7, 8.2, 8.4, 9, 10, 11, 12, 13, 16	**Select one:** _X_ Authored ___ Approved
	Signature: See DARRTS signature page			
Clinical Team Leader	Snezana Trajkovic, MD	OII/DDD	Section:1, 2, 3, 4.1, 7, 8.2, 8.4, 9, 10, 11, 12, 13, 16	**Select one:** ___ Authored _X _ Approved
	Signature: See DARRTS signature page			
Deputy Division Director (Clinical)	Shari L. Targum, MD, MPH	OII/DDD	Sections: 1	**Select one:** ___ Authored _X _ Approved
	Signature: See DARRTS signature page			

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
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
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation

PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Ruxolitinib inhibits Janus kinase (JAK) 1 and JAK2, which mediate the signaling of several cytokines and growth factors that are important for hematopoiesis and immune function. JAK signaling involves recruitment of signal transducers and activators of transcription (STATs) to cytokine receptors, activation and subsequent localization of STATs to the nucleus leading to modulation of gene expression.[1]

T-helper 2 (Th2) cells figure prominently in the complex pathogenesis of atopic dermatitis (AD),[2,3] and lesional skin includes increased levels of Th2 cytokines (IL-4, IL-13, IL-31).[4] Several inflammatory cytokines (interleukins, interferons) depend on JAK-STAT signaling.[5] Thus, disruption of this signaling may have therapeutic potential for treatment of inflammatory diseases, including atopic dermatitis.

Ruxolitinib is currently marketed in oral dosage forms for the following indications:

- treatment of intermediate or high-risk myelofibrosis (MF), including primary MF, post-polycythemia vera MF and post-essential thrombocythemia MF in adults.
- treatment of polycythemia vera (PV) in adults who have had an inadequate response to or are intolerant of hydroxyurea.
- treatment of steroid-refractory acute graft-versus-host disease (GVHD) in adult and pediatric patients 12 years and older.

The new drug application (NDA) includes information on ruxolitinib 0.75% and 1.5% cream. Incyte Corporation ("Incyte" or "the Applicant") seeks approval of the 1.5% concentration for treatment of mild to moderate atopic dermatitis(AD) and proposes to market the product under the proprietary name "Opzelura."

Ruxolitinib cream would be the first topical product in this product class and would add to the limited armamentarium of nonsteroidal topical treatment for AD.

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[1] Mechanism of action per package insert for Jakafi (Section 12.1).

[2] Lei Bao, Huayi Zhang & Lawrence S Chan (2013) The involvement of the JAKSTAT signaling pathway in chronic inflammatory skin disease atopic dermatitis, JAK-STAT, 2:3, e24137, DOI: 10.4161/jkst.24137

[3] Levy LL, Urban J & King BA. Treatment of recalcitrant atopic dermatitis with the oral Janus kinase inhibitor tofacitinib citrate. J Am Acad Dermatol 2015;73:395-9.

[4] Guttman-Yassky E, Silverberg JI, Nemoto O, Forman SB et al. Baricitinib in adult patients with moderate-to-severe atopic dermatitis: A phase 2 parallel, double-blinded, randomized placebo-controlled multiple-dose study. J Am Acad Dermatol 2019;80:913-21.

[5] Damsky WD and King BA. JAK inhibitors in dermatology: The promise of a new drug class. J Am Acad Dermatol 2017;76:736-44.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant provided substantial evidence of effectiveness from two adequate and well-controlled studies, INCB 18424-303 (303) and INCB 18424-304 (304), that evaluated ruxolitinib 1.5% cream for treatment of subjects 12 years and older with mild-to-moderate atopic dermatitis. Ruxolitinib 1.5% cream was statistically superior to vehicle in both studies in the target AD population for the primary endpoint, the proportion of subjects achieving Investigator's Global Assessment Treatment Success at Week 8, defined as a score of 0 or 1 with at least 2 grades reduction from baseline: Study 303 - 136/253 (53.8%) vs 19/126 (15.1%), ($p<0.0001$); Study 304 – 117/228 (51.3%) vs 9/118 (7.6%) ($p<0.0001$), respectively. Efficacy results for the primary endpoint and the secondary endpoints of Eczema Area and Severity Index (EASI) 75 and ≥4-point improvement on the Itch Numerical Rating Scale were consistent across the two studies, and the treatment effects were robust across different ways of handling missing data.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Atopic dermatitis (AD) is a chronic, relapsing, inflammatory cutaneous disorder, which is characterized by intensely pruritic, xerotic skin. Other clinical features may include erythema, edema, erosions, oozing, and lichenification. Although it may affect all age groups, AD is most common in children. AD may be associated with other atopic conditions e.g., rhinosinusitis, asthma, and psychosocial co-morbidities, including anxiety, depression.

T-helper 2 (Th2) cells figure prominently in the complex pathogenesis of atopic dermatitis (AD), and lesional skin includes increased levels of Th2 cytokines (IL-4, IL-13, IL-31). Several inflammatory cytokines (interleukins, interferons) depend on Janus kinase (JAK) signal transducers and activators of transcription (STAT). Thus, disruption of this signaling may have therapeutic potential for treatment of inflammatory diseases, including AD.

Effectiveness

The Applicant provided substantial evidence of effectiveness from two adequate and well-controlled studies, INCB 18424-303 (303) and INCB 18424-304 (304), that evaluated ruxolitinib 1.5% cream for treatment of subjects 12 years and older with mild-to-moderate atopic dermatitis. Ruxolitinib 1.5% cream was statistically superior to vehicle in both studies in the target AD population for the primary endpoint, the proportion of subjects achieving Investigator's Global Assessment Treatment Success at Week 8, defined as a score of 0 or 1 with at least 2 grades reduction from baseline: Study 303 - 136/253 (53.8%) vs 19/126 (15.1%), ($p<0.0001$); Study 304 – 117/228 (51.3%) vs 9/118 (7.6%) ($p<0.0001$), respectively. Efficacy results for the primary endpoint and the secondary endpoints of Eczema Area and Severity Index (EASI) 75 and ≥4-point improvement on the Itch Numerical Rating Scale were consistent across the two studies, and the treatment effects were robust across different ways of handling missing data.

Safety

The primary safety analyses were done on the Phase 3 vehicle-controlled (VC) Population, which consisted of 1249 subjects with mild-to- moderate AD, 499 of whom were treated with ruxolitinib 1.5% cream. A total of 92 subjects were 12 to 17 years of age. In the Phase 3 VC Population, 83 subjects (33.2%) in the vehicle group and 132 (26.5%) in the ruxolitinib 1.5% cream group experienced at least one AE. Treatment-emergent adverse events (TEAEs) were most frequently reported in the Infections and infestations system organ class (SOC), and nasopharyngitis was the most commonly reported TEAE in this SOC (and overall):

vehicle- 2 subjects (0.8%) and ruxolitinib 1.5% cream- 13 subjects (2.6%). Upper respiratory tract infection was the second most commonly reported TEAE in this SOC: vehicle- 5 subjects (2.0%) and ruxolitinib cream 1.5%- 12 (2.4%). The submitted evidence did not indicate that ruxolitinib 1.5% cream has significant potential for irritancy, and it did not show evidence of causing contact sensitization or photosensitivity reactions in dermal safety studies.

A total of 7 subjects treated with ruxolitinib cream experienced SAEs in the Phase 3 VC Population, 3 (0.6%) of whom were treated with the 1.5% concentration proposed for marketing. Pneumonia was the only SAE for which there was more than one report in a treatment group, and both events occurred in the 0.75% group (0.4%). The other SAE for which there was more than one report was cerebrovascular accident (CVA), and there were 2 reports of this event: one in the 0.75% arm and the other in the 1.5% arm (0.2% each); the subject in the 1.5% group also experienced an SAE of (unspecified) arrhythmia. The SAEs for the other 2 subjects in the 1.5% group were acute abdomen; and cholangitis and cholestatic jaundice.

The systemic exposure from ruxolitinib 1.5% cream may overlap with that from orally administered ruxolitinib, and the Applicant queried the safety database for TEAEs that might reflect systemic exposure to ruxolitinib or that might be seen with other JAK inhibitors that are indicated for treatment of inflammatory conditions: cytopenias, herpes zoster and other infections, nonmelanoma skin cancer, thromboembolic events, lipid elevations, and elevations of liver function tests. TEAEs suggestive of systemic effect were infrequent, uncomplicated, and generally resolved without any action taken with study treatment.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• AD is a chronic, relapsing, inflammatory cutaneous disorder, which is characterized by intensely pruritic, xerotic skin. Other clinical features may include erythema, edema, erosions, oozing, and lichenification. Although it may affect all age groups, AD is most common in children. It may be associated with other atopic conditions e.g., rhinosinusitis, asthma. • T-helper 2 (Th2) cells figure prominently in the complex pathogenesis of atopic dermatitis (AD), and lesional skin includes increased levels of Th2 cytokines (IL-4, IL-13, IL-31). Several inflammatory cytokines (interleukins, interferons) depend on Janus kinase (JAK) signal transducers and activators of transcription (STAT). Thus, disruption of this signaling may have therapeutic potential for treatment of inflammatory diseases, including AD.	AD may significantly impact the quality of life not only of the patient, but also of family members. The intense pruritus may disrupt sleep. The dysfunctional skin barrier, further compromised from scratching, may predispose patients to secondary infections. The primary and secondary disease-related skin changes may distort the appearance of the skin. The disease may also have impact on the mood, and affected individuals may experience depression and feelings of social isolation.
Current Treatment Options	• Topical corticosteroids (TCS) are first-line pharmacologic treatment for AD. Local adverse reactions from TCS may include atrophy, striae, telangiectasias, burning, hypopigmentation, and allergic contact dermatitis. Some local adverse reactions may be irreversible. TCS carry the risk of hypothalamic pituitary- adrenal (HPA) axis suppression, with the potential for glucocorticosteroid insufficiency. • Tacrolimus ointment and pimecrolimus cream are topical calcineurin inhibitors that are approved for treatment of AD. The labels specify that these products are second-line therapy for AD and are for "short-term and non-continuous chronic treatment…" The labels include Boxed Warnings that describe that rare cases of malignancy (e.g., skin and lymphoma) have been reported in patients treated with topical calcineurin inhibitors. • Crisaborole ointment, 2% is the first topical phosphodiesterase 4 (PDE-4) inhibitor and is a non-steroidal option for treatment of	There is a medical need for additional treatment options for mild to moderate AD. While approved therapies are safe and effective, they have the potential for local and systemic adverse reactions or have shown modest efficacy. Ruxolitinib 1.5% cream did not show evidence of significant potential to cause application site reactions. Although ruxolitinib 1.5% cream carries the risk of systemic adverse reactions, the risk profile is generally different from those of currently approved products. Therefore, ruxolitinib 1.5% cream may be an option for patients whose disease is not adequately controlled with available topical prescription therapies

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	mild to moderate AD. Although crisaborole ointment appears to have been well-tolerated in the clinical trials, the label reflects that treatment responses were modest in the pivotal clinical trials that supported approval.	or when those therapies are not advisable.
Benefit	• The Applicant provided data from two adequate and well-controlled studies, INCB 18424-303 (303) and INCB 18424-304 (304), that evaluated ruxolitinib 1.5% cream for treatment of subjects 12 years and older with mild-to-moderate atopic dermatitis. Ruxolitinib 1.5% cream was statistically superior to vehicle in both studies in the target AD population for the primary endpoint, the proportion of subjects achieving Investigator's Global Assessment Treatment Success at Week 8, defined as a score of 0 or 1 with at least 2 grades reduction from baseline: Study 303 - 136/253 (53.8%) vs 19/126 (15.1%), ($p<0.0001$); Study 304 – 117/228 (51.3%) vs 9/118 (7.6%) ($p<0.0001$), respectively. Efficacy results for the primary endpoint and the secondary endpoints of Eczema Area and Severity Index (EASI) 75 and ≥4-point improvement on the Itch Numerical Rating Scale were consistent across the two studies, and the treatment effects were robust across different ways of handling missing data.	The data submitted from the two adequate and well-controlled trials meet the evidentiary standard for providing substantial evidence of effectiveness. The Applicant has established that ruxolitinib 1.5% cream is effective for treatment of mild to moderate AD under the conditions of use evaluated in the clinical trials.
Risk and Risk Management	The primary safety analyses were done on the Phase 3 vehicle-controlled (VC) Population, which consisted of 1249 subjects with AD, and 499 subjects were treated with ruxolitinib 1.5% cream. A total of 92 subjects were 12 to 17 years of age. TEAEs were most frequently reported in the Infections and infestations system organ class (SOC), and nasopharyngitis was the most commonly reported TEAE in this SOC (and overall): vehicle- 2 subjects (0.8%) and ruxolitinib 1.5% cream- 13 subjects (2.6%). Upper respiratory tract infection was the second most commonly reported TEAE in this SOC: vehicle- 5 subjects	The Applicant comprehensively evaluated the safety of ruxolitinib 1.5% cream in subjects with mild to moderate AD. The types and frequency of safety evaluations were adequate to identify local TEAEs that might be observed with ruxolitinib 1.5% cream. The types and frequency of safety evaluations were also adequate to evaluate for systemic TEAEs that might be seen

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	(2.0%) and ruxolitinib cream 1.5%- 12 (2.4%). The submitted evidence indicates that ruxolitinib 1.5% cream does not have significant potential for irritancy, and it did not show evidence of causing contact sensitization or photosensitivity reactions in dermal safety studies. A total of 3 (0.6%) subjects treated with ruxolitinib 1.5% cream experienced SAEs: CVA and arrhythmia; acute abdomen; and cholangitis and cholestatic jaundice. The systemic exposure from ruxolitinib 1.5% cream may overlap with that of orally administered ruxolitinib, and the Applicant queried the safety database for TEAEs that might reflect systemic exposure to ruxolitinib or that might be seen with other JAK inhibitors that are indicated for treatment of inflammatory conditions (cytopenias, herpes zoster and other infections, nonmelanoma skin cancer, thromboembolic events, lipid elevations, and elevations of liver function tests. TEAEs suggestive of systemic effect were infrequent, uncomplicated, and generally resolved without any action taken with study treatment.	with oral ruxolinib or with oral JAK inhibitors that are approved for treatment of other inflammatory conditions. Prescription labeling, patient labeling (Medication Guide) and routine pharmacovigilance activities are believed adequate to manage the risks of ruxolitinib 1.5% cream. Because of the overlap in systemic exposure from ruxolitinib 1.5% cream with orally administered ruxolitinib, labeling should reflect the risk profile of oral ruxolitinib and oral JAK inhibitors that are indicated for treatment of inflammatory diseases. That is, the discussion of risk in the label for ruxolitinib 1.5% cream should generally align with the discussions in the labels for the oral JAK inhibitors, as referenced above.

1.4. Patient Experience Data

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

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	8; 14.2.2
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	8
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

Atopic dermatitis (AD) is a chronic, relapsing, inflammatory cutaneous disorder, which is characterized by intensely pruritic, xerotic skin. Other clinical features may include erythema, edema, erosions, oozing, and lichenification. Although it may affect all age groups, AD is most common in children. It is clinically diagnosed, which relies principally on disease pattern (morphology and distribution), disease history, and medical history (e.g., personal and/or family history of atopy). The dysfunctional skin barrier, further compromised from scratching, may predispose patients to secondary infections. The primary and secondary disease-related skin changes may distort the appearance of the skin. Affected individuals may experience depression, anxiety, and feelings of social isolation. Additionally, AD may significantly impact the quality of life not only of the patient, but also of family members.

2.2. Analysis of Current Treatment Options

The Applicant is proposing ruxolitinib 1.5% cream for the topical treatment of mild to moderate AD, and the following discussion will focus on the topical treatment of this disease.

Topical corticosteroids (TCS) are the most commonly used medications and are first-line pharmacologic treatment for AD. As listed in product labels, local adverse reactions from TCS may include atrophy, striae, telangiectasias, burning, itching, irritation, dryness, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, and miliaria. These may be more likely to occur with occlusive use, prolonged use, or use of higher potency corticosteroids. Some local adverse reactions may be irreversible.

Irrespective of the route of administration, corticosteroids carry the risk of hypothalamic pituitary- adrenal (HPA) axis suppression, with the potential for glucocorticosteroid insufficiency. As discussed in labels for TCS, factors that predispose to HPA axis suppression from TCS include use of more potent corticosteroids, use over large surface areas, prolonged use, occlusive use, use on an altered skin barrier, concomitant use of multiple corticosteroid-containing products, liver failure, and young age.

Calcineurin inhibitors are approved for treatment of AD only by topical administration, and the approved products are tacrolimus ointment and pimecrolimus cream. The labels specify that these products are second-line therapy for AD and are for “short-term and non-continuous chronic treatment…in non-immunocompromised adults and children who have failed to respond adequately to other topical prescription treatments for atopic

dermatitis, or when those treatments are not advisable."[6] The labels for topical calcineurin inhibitors include Boxed Warnings advising that the safety of their long-term use has not been established and that advise against continuous long-term use and that use should be limited to areas affected by AD. The boxed warnings describe that rare cases of malignancy (e.g., skin and lymphoma) have been reported in patients treated with topical calcineurin inhibitors; a causal relationship has not been established. Both labels include Warnings and/or Precautions regarding bacterial and viral skin infections and avoidance of sunlight, even when product is not on the skin.

The most-recently approved topical treatment for AD (approved 12/14/2016) is crisaborole ointment, 2%. Crisaborole ointment is the first topical phosphodiesterase 4 (PDE-4) inhibitor, and provides for a non-steroidal option for topical treatment of AD. Although the label reflects that crisaborole ointment appears to have been well-tolerated in the clinical trials, treatment responses were modest, with ~one third of subjects achieving treatment success in the pivotal safety and efficacy trials.

Nonpharmacologic care is important to good management of AD and includes the regular use of moisturizers, which may relieve pruritus, lessen erythema and fissurring, and improve lichenification. Moisturizers themselves may be the principal treatment for mild disease. Although there are no standardized or universal recommendations regarding the use of moisturizers, repeated application of generous amounts is thought to be key, irrespective of disease severity.

[6] Package inserts for tacrolimus ointment and pimecrolimus cream.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Ruxolitinib phosphate cream is not marketed. Ruxolitinib drug substance is currently marketed in tablet dosage forms for oral administration under the tradename Jakafi®. Jakafi® was approved on 11/16/2011 under NDA 202192, and Incyte is the owner of that NDA. Jakafi® is approved for the following indications:

- treatment of intermediate or high-risk myelofibrosis (MF), including primary MF, post-polycythemia vera MF and post-essential thrombocythemia MF in adults.
- treatment of polycythemia vera (PV) in adults who have had an inadequate response to or are intolerant of hydroxyurea.
- treatment of steroid-refractory acute graft-versus-host disease (GVHD) in adult and pediatric patients 12 years and older.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant developed ruxolitinib cream under IND 77101, submitted on 02/21/2007 for [redacted] (b) (4) On 09/19/2012, Incyte requested that the IND be placed on inactive status, after the [redacted] (b) (4) program was discontinued for administrative reasons. [redacted] (b) (4) The FDA advised the Applicant of the inactive status on 01/31/2013.

On 05/14/2015, the Applicant submitted a request to reactivate the IND, and the submission included protocol INCB 18424-204 (204) for evaluation of ruxolitinib cream for treatment of alopecia areata. The Applicant terminated study 204 early, as the study did not meet its primary endpoint (the study closed 10/03/2017). The Applicant did not identify any safety concerns in study 204 and did not pursue further development of ruxolitinib cream for alopecia areata [redacted] (b) (4). The Applicant is also evaluating the product for treatment of vitiligo. Phase 3 studies for evaluation of the product for treatment of vitiligo in subjects 12 years of age and older were ongoing at the time of this NDA review.

End-of-Phase 2 Meeting

The End-of-Phase 2 (EOP2) meeting, held 10/24/2018, included the following areas of agreements:

- The basic design of the vehicle-controlled period of the Phase 3 trials, with inclusion of subjects ≥ 12 years of age.
- The primary endpoint: Investigator's Global Assessment (IGA) Treatment Success = IGA grade of ≤ 1 with ≥ 2-grade improvement).

Comments regarding the safety database included the following:

- (b) (4)
- The safety database should be of sufficient size to support product safety, including information from a sufficient proportion of pediatric subjects.
- The sponsor should utilize the information they have about the adverse events of their product and plan the size of the safety database to observe expected adverse events with a good probability.

The meeting minutes do not include discussion of specific numbers regarding the size of the safety database.

Priority Review/Major Amendment

The Applicant redeemed a Rare Pediatric Disease Priority Review Voucher (PRV) with this NDA submission, which placed the NDA on a 6-month review timeline, with a goal date of 06/21/2021. On 05/28/2021, the Agency sent the Applicant an Information Request (IR), in the context of findings from a long-term safety trial conducted with another JAK inhibitor (tofacitinib) that showed an increased risk for adverse events, including major adverse cardiovascular events (MACE) and malignancies, compared to TNF blockers used for treatment of rheumatoid arthritis. The Agency requested that the Applicant provide an updated benefit-risk assessment and consider changes to the proposed indication and dosage and administration instructions for their product. The Applicant was also requested to provide additional analyses of adverse events. The Applicant's response to the IR, submitted on 06/04/2021, constituted a major amendment, which shifted the goal date to 09/21/2021.

Safety Labeling Change

On 08/23/2021, the FDA issued Safety Labeling Change (SLC) notifications to the holders of the applications for the JAK inhibitors tofacitinib, baricitinib, and upadacitinib. The SLC notifications require holders of approved drug and biological product applications to make safety labeling changes based upon new safety information that FDA becomes aware of after approval of the drug or biological product. The new safety information pertained to the high risks of death and sudden death, malignancy, and cardiovascular disorders from assessment of a postmarketing safety trial. The FDA determined that JAK inhibitors represent a class of products that have the potential for the same serious risks of death and sudden death, malignancy, and cardiovascular disorders. The SLC notifications advised that the new safety information should be included in the product labels.

Drug Safety Communication

The FDA issued a Drug Safety Communication (DSC) on 09/01/2021 to alert the public that the final results from the safety trial in subjects with rheumatoid arthritis (trial referenced above) showed "an increased risk of serious heart-related events such as

heart attack or stroke, cancer, blood clots, and death" in subjects treated with tofacitinib compared with TNF blockers. Additionally, subjects treated with tofacitinib showed an increased risk of blood clots. (Note: The FDA previously communicated information relating to this safety trial to the public in 02/2019, 07/2019, and on 02/04/2021).

The DSC also advised that the FDA would require new and updated warnings for baricitinib and upadacitinib, two other JAK inhibitors indicated for treatment of arthritis. However, two other JAK inhibitors, fedratinib and oral ruxolitinib, would not be included in the requirement for labeling updates, as those two medications are not indicated for the treatment of arthritis and other inflammatory conditions. Fedratinib and oral ruxolitinib required different updates to their prescribing information.

The safety information relating to the SLC notifications and DSC has implications for labeling for ruxolitinib 1.5% cream, as it is a JAK inhibitor.

Trade name

The Office of Prescription Drug Promotion (OPDP) determined "Opzelura" to be an acceptable proprietary name for ruxolitinib 1.5% cream.

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

4.1. Office of Scientific Investigations (OSI)

Four clinical sites from the pivotal Phase 3 trials, INCB 18424-303 and INCB 18424-304, underwent OSI audit:

- Dr. Robert Call: INCB 18424-304; site 416,
- Dr. Joseph Lillo: INCB 18424-303; site 327
- Dr. Amit Patel: INCB 18424-303; site 301) and
- Dr. Julie Shepard participated in both Phase 3 trials:

- site 206 in study INCB 18424-303
- site 435 in study INCB 18424-304 and

All sites were selected because of high enrollment and high efficacy. Dr Shepard's site had the additional basis for inspection of the investigator's participation in both pivotal trials.

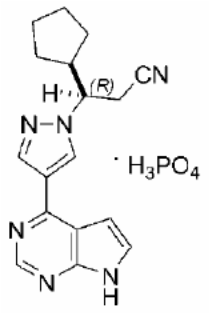
From the Clinical Inspection Summary, the findings from the inspections were not considered likely to have a significant impact on overall trial safety or efficacy results. Inspection findings included unreported protocol deviations, unreported concomitant medications, and unreported adverse events (AEs). Examples of unreported AEs include a "cold," umbilical hernia, low hemoglobin, and sciata pain. Although the AEs should have been reported, the OSI concluded that they were "unlikely to significantly affect overall reliability of safety and efficacy data or change proposed labeling," and this reviewer agrees with that assessment. The OSI concluded that the pivotal studies "appear to have been adequately conducted and the study data generated appear acceptable in support of the respective indication in the NDA."

4.2. Product Quality

1) Drug Substance

The active ingredient, ruxolitinib phosphate is a synthetic small molecule Janus kinase inhibitor with selectivity for JAK1 and JAK2 isoform. Ruxolitinib phosphate was first approved as the active ingredient of JAKAFI tablets under NDA 202192 on November 16, 2011.

Ruxolitinib phosphate is a non-hygroscopic white to off-white to light pink powder with a melting point of 197.6ºC and pKa values of 4.3 and 11.8. The solubility of this API has been evaluated from pH of 1 to 8 and the results indicate that its solubility increased at lower pH. Due to high solubility and high permeability, ruxolitinib phosphate has been classified as a BCS class 1 drug substance. Ruxolitinib phosphate has the chemical name, (R)-3-(4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-cyclopentylpropanenitrile phosphate, a molecular formula of C17H21N6O4P (C17H18N6 as free base), a molecular mass of 404.36 g/mole (306.37 g/mole as free base), and the molecular structure below:



Ruxolitinib phosphate for this application is manufactured in accordance with the current good manufacturing practices (cGMP) requirements by (b) (6) It is tested and release against a specification that assures the identity, strength, purity, and quality of the drug substance at release and throughout its assigned retest date of (b) (4) months when stored at USP controlled (b) (4). The manufacturing details and supporting stability data for this API has been referenced to NDA 202192 which has been reviewed and found to be adequate.

2) Drug Product

The drug product, OPZELURA (ruxolitinib) Cream, 1.5% is a non-sterile white to off-white, oil-in-water, solubilized emulsion containing 19.8mg ruxolitinib phosphate equivalent 15mg of ruxolitinib per gram of cream. It will be packaged and marketed as 60g cream in aluminum tube. This drug product is indicated for the topical treatment of atopic dermatitis in patients 12 years of age and older. OPZELURA is intended for topical administration as a thin layer to the affected skin areas for up to 20% of body surface area, twice daily.

OPZELURA also contains cetyl alcohol, dimethicone 350, edetate disodium, glyceryl stearate SE, light mineral oil, medium chain triglycerides, methylparaben, phenoxyethanol, polyethylene glycol 200, polysorbate 20, propylene glycol, propylparaben, stearyl alcohol, purified water, white petrolatum, and xanthan gum as inactive ingredients. All inactive ingredients used in the composition of OPZELURA

are compendial materials with the exception of glyceryl stearate SE. All compendial material are tested, released, and accepted in accordance to compendial procedures and requirement. The applicant has provided specification and justification for the use of the non-compendial glyceryl stearate SE which is also tested according to the compendial methods. The composition of the drug product has been reviewed and evaluated from the CMC and Pharm/Tox perspectives and has been found to be adequate.

OPZELURA cream is manufactured by (b) (4) in accordance with the cGMP requirements. It is tested and released against a drug product specification that assures the identity, strength, purity, and quality of the drug product at release and throughout its proposed expiration dating period of 24 months. The proposed expiration dating period of 24 months is supported by the stability data submitted in the application and is granted.

3) OPQ Recommendation:

- The applicant of this 505(b)(1) new drug application has provided sufficient CMC information to assure the identity, purity, strength, and quality of the drug substance, ruxolitinib phosphate and the drug product, OPZERULA® (ruxolitinib) Cream, 1.5%.
- Labels/labeling issues have been satisfactorily addressed.
- The Office Pharmaceutical Manufacturing Assessment has made an overall "Adequate" recommendation regarding the facilities involved in this NDA.
- The claim for categorical exclusion from the preparation of environmental assessment has been granted.

Therefore, from the OPQ perspective, this NDA is recommended for APPROVAL with expiration dating period of 24 months.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Ruxolitinib is a small molecule Janus Kinase (JAK) inhibitor. JAKs mediate the signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function. JAKAFI® (ruxolitinib) oral tablets have been approved under NDA 202192, with the maximum recommended human dose of 25 mg BID. In mouse models of dermatitis, topical administration of ruxolitinib cream significantly decreased expression of inflammatory cytokines in the skin, reduced dermatitis symptoms, and alleviated pruritic behaviors.

Pivotal repeat-dose toxicity studies were conducted in rats (oral), dogs (oral), and minipigs (dermal). The major safety signals identified in these studies are consistent with ruxolitinib's pharmacological activity. The target organs were identified as lymphoid organs, with noted toxicities including reduced circulating WBCs and lymphocytes and lymphoid depletion in lymph nodes, spleen and GALT. Such findings showed reversibility after a treatment-free recovery period. In oral dog studies, bacterial infection and demodicosis were also noted, likely secondary effects due to impaired immune function. The decrease in WBC and lymphocyte count noted in a chronic dermal toxicology study in minipigs was not considered significantly adverse as it was reversible after a recovery period and not associated with histopathological changes in lymphoid organs. In this minipig study the systemic NOAEL was identified as the high dose, 1.5% ruxolitinib cream BID, while the dermal NOAEL was identified as the mid dose, 1.0% cream BID, based on skin lesions noted at high dose.

Ruxolitinib was not genotoxic in a complete battery of genotoxicity tests. Ruxolitinib was not carcinogenic in a 6-month oral Tg.rasH2 transgenic mouse study, a 2-year oral rat carcinogenicity study, or a 2-year dermal mouse carcinogenicity study.

In a fertility study, ruxolitinib had no effect on fertility or reproductive function in male or female rats at doses up to 60 mg/kg/day. However, in female rats, doses ≥ 30 mg/kg/day resulted in increased post-implantation loss.

In an embryofetal toxicity study in rats, ruxolitinib was tested up to 60 mg/kg/day and no malformations were noted. Maternal mortality was observed at 60 mg/kg/day. A decrease in fetal weight was observed at 60 mg/kg/day. The NOAEL for both maternal toxicity and embryofetal toxicity was identified as 30 mg/kg/day. In an embryofetal toxicity study in rabbits, ruxolitinib was also tested up to 60 mg/kg/day and no malformations were noted. Maternal mortality was observed at 60 mg/kg/day. An increase in late resorption and a decrease in fetal weight were seen at 60 mg/kg/day. The NOAEL for both maternal toxicity and embryofetal toxicity was also identified as 30 mg/kg/day.

In a pre- and postnatal developmental study in rats, ruxolitinib was tested up to 30 mg/kg/day and there were no treatment-related adverse effects on embryofetal survival, postnatal growth, development parameters or offspring reproductive function. The NOAEL for developmental toxicity was identified as the high dose, 30 mg/kg/day.

In juvenile toxicity studies in rats, oral administration of ruxolitinib resulted in significant bone toxicity. When dosing started at postnatal day 7 (the equivalent of a human newborn) at doses of 1.5 to 75 mg/kg/day, evidence of fractures occurred at doses ≥ 30 mg/kg/day, and effects on body weight and other bone measures (e.g., bone mineral content, peripheral quantitative computed tomography, and x-ray analysis) occurred at doses ≥ 5 mg/kg/day. When dosing started at postnatal day 21 (the equivalent of a human 2-3 years of age) at doses of 5 to 60 mg/kg/day, effects on body weight and bone occurred at doses ≥ 15 mg/kg/day, which were considered adverse at 60 mg/kg/day. Males were more severely affected than females in all age groups, and effects were generally more severe when administration was initiated earlier in the postnatal period. The study results elicited a safety concern for the use of ruxolitinib in pediatric subjects. However, the nonclinical data support the proposed patient population (12 years of age and older) in this application as the ages of animals at the initiation of pivotal repeat-dose toxicology studies are generally equivalent to the human adolescent phase.

Ruxolitinib cream 1.5% was slightly irritating to rabbit skin and mildly irritating to rabbit eye. Ruxolitinib did not show skin sensitization potential in a murine local lymph node assay. Ruxolitinib cream 1.5% did not elicit a primary irritation or phototoxicity response in guinea pigs.

This NDA is approvable from a pharmacology/toxicology perspective. There is no recommended nonclinical PMC/PMR for this NDA.

5.2. Referenced NDAs, BLAs, DMFs

For pivotal nonclinical data that have been reviewed under IND 77101/NDA 202192, summary pharmacology/toxicology information is provided in this review. In nonclinical studies INCB018424 was used as a code name for OPZELURA (ruxolitinib).

5.3. Pharmacology

Primary pharmacology

Ruxolitinib, a small molecule kinase inhibitor, inhibits Janus Kinases (JAKs) JAK1 and JAK2 which mediate the signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function. JAK signaling involves recruitment of STATs (signal transducers and activators of transcription) to cytokine receptors, activation and subsequent localization of STATs to the nucleus leading to modulation of gene expression.

Literature shows that the pathology of atopic dermatitis has been linked to the activation of the JAK-STAT pathway. Multiple cytokines present during skin inflammation signal through class I/II cytokine receptors that lack intrinsic kinase activity and rely on the JAK-STAT pathway for signal transduction. Inhibition of JAK/STAT signaling, by targeting multiple cytokine pathways, has the potential to simultaneously reduce inflammation, cellular activation, and proliferation of key immune cells.

The potency of enzyme inhibition of ruxolitinib against human JAK family is demonstrated by mean IC_{50} values: 3.3, 2.8, 428, and 19 nM for JAK1, JAK2, JAK3, and TYK2, respectively. In vitro assays showed that in human T cells and peripheral blood mononuclear cells, ruxolitinib inhibited the signaling of multiple inflammatory cytokines (e.g., IL-6, IL-12, and IL-23) at concentrations ≤ 100 nM. Ruxolitinib inhibits IL-2 induced T cell proliferation as well as cytokine-induced production of inflammatory factors such as IL-17, IL-22 and MCP-1 with IC_{50} values in the range of 30-100 nM. In keratinocytes, ruxolitinib inhibited the IFN-γ–induced upregulation of various chemokines (RANTES, IP-10, MCP-1, and MIG) as well as expression of the adhesion molecule, ICAM-1, with IC_{50} values in the range of 43-110 nM. Ruxolitinib inhibited IL-6 stimulated STAT3 phosphorylation in whole blood from dogs (IC_{50} = 119 nM), rats (IC_{50} = 95 nM) and rabbits (IC_{50} = 600 nM), confirming the pharmacological activity of ruxolitinib in these species used in toxicology studies.

In vivo pharmacology studies showed that ruxolitinib 1.5% topical cream was efficacious (decreased ear swelling, downregulated inflammatory pathways, and ameliorated pruritus-induced behaviors and skin histopathology) in a thymic stromal lymphopoietin (TSLP)-induced acute dermatitis mouse model, a fluorescein isothiocyanate (FITC)-induced chronic dermatitis mouse model, and a spontaneous IL-33 transgenic mouse dermatitis model.

Secondary Pharmacology

Ruxolitinib was evaluated in a non-GLP Cerep ExpresSProfile screen at 0.1 and 1 µM. There was no significant (>50%) cross reactivity against any of the in vitro binding assays or enzyme assays contained in the screen. Ruxolitinib was also evaluated in a non-GLP Cerep Kinase Assay screen at 0.2 µM. There was no significant (>50%) cross reactivity against any of the in vitro kinase assays tested in this panel outside the JAK family. The study results did not indicate significant risk of unintended pharmacological activity of ruxolitinib due to binding to non-specific receptors/enzymes.

Safety Pharmacology

Neurological effects:

The neurologic effects of ruxolitinib were evaluated in an oral rat GLP study using a Functional Observation Battery (FOB) and locomotor activity measurements. Single oral (gavage) doses of 0, 15, 50 and 150 mg/kg ruxolitinib were administered to SD rats (10/sex/group). FOB (sensorimotor, neuromuscular and physiological observations)

and locomotor activity were recorded for all animals prior to dose administration and 30 minutes postdose. No treatment-related mortality was noted in this study. No treatment-related effects on FOB or locomotor activity were noted in low dose animals and mid dose females. A significant lower body temperature was noted in high dose females (35.1°C) compared to control females (37.1°C) at 30 minutes postdose. Total and ambulatory activity counts during the first 15 minutes of the 1 hour session were significantly reduced in mid dose males and high dose animals. The NOAEL for neurologic effects was identified as 15 mg/kg for males and 50 mg/kg for females.

Respiratory effects:

The respiratory effects of ruxolitinib were evaluated in an oral rat GLP study using head-out neck-sealed plethysmography chambers. Single oral (gavage) doses of 0, 15, 50 and 150 mg/kg ruxolitinib were administered to SD rats (8/sex/group). Respiratory parameters evaluated included respiratory rate, tidal volume and derived minute volume. Data was collected from 60 minutes predose and continuously for 4 hours postdose. No treatment-related effects on mortality or clinical signs were noted. A significant decrease in respiratory frequency was noted at high dose. This effect lasted for up to 3 hours postdose with a maximum decrease of 21-23%. A significant increase in tidal volume was noted in mid dose males and high dose animals. This effect lasted for up to 4 hours postdose with a maximum increase of 18-34%. The higher tidal volume noted in high dose animals may reflect a compensatory response to the lower respiratory rate. A significant decrease in minute volume was noted in high dose females (up to 17% noted from 0.75 to 1.75 hours postdose). The NOAEL for respiratory effects was identified as 15 mg/kg for males and 50 mg/kg for females.

Cardiovascular effects:

The cardiovascular effects of ruxolitinib were evaluated in a GLP in vitro hERG assay and in a GLP in vivo cardiovascular safety pharmacology study in Beagle dogs.

Ruxolitinib (10, 100 and 300 µM) was tested for hERG-channel inhibition in embryonic kidney cells (HEK293). Ruxolitinib inhibited hERG current by 3.8% at 10 µM, 40.3% at 100 µM and 74.1% at 300 µM. The IC_{50} was 131.6 µM, under the study conditions.

Single oral doses of 0, 3, 10 and 30 mg/kg ruxolitinib were administered to adult male conscious radiotelemetry-implanted Beagle dogs. A 3-4-day washout period was incorporated between each dose. Heart rate, arterial blood pressure (systolic, diastolic), body temperature and ECG were collected every 10 minutes for 24 hours postdose. No treatment-related effects on mortality were noted. Emesis was noted at high dose. A significantly lower pulse pressure as well as systolic, diastolic and calculated mean pressure (up to 53%, 41%, 31% and 33%, respectively) was noted at high dose compared to control. These changes peaked at 2-3 hours postdose after which mean arterial blood pressure began to recover. However, lower values for arterial blood pressure were still noted 24 hours postdose at high dose.

A significant increase in heart rate (up to 117% during hour 2) that lasted up to 10 hours postdose was noted at high dose compared to control. The observed increase in heart rate may reflect a compensatory response to the decreases in arterial blood pressure. A slight decrease in body temperature was noted at 3 and 4 hours (-0.24°C and -0.22°C, respectively) in high dose animals.

A significant shortening of PR interval for up to 6 hours postdose (up to -21%) was noted at high dose. A significant shortening of the RR interval for up to 6 hours postdose (up to -54% during hour 2) was noted at high dose. These changes might be due to the increases in heart rate. A slight prolongation of the heart-rate corrected QT interval (QTc) was noted between hours 11 – 14 (5%) and 19 – 24 (3%) in high dose animals. A slight lengthening of the QRS complex for up to 18 hours postdose (up to 9%) was noted in high dose animals.

The NOAEL for cardiovascular effects noted in dogs was identified as 10 mg/kg, under the conditions of this study.

5.4. ADME/PK

Summary of PK/TK data for ruxolitinib:

Type of Study	**Major Findings**
Absorption	
The systemic exposure and skin tissue distribution of ruxolitinib following oral or topical administration in minipigs (Study# DMB-20.57)	Oral, 40 mg/kg BID / Topical, 1.5% cream BID C_{max}: 153 nM / 4 nM T_{max}: 3.3 hr / 3.5 hr AUC_{0-12}: 1060 nM•hr / 35 nM•hr (Measured at 96 hr postdose; topical cream 4.5 mg/cm^2 applied to 10% BSA)
Distribution	
Dermal distribution of [^{14}C]-INCB018424 following topical administration to a Gottingen minipig (Study# DMB-07.136)	After 4 daily dermal doses of 1% [^{14}C]-ruxolitinib cream administered to a minipig, distribution of radioactivity in skin was generally limited to the upper layers of the skin. The highest concentration was associated with the pigmented layer in the epidermis. Levels in the dermis (below the pigmented layer) and hypodermis were below the limit of quantitation.
Quantitative whole-body autoradiography of rats following oral administration of [^{14}C]-INCB018424 (Study# 7456-241)	After a single oral dose of 25 mg/kg [^{14}C]-INCB018424 administered to LE rats, radioactivity was mainly observed in the liver, bile, large intestine, small intestine, uveal tract, adrenal gland, renal cortex and renal medulla. Elimination was rapid; most tissue concentrations were below the limit of quantitation at 24 hours postdose and no radioactivity was detected by 336 hours postdose.
In vitro protein binding of ruxolitinib in mouse, rat, rabbit, dog, minipig, monkey, and human plasma/serum (Study# DMB 08.158, 18.191, 09.61, 09.62 and 07.11)	The mean in vitro fraction unbound ruxolitinib (concentration range 0.39-19.5 µM) was 5.2%, 3.1%, 4.5%, 14%, 12%, 12%, 26%, 5.6%, and 3.3% for wild-type TgRasH2 mouse, CD-1 mouse, hairless mouse, rat, rabbit, dog, minipig, monkey, and human, respectively.

Type of Study	Major Findings
Metabolism	
Identification of in vivo metabolites of INCB018424 (Study# DMB-06.178) Toxicokinetics of INCB018424 metabolites from oral studies with INCB018424 in Tg.rasH2 mice, Sprague-Dawley rats and Beagle dogs (Study# DMB-10.54)	The in vivo metabolic profile of ruxolitinib was investigated in rats and minipigs. Ruxolitinib underwent extensive metabolism with the major metabolites derived from mono, di-oxidation, sulfation and glucuronidation. In general, the metabolite profiles and excretion patterns in humans were similar to those observed in nonclinical species. The toxicokinetics of eight metabolites previously observed in human plasma after oral dosing were evaluated in plasma from mice, rats and dogs administered at NOAEL oral doses. The results showed that human metabolites were adequately assessed in the toxicology studies conducted in mice, rats, and dogs.
Excretion	
INCB018424: Material balance and metabolism in male rats (Study# DMB-08.61); Excretion/mass balance in female rats and pharmacokinetics of radioactivity in male and female rats following a single oral dose of [^{14}C]INCB018424 (Study# DMB-09.82) Excretion/mass balance in male and female beagle dogs after a single oral administration of of [^{14}C]INCB018424 (Study# DMB-08.62) Placental transfer and lacteal excretion of [^{14}C]INCB018424 following administration of a single oral dose to pregnant Sprague Dawley rats (Study# DMB-10.50)	Following a single oral dose of 50 mg/kg [^{14}C]ruxolitinib in male SD rats, the extent of elimination was 52%, 37%, and 12% of the administered dose in urine, bile, and feces, respectively. Following a single oral dose of 25 mg/kg [^{14}C]ruxolitinib in female SD rats, the excretion profile was similar (45%, 40% and 20% recovered in urine, bile and feces, respectively). In both male and female rats, the excretion was rapid, with approximately 100% of the dose recovered by 24 h postdose. Following a single oral dose of 3 mg/kg [^{14}C]ruxolitinib in beagle dogs, 55% and 58% of the administered doses were recovered from feces and 34% and 36% were recovered from urine for males and females, respectively. By 24 hr postdose most of the dosed radioactivity was excreted (82% in males and 80% in females). Following a single oral dose of 30 mg/kg [^{14}C]ruxolitinib in lactating female SD rats at postnatal Day 10, milk, blood, and plasma were collected for up to 24 hours. The $AUC_{0-\infty}$ values in blood, plasma, and milk were 10475, 10798, and 145166 ng equivalents [^{14}C]ruxolitinib·hour/g, respectively. The elimination half-lives of radioactivity in blood, plasma, and milk were similar (2.22, 2.19, and 2.93 hours, respectively). Mean milk:plasma concentration ratios of radioactivity were greater than one at all measurable sampling times ranging from 4.02 at 1 hour postdose to 24.8 at 8 hours postdose. After reaching peak concentration at 2 hours postdose, concentrations of radioactivity in milk declined in parallel with plasma concentrations with no accumulation of radioactivity in the maternal milk.
TK data from general toxicology studies A 6-month oral (gavage) toxicity study of INCB018424 in rats with a 6-week recovery period (Study# (b) (4)-519048)	<u>Rat (oral daily dosing for 6 months)</u> $T_{1/2}$: 0.36-1.94 hours AUC_{0-t} (µM•hr) at Day 181: 5 mg/kg/day: 0.0533 (M), 0.361 (F) 15 mg/kg/day: 0.296 (M), 2.33 (F) 30 mg/kg/day: 0.662 (M), 7.4 (F)

Type of Study	Major Findings
	60 mg/kg/day: 1.32 (M), 25.8 (F) Accumulation: 1.2-6.5 fold in males and 1.8-3.2 fold in females comparing AUC at Day 181 to Day 1 Dose proportionality: The AUC increase was roughly dose proportional in males but higher than dose proportional in females
52-Week oral gavage chronic toxicity and toxicokinetic study with INCB018424 in dogs with a 6-week recovery period (Study# 7456-271)	<u>Dog (oral daily dosing for 52 weeks)</u> $T_{1/2}$: 0.98-3.21 hours AUC_{0-24h} (μM•hr) at Day 357: 0.75 mg/kg/day: 1.21 (M), 0.69 (F) 1.5 mg/kg/day: 2.36 (M), 2.57 (F) 3 mg/kg/day: 6.23 (M), 4.83 (F) 6 mg/kg/day: 16.8 (M), 17.1 (F) Accumulation: ~2 fold for all doses in males and the high dose in females, when comparing AUC at Day 357 to Day 1 Dose proportionality: The AUC increase was slightly higher than dose proportional
INCB018424: A nine-month dermal toxicity study in Göttingen minipigs with a six-week recovery period (Study# HCB00123)	<u>Minipig (dermal QD or BID dosing for 9 months)</u> AUC_{0-24h} (nM•hr) at Day 293: 1.0% QD: 68 (M), 90 (F) 1.0% BID: 147 (M), 145 (F) 1.5% BID: 167 (M), 219 (F) Accumulation: 17-24 fold in males and 18-40 fold in females, when comparing AUC at Day 293 to Day 1 Dose proportionality: The AUC increase was roughly dose proportional
TK data from reproductive toxicology studies	
Oral administration of INCB018424 via gavage: dose range study for effects on embryofetal development in Sprague Dawley rats (Study# 1603-07594)	<u>Maternal Rat (oral daily dosing during gestation days 7-20)</u> AUC_{0-24h} (μM•hr) at gestation day 13: 15 mg/kg/day: 0.75 30 mg/kg/day: 2.98 60 mg/kg/day: 19.0 120 mg/kg/day: 57.6
Oral administration of INCB018424 via gavage: definitive study for effects on embryofetal development in New Zealand White rabbits (Study# 1603-07597)	<u>Maternal Rabbit (oral daily dosing during gestation days 8-21)</u> AUC_{0-24h} (μM•hr) at gestation day 21: 30 mg/kg/day: 0.068 60 mg/kg/day: 0.606
Oral gavage study for effects on pre- and post-natal development, including maternal function with INCB018424 in rats (Study# 8221566)	<u>Maternal Rat (oral daily dosing from gestation day 6 to lactation day 20)</u> AUC_{0-24h} (μM•hr) at lactation day 10: 5 mg/kg/day: 0.14 15 mg/kg/day: 0.93 30 mg/kg/day: 2.68
TK data from carcinogenicity studies	

Type of Study	Major Findings
INCB018424: A 104-week oral (gavage) carcinogenicity study in rats (Study# (b) (4)-519075) INCB018424: A 104-Week Dermal Carcinogenicity Study in CD-1 Mice (Study# (b) (4) 519093)	Rat (oral daily dosing for 2 years) AUC_{0-24h} (µM•hr) at Day 366: 60 mg/kg/day: 2.99 (M), 23.7 (F) Mouse (dermal daily dosing for 2 years) AUC_{0-24hr} (µM•hr) at Day 188: 1.5% cream (~45 mg/kg/day): 2.37 (M), 2.70 (F)
TK data from juvenile toxicology studies INC424: An oral gavage toxicity study with a 12-week recovery period in the juvenile Sprague-Dawley rat (Study# 6700273)	Juvenile rat (oral daily dosing during postpartum days 7-63) AUC_{0-24h} (ng•hr/ml) at postpartum day 7: 1.5 mg/kg/day: 171 (M), 158 (F) 5 mg/kg/day: 811 (M), 785 (F) 15 mg/kg/day: 2502 (M), 3010 (F) AUC_{0-24h} (ng•hr/ml) at postpartum day 63: 1.5 mg/kg/day: Not reported (M), 45 (F) 5 mg/kg/day: Not reported (M), 136 (F) 15 mg/kg/day: 187 (M), 483 (F) Juvenile rat (oral daily dosing during postpartum days 21-63) AUC_{0-24h} (ng•hr/ml) at postpartum day 21: 5 mg/kg/day: 373 (M), 276 (F) 15 mg/kg/day: 1340 (M), 1140 (F) 60 mg/kg/day: 10000 (M), 7960 (F) AUC_{0-24h} (ng•hr/ml) at postpartum day 63: 5 mg/kg/day: 36 (M), 151 (F) 15 mg/kg/day: 133 (M), 697 (F) 60 mg/kg/day: 237 (M), 8360 (F)

5.5. Toxicology

5.5.1. General Toxicology

Study 1 A 6-month oral (gavage) toxicity study of INCB018424 in rats with a 6-week recovery period (Study# (b) (4) 519048, GLP)

Oral (gavage) doses of 0 (vehicle: 0.5% methylcellulose), 5, 10, 30 and 60 mg/kg/day ruxolitinib were administered to SD rats (15/sex/group) for 6 months, followed by a 6-week recovery period (8/sex/group). There were no test article-related deaths, ophthalmic findings or alterations in coagulation or urinalysis parameters. Lower body weights were noted in a dose-related manner for treated males (1.8%, 4.4%, 6.0% and 11.7% lower than control for the 5, 15, 30 and 60 mg/kg/day group males at the end of dosing period). The mean body weight for the 60 mg/kg/day males did not fully recover by the end of the recovery period. Reduced levels of circulating WBCs and lymphocytes were noted at all dose levels along with lower spleen weights in both sexes. Lymphoid depletion was documented in most spleen sections and in several mandibular lymph nodes at 60 mg/kg/day. Adrenal atrophy observed in histopathology at 60 mg/kg/day correlated with reduced weight of adrenal glands. Clinical and anatomical pathology findings at the recovery necropsy indicated that partial to full recovery was in progress in both genders at all dose levels. Considering that the

hematological changes noted at 5, 15 and 30 mg/kg/day were not associated with histopathological changes and reversibility was shown, such findings are not considered significantly adverse. The NOAEL was identified as 30 mg/kg/day. See the table in Section 5.4 for TK information.

Study 2 52-Week oral gavage chronic toxicity and toxicokinetic study with INCB018424 in dogs with a 6-week recovery period (Study# 7456-271, GLP)

Oral (gavage) doses of 0 (vehicle: 0.5% methylcellulose), 0.75, 1.5, 3 and 6 mg/kg/day ruxolitinib were administered to Beagle dogs (5/sex/group) for 52 weeks, followed by a 6-week recovery period (2/sex/group). Unscheduled deaths (1 female, 3 males) were noted at 6 mg/kg/day, due to opportunistic development of generalized demodicosis (likely the result of immunosuppression). There were no significant treatment-related effects on body weight, ECG, ophthalmology, clinical chemistry, or urinalysis parameters. Decreases in mean absolute lymphocyte count and eosinophil count were noted mainly at 6 mg/kg/day. Histopathology changes included decreases of lymphocytes in the gut-associated lymphoid tissue (GALT) of ileum, in the cortex of mandibular and mesenteric lymph nodes, and in the white pulp of spleen (noted at 3 and 6 mg/kg/day). Pyogranulomatous inflammation of the skin/subcutis and footpad affected most of the animals given 6 mg/kg/day and many of those given 3 mg/kg/day. Microscopically, pyogranulomatous inflammation was associated with mites within hair follicles consistent with demodicosis. Partial recovery was noted at the end of the recovery period. The development of generalized demodicosis was considered adverse at doses ≥ 3 mg/kg/day. The NOAEL was identified as 1.5 mg/kg/day, under the study conditions. See the table in Section 5.4 for TK information.

Study 3 INCB018424: A nine-month dermal toxicity study in Göttingen minipigs with a six-week recovery period (Study# HCB00123, GLP)

Topical doses of 0 (vehicle QD), 0 (vehicle BID), 1% ruxolitinib cream QD, 1% ruxolitinib cream BID, and 1.5% ruxolitinib cream BID (~3.3, 6.6, and 9.9 mg/kg/day ruxolitinib) were administered to Göttingen minipigs (4/sex/dose) for 9 months (applied at 10 mg/cm^2 to 10% BSA), followed by a 6-week recovery period (3/sex/group). There were no early deaths. Test article-related clinical signs were limited to relatively minor findings at the site of topical application. Dosing holidays (10 and 24 days, respectively) were implemented for two high dose males presented with multiple red, circular, raised lesions on the administration site. Treatment-related microscopic findings were noted in the skin, including hyperkeratosis, epidermal hyperplasia, erosions, and ulcerations. Hyperkeratosis and epidermal hyperplasia were also seen in vehicle control animals. Small epidermal erosions and ulcerations were noted in a small number of animals in dose groups (mainly high dose males). Considering that two high dose males were put on dosing holidays due to skin lesions, a dermal NOAEL was identified as the mid dose, 1% cream BID. There were no significant treatment-related effects on body weight, ECG, ophthalmology, clinical chemistry, or urinalysis parameters. A decrease in WBC count (mainly due to the decrease in lymphocyte count) was noted at all doses. This

finding is consistent with the test article's pharmacological activity. Considering that such decrease was reversible after the recovery period and was not associated with any histopathological changes, it is not considered a significantly adverse effect. The systemic NOAEL was identified as the high dose, 1.5% cream BID. See the table in Section 5.4 for TK information.

5.5.2. Genetic Toxicology

Ruxolitinib was tested in a complete battery of genotoxicity assays and no genotoxicity potential was noted. The following genotoxicity information is contained in the JAKAFI® label.

Ruxolitinib was not mutagenic in a bacterial mutagenicity assay (Ames test) or clastogenic in in vitro chromosomal aberration assay (cultured human peripheral blood lymphocytes) or in vivo in a rat bone marrow micronucleus assay.

5.5.3. Carcinogenicity

Three carcinogenicity studies were conducted with ruxolitinib, including a short term (26 weeks) oral carcinogenicity study in Tg.rasH2 mice, a 2-year oral carcinogenicity study in SD rats, and a 2-year dermal carcinogenicity study in CD-1 mice. The two oral carcinogenicity studies have been reviewed under NDA 202192. The dermal carcinogenicity study is reviewed under this NDA.

Study 4 INCB018424: 26-Week repeated dose oral carcinogenicity study in Tg.rasH2 mice (Study# AB22ZU.7G8R(b) (4), GLP)

Oral (gavage) doses of 0 (vehicle: 0.5% methylcellulose), 15, 45, and 125 mg/kg/day ruxolitinib were administered to Tg.rasH2 mice once daily for 26 weeks. Urethane (1000 mg/kg; three IP injection on Week 1) was used as positive control in this study. In main study animals, there were deaths in the low dose (1 M and 1 F) and mid dose (3 M and 4 F) groups but not in the high dose group. No ruxolitinib-related clinical sign was noted. There was a decrease in body weight gain in the high dose animals (11% in male and 15% in female). There were no significant neoplastic findings. For nonneoplastic findings, ruxolitinib increased the incidence/severity of inflammatory lesions of the nasal cavity (i.e., minimal to moderate exudative inflammation).

Study 5 INCB018424: A 104-week oral (gavage) carcinogenicity study in rats (Study#(b) (4)-519075, GLP)

Oral (gavage) doses of 0 (vehicle: 0.5% methylcellulose), 10, 20 and 60 mg/kg/day ruxolitinib were administered to SD rats once daily for 2 years. A dose-dependent increase in mortality was noted in male rats. Female rats experienced higher mortality rates in all groups including controls, but the increase in mortality did not correlate with dose. No particular cause of death appeared related to study drug administration. Ruxolitinib treatment resulted in dose-dependent mean body weight losses and lower mean body weights in the three male dose groups. Lower mean body weight gains

and/or body weight losses were noted in high dose females. There were no significant neoplastic findings. Lymphoid depletion in spleen (mainly seen at the high dose) was noted as a test article-related non-neoplastic finding in this study. See the table in Section 5.4 for TK information.

Study 6 INCB018424: A 104-Week Dermal Carcinogenicity Study in CD-1 Mice (Study# (b) (4)-519093, GLP)

Topical doses of 0 (untreated control), 0 (vehicle control), 0.5%, 1.0%, and 1.5% ruxolitinib cream (applied at 100 µl/dose to ~10% BSA; ~15, 30, and 45 mg/kg/day ruxolitinib) were administered to CD-1 mice once daily for 2 years. There were no significant treatment-related effects on mortality. No significant toxicity was noted in this study. A complete list of tissues was examined histopathologically for all main study animals. There were no biologically significant test article-related neoplastic findings in this study. See the table in Section 5.4 for TK information.

Note: This 2-year dermal mouse carcinogenicity study has been reviewed by the Executive Carcinogenicity Assessment Committee (CAC). The Committee concurred that this study was adequate (noting prior approval of the study protocol) and there were no drug-related neoplasms in this study. See Section 19.3 for the detailed review of the study.

5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

Study 7 Oral gavage study of fertility and early embryonic development to implantation with INCB018424 in rats (Study# 8212204, GLP)

Ruxolitinib was administered via oral gavage to male and female SD rats at 0 (vehicle: 0.5% methylcellulose), 10, 30 and 60 mg/kg/day. All males were dosed for at least 10 weeks and included at least 28 days prior to mating and throughout the mating phase. Females were dosed for at least 14 days prior to mating (premating phase), throughout the mating phase, and through Gestation Day 7 (GD 7). Treated males were paired with treated females during the mating phase. In males, reduction in body weight was observed at doses ≥ 30 mg/kg/day. There were no significant treatment-related effects on male reproductive function (no effects on sperm count, concentration, or motility). There were no significant treatment-related effects on the estrous cycling, mating and fertility indices, or the numbers of corpora lutea or implantation sites. A treatment-related increase in post-implantation loss and decrease in the number of live fetuses were noted at 30 and 60 mg/kg/day. The NOAEL for reproductive function and fertility were identified as the high dose, 60 mg/kg/day, in both males and females. The NOAEL for embryofetal viability was 10 mg/kg/day. TK evaluation was not conducted in this study. The applicant used TK data from a GLP dose-ranging embryofetal toxicity study in SD rats (Study# 1603-07594) for safety margin calculation. See the table in Section 5.4 for TK information.

Embryofetal Development

Study 8 Oral administration of INCB018424 via gavage: definitive study for effects on embryofetal development in Sprague Dawley rats (Study# 1603-07595, GLP)

Ruxolitinib was administered via oral gavage to pregnant female SD rats at 0 (vehicle: 0.5% methylcellulose), 15, 30 and 60 mg/kg/day during GDs 7-20. Maternal mortality was observed at 60 mg/kg/day. A significant decrease in fetal weight (up to 9%) was observed at 60 mg/kg/day. No malformations were noted in this study. The NOAEL for both maternal toxicity and embryofetal toxicity was identified as 30 mg/kg/day. TK evaluation was not conducted in this study. The applicant used TK data from the dose-ranging study (Study# 1603-07594) for safety margin calculation. See the table in Section 5.4 for TK information.

Study 9 Oral administration of INCB018424 via gavage: definitive study for effects on embryofetal development in New Zealand White rabbits (Study# 1603-07597, GLP)

Ruxolitinib was administered via oral gavage to pregnant female NZW rabbits at 0 (vehicle: 0.5% methylcellulose), 10, 30 and 60 mg/kg/day during GDs 8-21. Maternal mortality was observed at 60 mg/kg/day. An increase in late resorption and a decrease in fetal weight (~8%) were seen at 60 mg/kg/day. No malformations were noted in this study. The NOAEL for both maternal toxicity and embryofetal toxicity were identified as 30 mg/kg/day. See the table in Section 5.4 for TK information.

Prenatal and Postnatal Development

Study 10 Oral gavage study for effects on pre- and post-natal development, including maternal function with INCB018424 in rats (Study# 8221566, GLP)

Ruxolitinib was administered via oral gavage to F0 female SD rats at 0 (vehicle: 0.5% methylcellulose), 5, 15 and 30 mg/kg/day from GD 6 through lactation day (LD) 20. The pregnant and lactating F0 females as well as their offspring (F1) and the subsequent generation (F2) were evaluated for potential effects. A slightly prolonged gestation period, reduced number of implantation sites, and reduced number of pups delivered were observed in the high dose F0 females. Reduced body weights were observed in the F1 pups at the high maternal dose. This effect seemed to be due to reduced initial weights on LD 0 and a short period of decreased mean body weight gain. Overall, there were no significantly adverse findings in embryofetal survival, postnatal growth, development parameters or offspring reproductive function. The NOAEL for developmental toxicity was identified as the high dose, 30 mg/kg/day. See the table in Section 5.4 for TK information.

5.5.5. Other Toxicology Studies

Juvenile Animal Toxicity

Study 11 INC424: An oral gavage toxicity study with a 12-week recovery period in the juvenile Sprague-Dawley rat (Study# 6700273, GLP)

Bone toxicity of ruxolitinib was identified in a preliminary non-GLP juvenile rat toxicity study (Study# 6700272). In that study, oral (gavage) doses of 0, 5, 15, 30, 50, and 75 mg/kg/day ruxolitinib were administered to juvenile SD rats during postpartum Days 7-41. Mortality/moribundity was noted at doses ≥ 30 mg/kg/day. The death of most of these animals was treatment-related based on radiography and macroscopic evidence of bone fractures and/or on microscopic bone findings (fracture, callus, and physeal degeneration/necrosis). A dose-related decrease in mean body weight gain was noted at doses ≥ 30 mg/kg/day.

This definitive study was designed to further evaluate the juvenile toxicity of ruxolitinib, especially its effects on bone development in juvenile rats. Oral (gavage) doses of 0 (vehicle: 0.5% methylcellulose), 1.5, 5, 15, 30, 60 mg/kg/day ruxolitinib were administered to juvenile SD rats (for Groups 1-10, 12/sex/group for main study and 12/sex/group for 12-week recovery) with the following design: 0, 1.5, 5, and 15 mg/kg/day administered during postpartum Days 7-63 (Groups 1-4); 0 and 15 mg/kg/day administered during postpartum Days 14-63 (Groups 5 and 6); 0, 5, 15, and 60 mg/kg/day administered during postpartum Days 21-63 (Groups 7-10, with additional 20/sex/group animals for fertility assessment); and 0 and 30 mg/kg/day administered during postpartum Days 7-10 (Groups 11 and 12, 8/sex/group for main study with no recovery animals). For fertility assessment, animals in Groups 7-10 were mated 4 weeks after the end of the dosing period (~postpartum Day 91).

There were 9 unscheduled deaths: 1 male in Group 2, 1 male in Group 3, 1 male and 1 female in Group 4, 1 male in Group 6, 2 control females in Group 7, 1 recovery male in Group 10, and 1 female in Group 10. It's difficult to determine if some of these early deaths were treatment-related due to low incidence and undetermined cause of death. A decrease in body weight was noted at doses ≥ 15 mg/kg/day. Reductions in food consumption were noted at all doses. Decreases in WBC and lymphocyte count were noted at all doses. There were no significant treatment-related effects on estrous cycle, parenteral performance parameters, or ovarian or uterine parameters.

A marked decrease in PINP (a biomarker of bone formation) was noted at 30 mg/kg/day (the only dose examined). In radiography examination, increased radio-opaque transverse lines (mid diaphysis) were noted in the tibia of males at doses ≥ 5 mg/kg/day and in females at doses ≥ 15 mg/kg/day. Such finding was still noted at doses ≥ 15 mg/kg/day after the recovery period. A reduction in bone (lumbar spine and femur) length was seen at doses ≥ 15 mg/kg/day. Such reduction was still seen at 60 mg/kg/day after the recovery period. Bone densitometry evaluation showed that dose-

dependent reductions in total area and bone mineral content were noted at doses ≥ 5 mg/kg/day and generally persisted after the recovery period.

At the end of treatment, deceases in organ weights were noted in adrenal gland (at doses ≥ 5 mg/kg/day), spleen (at doses ≥ 5 mg/kg/day) and thymus (at doses ≥ 15 mg/kg/day). Generally, no significant changes in organ weights were noted after the recovery period. After 4 days of dosing from PPD 7 to 10 at 30 mg/kg/day, there were histopathology findings in bones from forelimb and hindlimb (degeneration/necrosis of the physis and/or primary spongiosa of various long bones). Recovery was not evaluated. Histopathology findings in main study animals included cortical atrophy in adrenal gland and decreased cellularity in bone marrow and spleen (at doses ≥ 15 mg/kg/day).

Bone toxicity was identified as a major juvenile toxicity in the preliminary juvenile rat study and confirmed in this definitive study. The adverse effects were generally more severe when administration was initiated earlier in the postnatal period. This may be partly due to the TK profile in juvenile rats: systemic exposure to ruxolitinib decreased markedly with the increase of age, which was more evident in males. When taking into consideration all the results of bone evaluation, a NOEL was identified as 1.5 mg/kg/day when dosing started from postpartum Day 7, based on radiography and bone densitometry findings noted at doses ≥ 5 mg/kg/day. The 5 mg/kg/day dose may be considered as the NOAEL, as the bone densitometry findings were less severe compared to the 15 mg/kg/day dose. When dosing started from postpartum Day 21, effects on body weight and bone occurred at doses ≥ 15 mg/kg/day, which were considered adverse at 60 mg/kg/day. See the table in Section 5.4 for TK information.

The juvenile animal toxicity study results elicited a safety concern for the use of ruxolitinib in pediatric subjects. However, the nonclinical data support the proposed patient population (12 years of age and older) in this application as the ages of animals at the initiation of pivotal repeat-dose toxicology studies (7 weeks of age for rats in the 6-month study, 4-5 months of age for dogs in the 12-month study, and 4 months of age for minipigs in the 9-month study) are generally equivalent to the human adolescent phase.

Dermal Irritation

Study 12 Primary dermal irritation/corrosion study with INCB018424 in rabbits (Study# 7456-189)

Topical doses of 0.06 g test articles (vehicle or 0.5%, 1.0% or 1.5% ruxolitinib cream) were applied to an intact skin site and an abraded skin site on the backs of NZW rabbits (3 males/group) for 24 hours under occlusion. Test articles were removed at 24 hr postdose and dermal reactions were evaluated at 1, 24, 48 and 72 hours following removal of test article. The 0.5%, 1.0% and 1.5% ruxolitinib cream and vehicle cream were slightly irritating to intact and abraded skin of rabbits, under the conditions of this study.

Ocular Irritation

Study 13 Primary eye irritation/corrosion study with INCB018424 in rabbits (Study# 7456-190)

Ocular instillation doses of 0.1 ml test articles (vehicle or 0.5%, 1.0% or 1.5% ruxolitinib cream) were applied to the right eye of NZW rabbits (3 males/group) for 24 hours. The left eye was the untreated control for each rabbit. Test articles were gently washed out at 24 hr after instillation. Eye irritation was evaluated at 1, 24, 48 and 72 hours following instillation. The vehicle cream was minimally irritating and the 0.5%, 1.0% and 1.5% ruxolitinib cream formulations were mildly irritating to rabbit eyes, under the conditions of this study.

Dermal Sensitization

Study 14 Murine local lymph node assay with INCB018424 (Study# 7456-194)

Topical doses of 25 µl 0% (vehicle: N,N-dimethylformamide), 0.0625%, 2.5% and 10% (maximum concentration in this vehicle) ruxolitinib formulations were administered to both ears of female CBA/J mice (5/group) once daily for three consecutive days. The mean stimulation indices (SIs) for 0%, 0.625%, 2.5% and 10% ruxolitinib formulations were 1, 0.4, 0.6 and 0.4, respectively. Since the mean SIs were all below the nominal sensitizing criteria of 3.0, ruxolitinib is classified as a non-sensitizer based on the results of this assay.

Phototoxicity

The light absorption spectrum of ruxolitinib from 290 – 700 nm was determined. The spectrum was generated using ruxolitinib as a free base at a concentration of 1 mg/ml in 5 mM KH_2PO_4/K_2HPO_4 buffer in 50% water/50% methanol at a pH of 4.0. An absorption peak was noted at approximately 320 nm. Therefore, a nonclinical phototoxicity study in guinea pigs was conducted to address the concern for phototoxicity.

Study 15 Topical primary irritation and phototoxicity screening test of INCB018424 in male albino hairless guinea pigs (Study# HCB00041)

In the primary irritancy phase of the study, five male albino hairless guinea pigs received a single topical application of 0.5 g 0% (vehicle), 0.5%, 1.0% or 1.5% ruxolitinib cream to four separate skin sites. Formulations were topically administered using Hilltop® chambers for 2 hours. Observations for clinical and dermal signs were performed immediately and at 1, 4, 24, 48 and 72 hours after chamber removal.

In the phototoxicity phase of the study, five male albino hairless guinea pigs received a single topical application of 0.5 g 0% (vehicle), 0.5% or 1.5% ruxolitinib cream to three separate skin sites. Formulations were topically administered using Hilltop® chambers

for 2 hours. Subsequently the test articles were removed, and the treatment sites were exposed to ~2.25 instrumental minimal erythema doses (MED) of solar-simulated ultraviolet radiation (UVR). Observations for clinical and dermal signs were performed immediately and at 1, 4, 24, 48 and 72 hours after UVR exposure.

No treatment-related findings in clinical or dermal signs were noted in either phase of this study. Neither vehicle cream or ruxolitinib cream up to 1.5% elicited a primary irritation or phototoxicity response in guinea pigs, under the conditions of this study.

Potential Impurity Evaluation

In total 23 potential impurities were evaluated in a series of in silico platforms, including: Novartis in silico ToxCheck (v. 3.0), DEREK (v.11.0.0) and MCASE (MC4PC v. 2.0.0.95) to evaluate their genotoxicity potential. The Novartis in silico ToxCheck and DEREK (Deductive Estimation of Risk on Existing Knowledge) systems are rule-based expert systems and the MCASE (Multiple Computer Automated Structure Evaluation) is a statistical-based system. Six compounds (b) (4) were predicted to be mutagenic based on in silico testing and subsequently tested in the Ames test. The test results were all negative.

Four additional impurities related to the starting material (b) (4) were evaluated for potential mutagenicity using Derek Nexus (v. 6.01) and Sarah Nexus (v 3.0.0). Sarah Nexus is a statistical-based methodology for the prediction of mutagenicity. A combined assessment was performed within Nexus Version 2.2.2. All four of these impurities were predicted to be inactive in Derek and negative in Sarah.

Overall, there are no significant safety concerns for the tested potential impurities.

6 Clinical Pharmacology

6.1. Executive Summary

The Applicant is seeking approval of ruxolitinib cream 1.5% (w/w) (OPZELURA®) for a topical treatment of atopic dermatitis (AD) in subjects 12 years of age and older. Ruxolitinib is a Janus kinase (JAK) inhibitor which is known to mediate signal transduction of inflammatory cytokines and is sought to treat several inflammatory indications including psoriasis. The Applicant received an FDA-approval on oral ruxolitinib (JAKAFI®) to treat myelofibrosis, polycythemia vera, and acute graft-versus-host disease in 2011 (NDA 202192).

Under this NDA, the Applicant has submitted data and study reports to support a topical ruxolitinib cream 1.5% to treat subjects with AD. The Applicant conducted a maximal use study (MUsT) to evaluate pharmacokinetics (PK) and safety of twice daily (BID) topical application of ruxolitinib cream 1.5% in subjects 13 years of age and older with ≥25% body surface area (BSA) involvement of AD (Study INCB 18424-103). Results from MUsT showed that plasma concentration of ruxolitinib was measurable in all subjects who received topical application of ruxolitinib cream 1.5%, and systemic exposure of ruxolitinib tended to be higher in subjects with larger %BSA involvement. Phase 3 trials to evaluate ruxolitinib cream 0.75% and 1.5% were conducted in subjects 12 years of age and older with up to 22% BSA involvement with AD. Trough level PK assessment of ruxolitinib in Phase 3 trials indicated that the systemic exposure tends to increase with an increase in %BSA treated and increase in disease severity. The Applicant proposed to limit the BSA to 20% in the proposed label which is reasonable as they have not studied greater % BSA involvement in the Phase 3 trials.

Recommendation

The office of Clinical Pharmacology/Division of Inflammation and Immune Pharmacology finds NDA 215309 acceptable.

PMR recommendation

- Conduct a maximal use pharmacokinetic (PK) study for the ≥2 years to <12 years age group and target at least 16 completers.
- Conduct an open-label safety study in 100 subjects ≥ 3 months to < 24 months with atopic dermatitis with ruxolitinib cream applied twice daily (BID) for 4 weeks with a 48-week extension treatment period and assess PK under maximal use conditions in a subset of at least 16 subjects (Clinical & Clinical Pharmacology)

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Pharmacokinetics of ruxolitinib under maximal use conditions:
Study INCB 18424-103 was an open-label MUsT study to evaluate ruxolitinib 1.5% cream applied to ≥25% BSA in adult subjects and adolescent subjects (≥13 years) with AD. Initial MUsT study plan was to enroll subjects including 12 years of age, but the study did not have any subjects 12 years of age. The lack of 12 year old subjects will not be an issue because of general similarity between a 12 year and 13 year old subject and the fact that there were 14 subjects within the lowest age range of 13 years to 15 years. This should provide adequate assessment of systemic exposure and systemic safety and the findings would be applicable to 12 year old. The adequacy of safety data in the adolescent population from the Phase 3 trials is deferred to clinical. A total of 41 subjects were enrolled including 20 adult subjects and 21 pediatric subjects (13 – 17 years of age, inclusive). Twenty-eight subjects had ≥25% and <40% BSA involvement at baseline and the remaining 13 subjects had ≥40% BSA with a maximum at 90% BSA involvement. Study subjects received BID topical treatment with ruxolitinib 1.5% cream for 28 days on the affected BSA. The area of drug application is considered as maximum BSA for the indication of atopic dermatitis. The mean of total amount of dose applied daily was 20.2 g and ranged from 2.4 g to 75.2 g. The large range of dosing is because dose depends on the body surface area that the drug is applied to.

Plasma levels of ruxolitinib was detectable in all adult and pediatric subjects who received BID application of ruxolitinib cream 1.5% for 28 days. In adult subjects, the mean ± SD C_{max} and AUC_{0-tau} of plasma ruxolitinib on Day 1 were 449 ± 883 nM and 3215 ± 6184 h*nM, respectively. In adolescent subjects (13 – 17 years of age), the mean ± SD C_{max} and AUC_{0-tau} for plasma ruxolitinib on Day 1 were 110 ± 255 nM and 801 ± 2019 h*nM, respectively.

By Day 28, the mean ± SD C_{max} and AUC_{0-tau} of plasma ruxolitinib in adult subjects were 242 ± 548 nM and 1971 ± 4220 h*nM, respectively. The mean ± SD C_{max} and AUC_{0-tau} of plasma ruxolitinib in adolescent subjects were 52 ± 78 nM and 435 ± 721 h*nM, respectively.

The available data suggest that there was no drug accumulation on multiple dosing. The systemic exposure in both adult and adolescent subject decreased through the 28-day treatment, and it is likely that the resolution of the disease could have contributed to the lower systemic exposure of ruxolitinib on Day 28. The decrease of plasma ruxolitinib concentration was more apparent in subject group with ≥40% BSA group compared to the subject group with <40% BSA. Additional analyses by this reviewer showed that systemic exposure of ruxolitinib increases with an increase in %BSA involvement at baseline in both adult and adolescent subjects. Overall, the larger %BSA involvement was associated with the greater amount of drug applied (i.e., active pharmacological ingredient, API) and the greater systemic exposure of ruxolitinib.

Although available data shows that the systemic exposure in adolescent subjects was lower than adults, such conclusions should not be made because the higher exposure in adults was due to the drug applied to higher %BSA involvement compared to adolescent. In clinical practice, AD is more common in pediatric subjects and for similar %BSA treated, the systemic exposure in adults and adolescent subjects is expected to be similar.

Summary of safety in MUsT

No clinically significant adverse event was observed. There was one subject ((b) (6)) with transient decrease of neutrophil count at Day 15, but this event was resolved by Day 28. Subject (b) (6) with 90% BSA and the highest plasma ruxolitinib concentration throughout the treatment period showed the greatest change from the baseline in the blood cell counts and hemoglobin but did not experience any hematological toxicities or safety events. There was no subject that experienced any hematological toxicities or safety events in the study. See Clinical review for further information on safety.

Pharmacokinetics of ruxolitinib in phase 3 trials:

Studies INCB 18424-303 (303) and INCB 18424-304 (304) are two identical, double-blind, randomized studies of subjects with 3% to 22% BSA involvement and an Investigator's global assessment (IGA) score of 2 or 3 at baseline composed of vehicle-controlled (VC) period (Day 1 through Week 8), and long-term safety (LTS) period (Weeks 8 through 52). The Applicant evaluated ruxolitinib cream 0.75% BID and 1.5% BID in both trials. A total number of 951 subjects were in PK assessments (C_{trough} level): 477 and 474 subjects in Studies 303 and 304, respectively.

The pooled PK data from two phase 3 trials showed that the mean ± SD C_{trough} of ruxolitinib 0.75% and 1.5% was 24 ± 35 nM and 36 ± 55 nM, respectively, indicating an increase in plasma ruxolitinib concentration as the formulation strength doubled. Higher C_{trough} level was observed in subjects with baseline IGA score 3 compared to subjects with IGA score 2. Subjects with higher IGA had larger, more extensive lesion area (and %BSA) of AD and potentially more severe lesions with greater skin barrier disruption, and they tended to use more ruxolitinib cream per application compared with subjects with IGA score 2. Thus, the difference in C_{trough} level between the two IGA score groups is not unexpected.

The mean values of C_{trough} were relatively stable across visits during the LTS period. In Study 303, the mean C_{trough} ranged between 13 and 21 nM for ruxolitinib cream 0.75% BID group and 18 to 26 nM ruxolitinib cream 1.5% BID group. The LTS PK data in Study 304 were similar; the mean trough concentrations were within the range of 9 to 19 nM for the treatment group of 0.75% BID and 13 to 28 nM for the treatment group of 1.5% BID.

Summary of safety in phase 3 trials (interim, data cutoff date 06/22/2020)

In both phase 3 trials (303 and 304), there were no deaths and no serious treatment emergent adverse events (TEAEs) were reported. In Study 303, approximately one-

third of subjects in each treatment group had at least 1 TEAE, and 2.4%, 0.8%, and 2.4% of subjects in the vehicle cream, ruxolitinib 0.75% cream, and ruxolitinib 1.5% cream treatment groups, respectively, had at least 1 Grade 3 or higher TEAE. The most frequently reported TEAEs in the active treatment groups during the VC period were nasopharyngitis, upper respiratory tract Infection, and headache.

In Study 304, less than one-third of subjects in each treatment group had at least one TEAE, and 0%, 2.0%, and 1.2% of subjects in the vehicle cream, ruxolitinib 0.75% cream, and ruxolitinib 1.5% cream treatment groups, respectively, had at least one Grade 3 or higher TEAE. The most frequently reported TEAEs in the active treatment groups during the VC period were nasopharyngitis and headache in Study 304. Refer to Section 8.2. Review of Safety for more details.

Metabolism of ruxolitinib:
The Applicant investigated in vitro metabolism of ruxolitinib in Study DMB-07.02 using human recombinant CYP enzymes and in Study DMB-09.93 using human liver microsomes. Study results showed that recombinant enzyme preparations of CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 metabolized ruxolitinib with 86%, 60%, 53%, 82%, and 2% of the initial concentration of ruxolitinib remaining after 30 minutes of incubation (60 minutes for CYP2C9), respectively. In the presence of CYP3A4 inhibitor (i.e., ketoconazole), 74% of the parent remained, whereas other selective CYP inhibitors had minimal effect. The study results suggest that CYP3A4 is the predominant CYP isozyme responsible for the metabolism of ruxolitinib.

There are at least 5 known metabolites of ruxolitinib, but the Applicant did not conduct assessment of metabolites in the MUsT. In response to an information request, the Applicant noted that the plasma concentrations of the ruxolitinib metabolites were low relative to the parent in phase 2b study (INCB 18424-203) supporting their rationale not to assess the metabolite in the maximal use PK study. Although the assessment of systemic exposure of the metabolites would have been desirable under maximal use conditions, the fact that the sponsor plans to limit the %BSA to not more than 20% in the label and the fact that the systemic exposure in MUsT in subjects below the %BSA of 40% was lower than the lowest oral dose of 5 mg; the lack of metabolite PK assessment in MUsT would be considered acceptable.

Drug interaction of ruxolitinib:
Results from in vitro drug-drug interaction (DDI) studies suggest that ruxolitinib cream 1.5% does not inhibit or induce CYP Enzymes and it did not inhibit drug transporters. Hence the effect of ruxolitinib on other drugs due to drug interactions is unlikely.

Since ruxolitinib is a substrate of CYP3A4, this product will be labeled to avoid concomitant use with strong inhibitors of CYP3A4.

Dosing in subjects with renal or hepatic impairment:
Since the %BSA in the approved labeling will be limited to 20% and the systemic exposure in subjects that would use the product as per the approved labeling is

expected to be lower than the lowest oral dose of 5 mg; no specific dosing recommendation is being proposed for subjects with renal or hepatic impairment.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed dosing regimen is to apply a thin layer of ruxolitinib cream 1.5% twice daily to affected areas via topical route to a BSA not more than 20% is reasonable as the maximum %BSA treated in phase 3 trials did not exceed 22%. Based on the mean drug usage data in the phase 3 trials, the Agency recommended that the weekly dosing to be limited to 60 grams (Table 1).

Table 1 Summary of dosing in Phase 3 vehicle-controlled population *(Source: Table 6 of Applicant's report - Section 2.7.4)*

Variable	Vehicle Cream BID (N = 250)	Ruxolitinib Cream Regimen		Total (N = 1249)
		0.75% BID (N = 500)	1.5% BID (N = 499)	
Duration of treatment (days)				
Mean (SD)	51.12 (13.889)	54.48 (11.357)	55.34 (9.816)	54.15 (11.443)
Median	56.00	56.00	56.00	56.00
Min, max	1.0, 76.0	1.0, 151.0	1.0, 100.0	1.0, 151.0
Total weight of medication applied (grams)				
Mean (SD)	252.19 (219.393)	251.69 (201.950)	232.94 (189.809)	244.30 (200.930)
Median	192.63	194.07	172.86	186.30
Min, max	-78.3, 1020.4	-163.3, 998.1	-136.5, 956.5	-163.3, 1020.4
Average weight of medication applied daily (grams)				
Mean (SD)	8.13 (27.379)	7.64 (31.542)	6.83 (22.243)	7.41 (27.296)
Median	3.84	3.60	3.13	3.45
Min, max	-1.1, 293.2	-2.8, 503.9	-2.4, 222.0	-2.8, 503.9

Note: The negative study drug weights were reported in 4 subjects during the vehicle controlled period in Study INCB 18424-303.

Therapeutic Individualization

The applicant did not conduct studies for therapeutic individualization of the proposed ruxolitinib cream 1.5% product and such assessment is not warranted.

Outstanding Issues

None.

6.3 Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Maximal use PK study: Ruxolitinib, a JAK inhibitor, was developed as a topical cream formulation for treatment of atopic dermatitis in subjects 12 years and older. A MUsT study in adult and pediatric subjects (13 -17 years of age) evaluated ruxolitinib cream 1.5% following BID topical application for 4 weeks. Plasma concentration of ruxolitinib was measurable in all subjects in the study.

Day 1: The mean ± SD C_{max} and AUC_{0-tau} of plasma ruxolitinib in overall subjects (N = 40) were 271 ± 650 nM and 1948 ± 4607 h*nM, respectively. The mean ± SD C_{max} and AUC_{0-tau} of plasma ruxolitinib in adult subjects (N = 19) were 449 ± 883 nM and 3215 ± 6184 h*nM, respectively (Table 2). One adult subject ([redacted] (b) (6)) was excluded due to all plasma ruxolitinib levels below quantifiable level (BQL). The mean ± SD C_{max} and AUC_{0-tau} of plasma ruxolitinib in older adolescent subjects (16 – 17 years of age, N = 7) were 102 ± 118 nM and 690 ± 758 h*nM, respectively (Table 2). The mean ± SD C_{max} and AUC_{0-tau} of plasma ruxolitinib in younger adolescent subjects (13 – 15 years of age, N = 14) were 114 ± 305 nM and 856 ± 2448 h*nM, respectively (Table 2). The mean ± SD of total affected %BSA at baseline in all subjects was 38.1 ± 16.3 %. The time to reach peak plasma concentration (T_{max}) in all subjects was 6.9 ± 4.6 hours (mean ± SD).

Day 28: The mean ± SD C_{max} and AUC_{0-tau} of plasma ruxolitinib in overall subjects (N = 38) were 137 ± 377 nM and 1120 ± 2930 h*nM, respectively. The mean ± SD C_{max} and AUC_{0-tau} of plasma ruxolitinib in adult subjects (N = 17) were 242 ± 548 nM and 1971 ± 4220 h*nM, respectively (Table 3). The mean ± SD C_{max} and AUC_{0-tau} of plasma ruxolitinib in older adolescent subjects (16 – 17 years of age, N = 7) were 24.5 ± 12.9 nM and 196 ± 149 h*nM, respectively (Table 3). The mean ± SD C_{max} and AUC_{0-tau} of plasma ruxolitinib in younger adolescent subjects (13 – 15 years of age, N = 14) were 66.2 ± 93.3 nM and 554 ± 863 h*nM, respectively (Table 3). The mean terminal half-life of ruxolitinib was 116 hours based on data available from 9 subjects. It should be noted that there was high variability in the estimation of terminal half-life.

There was no drug accumulation observed. Overall, systemic exposure of ruxolitinib in both adult subjects and adolescent subjects decreased following the 4-week treatment of BID topical application of ruxolitinib cream 1.5% and this may have been due to resolution of skin disease over time. Also, the systemic exposure of adult subjects was higher than adolescent subjects and this was because adults has higher %BSA involvement and used higher dose than adolescent subjects.

Based on the Applicant's BSA stratification, subjects with ≥40% BSA showed 14-fold higher C_{max} and AUC compared to subjects with <40% BSA on Day 1 (Table 2).

Table 2 Summary of ruxolitinib PK parameters by stratified age groups on Day 1 (Source: Table 5 of Study report dmb-20-55-3)

Strata	N	Total Affected BSA (%) at Baseline	Cmax (nM)	Tmax (h)	AUC(0-t) (h*nM)	C12h (nM)
Overall	40	38.4 ± 16.4 (35.9, 35.7%)	271 ± 650 (57.1, 480%)	4.00 (1.00, 12.0)	1950 ± 4610 (414, 458%)	119 ± 245 (34.7, 371%)
12-15 years	14	30.1 ± 4.64 (29.8, 14.1%)	114 ± 305 (28.5, 286%)	12.0 (1.00, 12.0)	856 ± 2450 (199, 265%)	60.7 ± 113 (25.5, 218%)
16-17 years	7	35.1 ± 10.1 (34.0, 26.8%)	102 ± 118 (48.1, 267%)	4.00 (2.00, 12.0)	690 ± 758 (371, 226%)	47.4 ± 43.4 (29.7, 190%)
≥ 18 years	19	45.6 ± 20.5 (41.9, 43.0%)	449 ± 883 (101, 681%)	4.00 (1.00, 12.0)	3220 ± 6190 (739, 666%)	188 ± 332 (46.0, 692%)
≥ 25 and < 40% BSA	27	29.3 ± 2.61 (29.2, 8.97%)	51.4 ± 69.7 (25.3, 193%)	12.0 (1.00, 12.0)	359 ± 510 (181, 179%)	39.0 ± 51.3 (20.0, 196%)
≥ 40% BSA	13	57.2 ± 17.1 (55.1, 28.0%)	727 ± 1010 (310, 312%)	4.00 (1.00, 12.0)	5250 ± 7140 (2310, 282%)	284 ± 381 (109, 495%)

Note: Summary values are mean ± SD (geometric mean, geometric CV%) except for T_{max} in median (min, max) if n > 2; otherwise, individual value is presented.

Table 3 Summary of ruxolitinib PK parameters by stratified age groups on Day 28 (Source: Table 6 of Study report dmb-20-55-3)

Strata	N	Total Affected BSA (%) at Baseline	C_{max} (nM)	T_{max} (h)	C_{min} (nM)	AUC(0-12h) (h*nM)	T1/2 (h)	C12h (nM)	C_{max}/C12h (unitless)	C_{max}/C_{min} (unitless)
Overall	38	37.6 ± 16.5 (35.1, 35.4%)	137 ± 377 (43.9, 219%)	4.00 (0.0, 12.0)	62.6 ± 165 (NC)	1120 ± 2930 (349, 241%)	116 ± 251 (32.5, 267%) [n = 9]	80.8 ± 166 (31.2, 224%)	1.67 ± 1.37 (1.41, 54.6%)	2.72 ± 1.91 (2.32, 56.8%) [n = 33]
12-15 years	14	30.1 ± 4.64 (29.8, 14.1%)	66.2 ± 93.3 (38.7, 141%)	12.0 (0.0, 12.0)	32.8 ± 64.5 (NC)	555 ± 863 (287, 178%)	266 ± 442 (45.2, 2090%) [n = 3]	52.1 ± 75.0 (29.7, 141%)	1.62 ± 1.71 (1.30, 58.8%)	3.20 ± 2.39 (2.64, 67.0%) [n = 11]
16-17 years	7	35.1 ± 10.1 (34.0, 26.8%)	24.5 ± 12.9 (22.5, 43.6%)	1.00 (0.0, 12.0)	11.0 ± 12.2 (NC)	196 ± 149 (160, 75.5%)	18.3 ± 7.02 (17.6, 40.9%) [n = 2]	16.9 ± 15.2 (12.4, 103%)	2.15 ± 1.52 (1.81, 66.7%)	2.90 ± 1.59 (2.58, 55.7%) [n = 6]
≥ 18 years	17	44.7 ± 21.6 (40.7, 45.1%)	242 ± 548 (64.3, 381%)	4.00 (0.0, 12.0)	108 ± 235 (NC)	1970 ± 4230 (566, 345%)	51.3 ± 49.0 (34.5, 143%) [n = 4]	131 ± 232 (47.5, 319%)	1.52 ± 0.994 (1.35, 45.6%)	2.32 ± 1.66 (2.03, 50.0%) [n = 16]
≥ 25 and < 40% BSA	27	29.2 ± 2.65 (29.1, 9.09%)	49.2 ± 51.2 (30.3, 147%)	4.00 (0.0, 12.0)	23.5 ± 29.3 (NC)	427 ± 499 (237, 173%)	159 ± 305 (40.1, 412%) [n = 6]	41.3 ± 48.8 (22.2, 182%)	1.64 ± 1.46 (1.37, 56.0%)	2.80 ± 1.89 (2.39, 57.2%) [n = 23]
≥ 40% BSA	11	58.1 ± 18.2 (55.7, 29.9%)	353 ± 669 (109, 287%)	1.00 (0.0, 12.0)	159 ± 290 (NC)	2830 ± 5170 (904, 265%)	28.0 ± 26.0 (21.4, 106%) [n = 3]	178 ± 284 (72.3, 217%)	1.74 ± 1.19 (1.51, 53.0%)	2.55 ± 2.05 (2.15, 58.3%) [n = 10]

N = number of participants; n = number of observations; NC = not calculable.
Note: Summary values are mean ± SD (geometric mean, geometric CV%) except for T_{max} in median (min, max) if n > 2; otherwise, individual values are presented.

Phase 3 trials: Two strengths of ruxolitinib cream (i.e., 0.75% and 1.5%) were evaluated in subgroup of subjects in phase 3 trials. Subjects with up to 22% BSA involvement applied topical ruxolitinib cream BID to the lesion area for 8 weeks during VC period and for additional LTS period through 52 weeks. The overall range of BSA

was from 1.21 m^2 to 3.07 m^2, with an overall mean ± SD value of 1.9 ± 0.297 m^2. The overall mean ± SD values of study drug product application rate were 1.47 ± 1.07 mg/cm^2. The mean ± SD values of average application dose of API were 18.8 ± 15.9 mg and 36.7 ± 29.9 mg for the ruxolitinib cream 0.75% BID and 1.5% BID treatment groups, respectively.

The mean values of trough concentration of ruxolitinib in plasma were within a range of 23 to 26 nM and 34 to 39 nM for ruxolitinib cream 0.75% BID and 1.5% BID, respectively, across Weeks 2, 4, and 8 through the VC period (Figure 1). The mean ± SD C_{trough} of ruxolitinib 0.75% and 1.5% in Study 303 was 25 ± 37 nM and 33 ± 40 nM, respectively. The mean ± SD C_{trough} of ruxolitinib 0.75% and 1.5% in Study 304 was 23 ± 33 nM and 38 ± 67 nM, respectively (Table 4). When pooled, the mean ± SD C_{trough} of ruxolitinib 0.75% and 1.5% was 24 ± 35 nM and 36 ± 55 nM, respectively (Table 4). The high strength (1.5%) of ruxolitinib cream showed the higher plasma C_{trough} of ruxolitinib compared to the low strength (0.75%) of ruxolitinib cream (Figure 1 and Table 4). PK data per stratification of geographic region and baseline IGA score showed that higher concentration at steady state (Css) was observed in subjects with a baseline IGA of 3 versus an IGA of 2 and in subjects in Europe versus North America; this difference was most pronounced for subjects in Europe with a baseline IGA of 3 (Figure 2). In the pooled phase 3 data, a higher proportion of subjects with > 15% BSA was enrolled in the stratum of baseline IGA 3 and Europe (131 [46.5%] out of a subtotal of 282 subjects) than the stratum of IGA 3 and North America (77 [17.6%] out of a subtotal of 438 subjects). Thus, the regional difference of Css is likely to be attributable to the difference of %BSA involvement in subjects from different regions (i.e., North America vs. Europe, Figure 2).

The mean values of trough concentrations were relatively stable across visits during the LTS period (Figure 3). In Study 303, the mean trough concentrations were within the range of 13 to 21 nM for the treatment group of 0.75% BID and 18 to 26 nM for the treatment group of 1.5% BID. The LTS PK data in Study 304 were similar; the mean trough concentrations were within the range of 9 to 19 nM for the treatment group of 0.75% BID and 13 to 28 nM for the treatment group of 1.5% BID. The lower mean trough concentrations during the LTS period than the VC period were likely attributable to multiple factors such as the decreased application amount of ruxolitinib cream, which was only applied to the areas of active AD lesions during the LTS period. Another factor was that not all subjects were on treatment at the regular in-clinic study visits when PK blood samples were collected. Unlike the VC period, the treatment in the LTS period of the study was intermittent. Therefore, at regular in-clinic study visits (approximately 4 weeks apart) some subjects were on treatment at that time, but others were off therapy (in remission).

Figure 1 Plasma ruxolitinib trough concentration (mean ± SE) during VC period in pooled phase 3 trial data *(Source: Figure 7 of Summary of Clinical Pharmacology)*

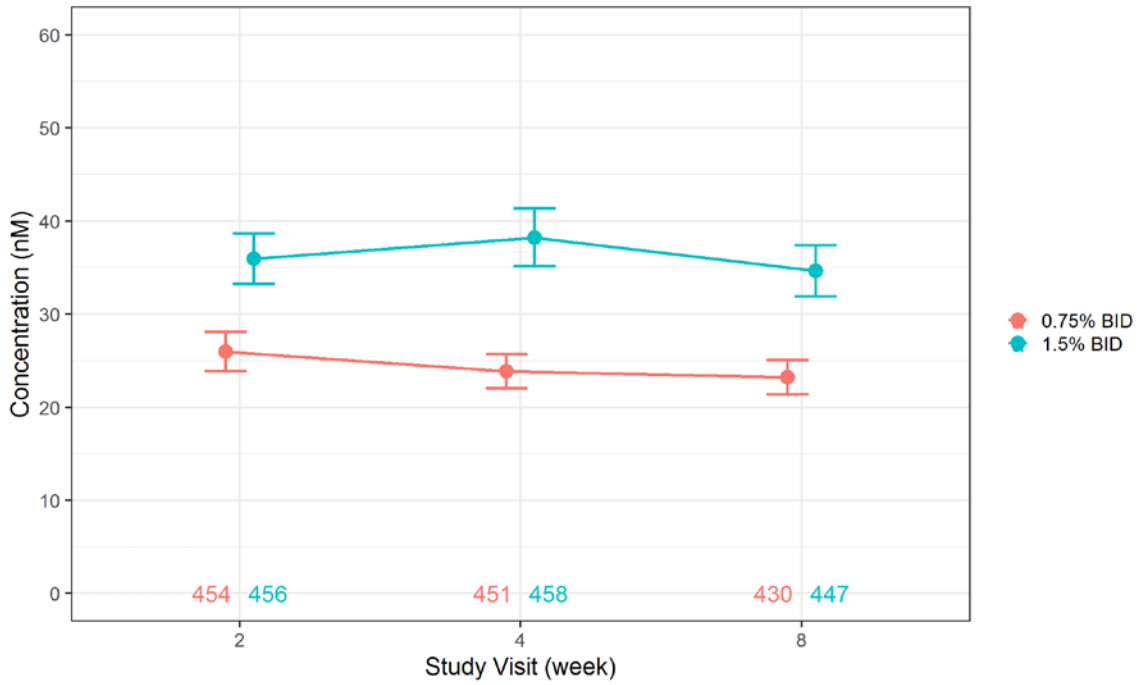


Table 4 Summary of ruxolitinib PK parameters by stratified age groups on Day 28 (Source: Table 6 of Study report dmb-20-55-3)

Ruxolitinib Treatment	INCB 18424-303[a]				INCB 18424-304[b]				Pooled[c]			
	N	%BSA Treated	C_{ss} (nM)	Bioavailability (%)	N	%BSA Treated	C_{ss} (nM)	Bioavailability (%)	N	%BSA Treated	C_{ss} (nM)	Bioavailability (%)
0.75% BID	236	9.86 ± 5.32 (8.00)	25.0 ± 37.1 (10.7)	8.16 ± 9.80 (5.42)	236	9.98 ± 5.33 (9.00)	22.7 ± 32.9 (9.08)	7.20 ± 7.84 (4.52)	472	9.92 ± 5.32 (8.50)	23.8 ± 35.0 (9.86)	7.68 ± 8.88 (4.75)
1.5% BID	241	9.27 ± 5.19 (8.00)	33.4 ± 40.2 (14.5)	6.40 ± 7.19 (4.11)	238	9.93 ± 5.40 (9.00)	38.0 ± 66.8 (12.3)	6.03 ± 8.11 (3.19)	479	9.60 ± 5.30 (8.00)	35.7 ± 55.0 (13.4)	6.22 ± 7.66 (3.64)
Pooled	477	9.56 ± 5.26 (8.00)	–	–	474	9.96 ± 5.36 (9.00)	–	–	951	9.76 ± 5.31 (8.10)	–	–

Note: Summary values are presented as mean ± SD (geometric mean) for C_{ss}, otherwise mean ± SD (median).

Figure 2 Boxplots of ruxolitinib steady-state concentration in pooled phase 3 data – stratified by geographic region and baseline IGA *(Source: Figure 8 of Summary of Clinical Pharmacology)*

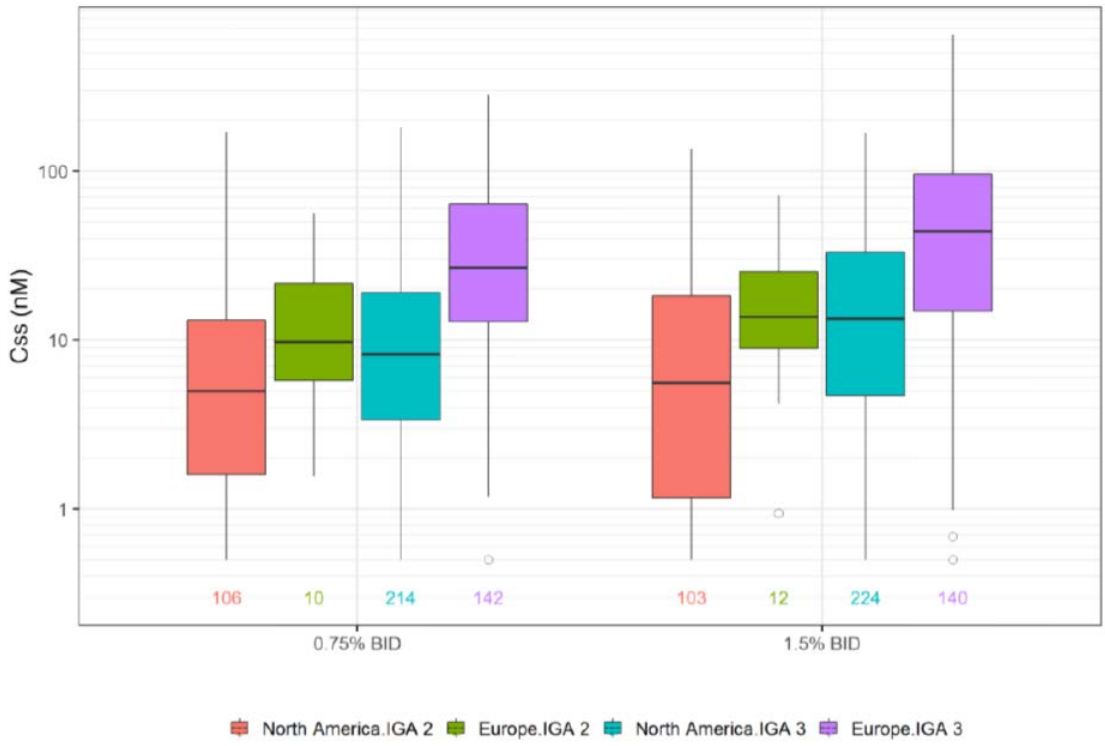
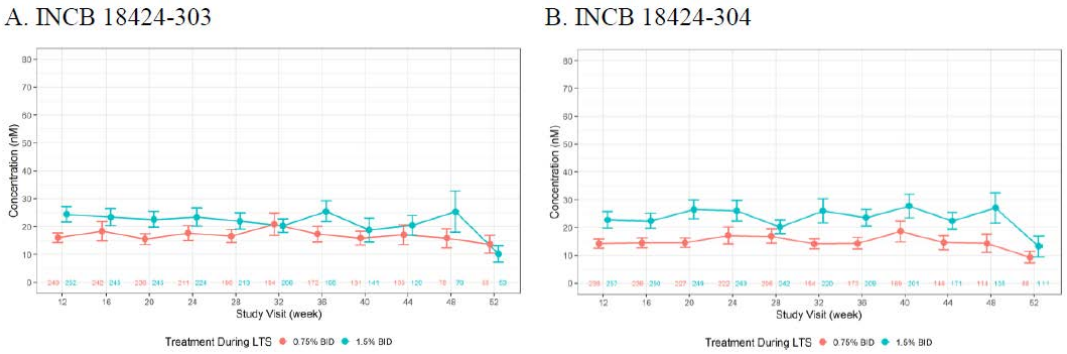


Figure 3 Plasma ruxolitinib trough concentration (mean ± SE) during LTS period in phase 3 trials *(Source: Figure 10 of Summary of Clinical Pharmacology)*



In-vitro metabolism and in vitro DDI studies:
The Applicant conducted a total of 11 in vitro metabolism and drug interaction studies to assess the metabolism of ruxolitinib and drug interaction potential of ruxolitinib. These studies were conducted with the oral ruxolitinib NDA and no new studies were conducted for the topical dosage form. The results of the in vitro metabolism studies indicate that CYP3A4 is mainly responsible for ruxolitinib metabolism.

There were 8 oxidative metabolites identified in vitro, which are pharmacologically active, but their activity is 20% to 50% of the activity of the parent compound. Results from in vivo study with topical ruxolitinib cream 1.5% demonstrated that plasma metabolite concentrations following topical application were low relative to the parent. The systemic exposures of the metabolites were not assessed in MUsT and this is considered acceptable (see Section 6.2.1).

In vitro DDI studies assessed the potential of ruxolitinib to inhibit or induce CYP enzymes and also assessed the potential of ruxolitinib to inhibit transporters. In vitro study using ruxolitinib concentration up to 25 mM demonstrated that ruxolitinib was not a potent inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 with IC50 values >25 mM. A major metabolite of ruxolitinib, M18, up to 3 mM also did not inhibit tested CYP enzymes. Ruxolitinib up to 30 mM did not induce CYP3A4 and up to 10 mM did not induce CYP1A2 or CYP2B6 activity.

Ruxolitinib and its major metabolite, M18 were also tested in vitro for inhibitory potential against a panel of human drug transporters (BCRP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1, and OAT3) using individual cell lines that overexpress these transporters. The results showed that ruxolitinib and its major metabolite, M18 did not inhibit any transporters. Furthermore, the IC50 for tested transporters including P-gp is over 10-fold of clinical steady-state concentration (1.2 mM) following oral ruxolitinib 25 mg. Thus, there is a low potential that ruxolitinib or M18 at therapeutic concentration following

topical application of ruxolitinib cream 1.5% will inhibit any of the aforementioned transporters.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

No. For topical product, PK assessed under maximal use conditions supports systemic safety rather than efficacy.

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

Yes. The applicant evaluated the twice daily topical application of the product in subjects aged 13 years and older with AD in a MUsT and in subjects aged 12 years and older with AD in the Phase 3 trials. See Section 6.2.2 for further details.

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

In general, there was an increase in the systemic exposure with increase in %BSA, baseline IGA score (disease severity), ruxolitinib cream strength (See Appendix. studies INCB18424-103, INCB18424-303, INCB18424-304 and pharmacometrics review). No specific dosing is being recommended for subjects with renal or hepatic impairment (See Section 6.2.1).

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

Food-drug interactions are not applicable for topical products. Results of in vitro metabolism, enzyme, transporter inhibition and induction assays, support a low potential for DDI at clinically relevant doses.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Study Identifier (Type of Study); Location of Study Report	**Primary Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s), Dosage Regimen, and Route of Administration**	**Number of Participants Enrolled**	**Healthy Participants or Diagnosis of Participants**	**Estimated Duration of Treatment**	**Study Status; Type of Report**
INCB 18424-303 (Efficacy, safety); 5.3.5.1	Efficacy	Randomized, double-blind, vehicle-controlled multicenter, Phase 3 study	Ruxolitinib 1.5% or 0.75% cream applied topically as a thin film BID Vehicle cream applied topically as a thin film BID	631 (VC period 253: ruxolitinib 1.5% cream, 252: ruxolitinib 0.75% cream, 126: vehicle cream) (LTS period 225: 1.5%/1.5% 222: 0.75%/ 0.75% 47: vehicle/ 1.5% 48: vehicle/ 0.75%	Adolescent and adult participants with atopic dermatitis eligible for topical therapy (3% to 20% BSA [excluding the scalp] and IGA of 2 or 3 at baseline)	52 weeks Total 8 weeks (VC period) 44 weeks (LTS period)	Ongoing; Interim

Study Identifier (Type of Study); Location of Study Report	**Primary Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s), Dosage Regimen, and Route of Administration**	**Number of Participants Enrolled**	**Healthy Participants or Diagnosis of Participants**	**Estimated Duration of Treatment**	**Study Status; Type of Report**
INCB 18424-304 (Efficacy, safety); 5.3.5.1	Efficacy	Randomized, double-blind, vehicle-controlled multicenter, Phase 3 study	Ruxolitinib 1.5% or 0.75% cream applied topically as a thin film BID Vehicle cream applied topically as a thin film BID	618 (VC period 246: ruxolitinib 1.5% cream, 248: ruxolitinib 0.75% cream, 124: vehicle cream) (LTS period 221: 1.5%/1.5% 204: 0.75%/ 0.75% 52: vehicle/ 1.5% 53: vehicle/ 0.75%	Adolescent and adult participants with atopic dermatitis eligible for topical therapy (3% to 20% BSA [excluding the scalp] and IGA of 2 or 3 at baseline)	52 weeks total 8 weeks (VC period) 44 weeks (LTS period)	Ongoing; Interim
INCB 18424-103 (Maximum use); 5.3.3.2	Safety and tolerability	Open-label, maximum use, multicenter, Phase 1 study	Ruxolitinib 1.5% cream BID applied topically to affected areas identified at baseline during 4-week treatment period, and to lesional skin only during optional 4-week extension	41	Adolescents or adults aged 12-65 years with atopic dermatitis with a disease duration of ≥ 2 years (≥ 25% BSA and IGA ≥ 2)	4 weeks of BID treatment, optional 4-week extension	Complete; Full

7.2. Review Strategy

The safety review will generally focus on the following pools, comprised of subjects with AD:

- Pool 1: "Phase 3, Atopic Dermatitis Vehicle-Controlled Population" (n= 1249), which provided the vehicle-controlled analyses, with treatment through Week 8 and
- Pool 2: the "Phase 2/3 Atopic Dermatitis Population," (n= 1544), which provided for the long-term analyses from subjects who continued treatment from the Phase 3 studies.

The names of all clinical studies begin with "INCB 18424-," with specific studies identified by the number that follows the hyphen. In the safety review, studies are referenced by the specific identifying number. For example, the pivotal studies for AD were "INCB 18424-303" and "INCB 18424-304" and are referenced as "303" and "304."

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Studies INCB 18424-303 and INCB 18424-304

Trial Design

Study INCB 18424-303 (Study 303) and Study INCB 18424-304 (Study 304) were identical randomized, double-blind, vehicle-controlled Phase 3 trials in subjects with atopic dermatitis. The studies enrolled subjects 12 years of age and older with atopic dermatitis involvement of 3% to 20% body surface area (BSA) excluding the scalp and an Investigator's Global Assessment (IGA) of mild (2) or moderate (3) at baseline. Each study was designed to enroll approximately 600 subjects randomized 2:2:1 to ruxolitinib 1.5% cream, ruxolitinib 0.75% cream, or vehicle cream. Subjects applied treatment twice daily for 8 weeks. Areas identified for treatment at baseline were treated throughout the 8-week treatment period even if they improved. With investigator approval, subjects could treat additional areas as long as the total treated BSA did not exceed 20%.

Following the 8-week double-blind period, subjects from all treatment arms who completed Week 8 assessments, had no more than 20% BSA, and with no safety concerns could continue into the 44-week long-term safety period, regardless of IGA response during the vehicle-controlled period. The long-term safety period was designed to assess intermittent treatment to active lesions with treatment pauses when lesions are cleared. Subjects who received active treatment during the vehicle-controlled period continued to apply the originally randomized treatment in the long-term safety period. Subjects who initially received vehicle were randomized to either ruxolitinib 0.75% or 1.5% during the long-term safety period. Subjects were evaluated every 4 weeks during the long-term safety period. Subjects with an IGA score ≥1 would continue treatment while subjects with an IGA score of 0 would enter a no-treatment cycle. Subjects could restart treatment between visits if lesions returned.

Study Endpoints

Efficacy was assessed using the IGA scale, the Eczema Area and Severity Index Score (EASI), an Itch Numerical Rating Scale (NRS), and Patient-Reported Outcomes Measurement Information System (PROMIS) Short Form – Sleep-Related Impairment (8a) and Short Form – Sleep Disturbance (8b). Additional efficacy scales included Scoring Atopic Dermatitis (SCORAD), BSA, Dermatology Life Quality Index (DLQI), Patient Global Impression of Change (PGIC), Patient-Oriented Eczema Measure (POEM), EQ-5D-5L, Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP), and Skin Pain NRS.

The IGA scale was as follows.

Table 5 – Investigator's Global Assessment Scale

Grade	Severity	Status
0	Clear	No erythema or induration/papulation, no oozing/crusting; there may be minor residual discoloration.
1	Almost clear	There may be trace faint pink erythema, with almost no induration/papulation, and no oozing/crusting.
2	Mild	There may be faint pink erythema, with mild induration/papulation and no oozing/crusting.
3	Moderate	There may be pink-red erythema with moderate induration/papulation and there may be some oozing/crusting.
4	Severe	There may be deep or bright red erythema with severe induration/papulation and with oozing/crusting.

Source: pg 20 of Statistical Analysis Plan for Study INCB 18424-303/304

The Itch NRS was assessed daily by subjects. The scale assessed the worst level of itching in the past 24 hours from 0 (no itch) to 10 (worst imaginable itch). The PROMIS sleep scales each have 8 questions on a 5-point scale (1-5) yielding a total score that ranges from 8 to 40 with higher scores indicating greater severity of sleep impairment or disturbance. During the double-blind period the recall period is 24 hours.

The primary efficacy endpoint was the proportion of subjects with an IGA score of 0 or 1 with at least 2 grades reduction from baseline at Week 8. The key secondary endpoints were

- EASI 75 (≥ 75% improvement) at Week 8
- Proportion of subjects with ≥ 4-point improvement in Itch NRS from baseline to Week 8
- Proportion of subjects with ≥ 6-point improvement in PROMIS Short Form – Sleep Disturbance (8b) at Week 8
- Proportion of subjects with ≥ 6-point improvement in PROMIS Short Form – Sleep Impairment (8a) at Week 8

The PROMIS Short Form – Sleep Impairment (8a) endpoint was originally designated as an 'other' secondary endpoint. The endpoint was elevated to the key secondary family and included in the multiplicity hierarchy in the Statistical Analysis Plan (SAP).

The Itch NRS and PROMIS endpoints were analyzed by averaging the 7 daily scores from just prior to the visit. If 4 or more daily scores are missing (out of the 7), the scores were set to missing.

The studies also included a large number of other secondary endpoints. The protocol noted that while IGA success was the primary efficacy endpoint for US regulatory submissions, (b) (4)

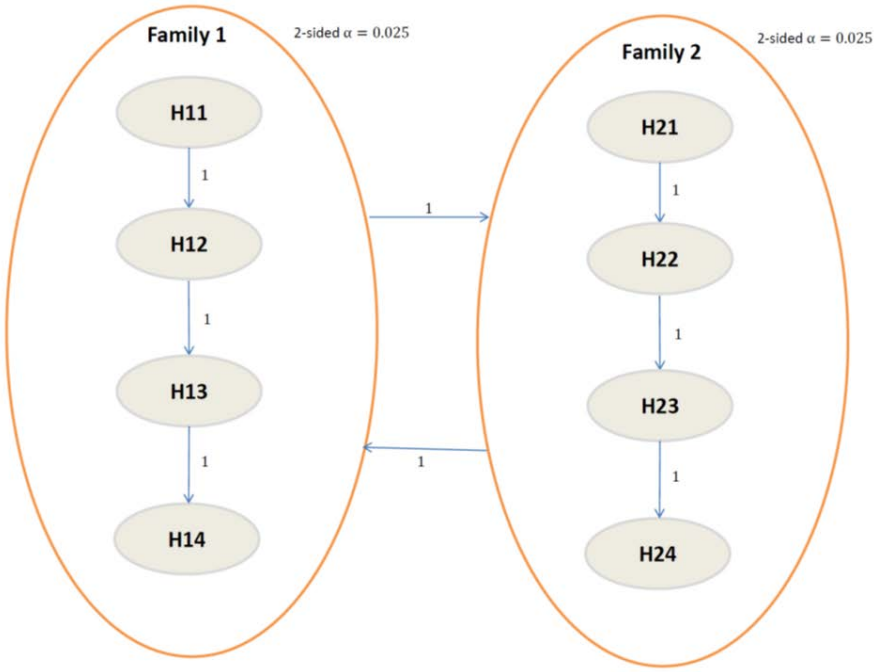
Statistical Analysis Plan

The primary analysis population was the ITT population, defined as all randomized subjects. The primary endpoint was analyzed with logistic regression with terms for treatment group, baseline IGA, and region, based on the Wald test. Exact logistic regression was to be used if any of the dose levels have an expected cell count less than 5. The analysis also included confidence intervals for the odds ratio.

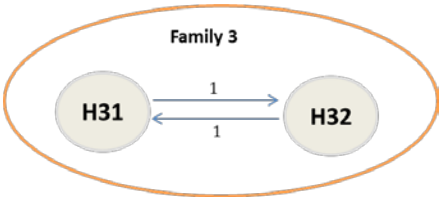
Multiplicity was handled by assigning two-sided α=0.025 to each ruxolitinib arm and analyzing the endpoints of IGA success, EASI 75, Itch NRS success, and PROMIS Sleep Disturbance (8b) success sequentially within each dose group comparison. If all 4 hypotheses are statistically significant in either family, then the alpha can be passed to the other family. If all 8 hypotheses are statistically significant, then the PROMIS Sleep Impairment (8a) success endpoint for the two doses will be analyzed using Hochberg's method with overall two-sided α=0.05. This approach can be described graphically as follows (Figure 4), where Families 1 and 2 represent the primary and first 3 secondary endpoints for each of the two dose levels and Family 3 represents the fourth secondary endpoint (Sleep Impairment) for both dose levels.

Figure 4 – Graphical Representation of Multiplicity Control Scheme

Step 1:



Step 2:



Source: pg. 14 of Statistical Analysis Plan for Study INCB 18424-303/304

The primary method of handling missing data was to treat subjects with missing data as non-responders. Multiple imputation was specified as an alternative method. The protocol and SAP included limited details about how the multiple imputation would be conducted. The SAP stated that for datasets with monotone missing patterns, missing values will be imputed sequentially with covariates constructed from their corresponding sets of preceding variables (treatment group and stratification factors). For datasets with arbitrary missing data patterns, the fully conditional specification method will be used. The SAP did not specify the number of imputations, the randomization seeds, or how the determination would be made as to whether a dataset had a monotone or arbitrary missing data pattern. The statistical programs submitted by the applicant indicate that the analyses were conducted with 10 imputations and the fully conditional specification method, but the applicant did not provide information about when these details were specified. The applicant also proposed handling missing data with LOCF and conducting a longitudinal logistic regression with repeated measures by visit (IGA response at Week 2, 4, and 8 as dependent variables and treatment, stratification factors, visit, and treatment-by-visit interaction). The SAP also included a tipping point analysis that replaces missing data by a range of values to see how far the values must be changed to the results to tip from significant to non-significant.

The key secondary endpoints were analyzed similarly to the primary endpoint. The Itch NRS success endpoint was analyzed among subjects who had a baseline score ≥4, in order to include only subjects capable of demonstrating at least a 4-point improvement from baseline. Similarly, the PROMIS endpoints were intended to include only subjects capable of demonstrating at least a 6-point improvement from baseline. However, the SAP noted that subjects with baseline ≥6 would be included in the analyses, which fails to take into account that because the PROMIS scores range from 8 to 40 (sum of 8 items measured from 1 to 5), rather than having a minimum score of 0. Thus, the applicant's analysis includes subjects who were not capable of demonstrating a 6-point improvement. To include subjects capable of demonstrating a 6-point improvement, only subjects with baseline scores ≥14 should be included in the analysis.

Protocol Amendments

Two minor protocol amendments were incorporated during the study. The amendments were primarily intended to clarify procedures and did not impact design or endpoints.

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant stated that, "All studies were conducted in compliance with Good Clinical Practice and ethical principles that have their origin in the Declaration of Helsinki and are consistent with US, European, and International Council on Harmonisation guidelines on drug development" (p. 9 of Clinical Overview).

Financial Disclosure

The Applicant reported no clinical investigators with disclosable financial interests or arrangements.

Patient Disposition

Study 303 enrolled 631 subjects at 78 sites, including 48 sites in North America and 30 in Europe. Study 304 enrolled 618 subjects at 65 sites, included 37 sites in North America and 28 in Europe. In Study 303, approximately 12% of subjects i discontinued treatment and 14% of subjects discontinued the study during the 8-week vehicle-controlled period. In Study 304, approximately 9% of subjects discontinued treatment and 13% of subjects discontinued the study during the 8-week vehicle-controlled period. Treatment and study discontinuation rates were higher on vehicle than ruxolitinib 1.5% in both studies. The most common reasons for discontinuation were withdrawal by participant, loss-to-follow-up, and adverse events. See Table 6.

Table 6 – Disposition of Subjects (Vehicle-Controlled Period)

	Study 303			Study 304		
	Vehicle	Ruxo 0.75%	Ruxo 1.5%	Vehicle	Ruxo 0.75%	Ruxo 1.5%
Subjects Randomized	126	252	253	124	248	246
Discontinued Treatment	25 (20%)	27 (11%)	21 (8%)	18 (15%)	28 (11%)	11 (5%)
Reasons for treatment discontinuation						
Adverse event	5 (4%)	3 (1%)	2 (1%)	3 (2%)	1 (<1%)	1 (<1%)
Lack of efficacy	1 (1%)	1 (<1%)	0	--	--	--
Lost to follow-up	5 (4%)	12 (5%)	7 (3%)	3 (2%)	13 (5%)	4 (2%)
Physician decision	--	1 (<1%)	--	1 (1%)	--	1(<1%)
Pregnancy	1 (1%)	--	--	--	--	--
Protocol violation	--	2 (1%)	--	--	2 (1%)	--
Noncompliance with study drug	--	1 (<1%)	--	--	1 (<1%)	--
Withdrawal by participant	12 (10%)	7 (3%)	12 (5%)	9 (7%)	10 (4%)	5 (2%)
Other	1 (1%)	--	--	1 (1%)	1 (<1%)	--

Discontinued Study	31 (25%)	30 (12%)	28 (11%)	19 (15%)	39 (16%)	22 (9%)
Reasons for study discontinuation						
Adverse event	4 (3%)	2 (1%)	1 (<1%)	1 (1%)	1 (<1%)	--
Lack of efficacy	1 (1%)	--	--	--	--	--
Lost to follow-up	5 (4%)	12 (5%)	8 (3%)	3 (2%)	13 (5%)	4 (2%)
Physician decision	1 (1%)	1 (<1%)	--	3 (2%)	--	1 (<1%)
Pregnancy	1 (1%)	--	--	--	--	--
Protocol violation	--	3 (1%)	--	--	2 (1%)	--
Withdrawal by participant	17 (14%)	11 (4%)	19 (8%)	11 (9%)	21 (9%)	15 (6%)
Other	2 (2%)	1 (<1%)	--	1 (1%)	2 (1%)	2 (1%)

Source: pg 35 of Study Report 303 and pg 35 of Study Report 304 and reviewer analysis.

A database lock was conducted after all subjects completed the 8-week double-blind study period. The long-term safety follow-up period was ongoing at the time the study reports were written. Of the 631 subjects who entered Study 303, 542 entered the long-term safety follow-up period. At the time of database lock, 21% had completed treatment during the long-term safety period, 61% were ongoing, and 18% had discontinued. Similarly, of the 618 subjects who entered Study 304, 530 entered the long-term safety follow-up period. At the time of database lock, 39% had completed treatment during the long-term safety period, 19% were ongoing, and 23% had discontinued. See Table 7.

Table 7 - Disposition of Subjects (Long-Term Safety Period)

	Study 303			
Treatment during vehicle-controlled period	Vehicle N=126		Ruxo 0.75% N=252	Ruxo 1.5% N=253
Treatment during LTS	Ruxo 0.75%	Ruxo 1.5%	Ruxo 0.75%	Ruxo 1.5%
Entered LTS	48	47	222	225
Completed treatment during LTS	9 (19%)	10 (21%)	49 (22%)	47 (21%)
Ongoing during LTS	30 (63%)	32 (68%)	131 (59%)	138 (61%)
Discontinued study drug during LTS	9 (19%)	5 (11%)	42 (19%)	40 (18%)
	Study 304			
Treatment during vehicle-controlled period	Vehicle N=124		Ruxo 0.75% N=248	Ruxo 1.5% N=246
Treatment during LTS	Ruxo 0.75%	Ruxo 1.5%	Ruxo 0.75%	Ruxo 1.5%
Entered LTS	53	52	204	221
Completed treatment during LTS	21 (40%)	23 (44%)	69 (34%)	91 (41%)
Ongoing during LTS	15 (28%)	19 (37%)	84 (41%)	86 (39%)
Discontinued study drug during LTS	17 (32%)	10 (19%)	51 (25%)	44 (20%)

LTS=Long-term safety period
Source: pg 37 of Study Report 303 and pg 37 of Study Report 304 and reviewer analysis.

Protocol Violations/Deviations

The most common protocol deviations were missing study procedures or missing endpoint assessments. See Table 8. The protocol violations listed in Table 8 include both major and minor protocol violations. The most common protocol violations were missed endpoint assessments and deviations in study procedures or assessments. The applicant identified one site in Study 304 (Site 461; 41 subjects) as having serious noncompliance with the protocol and accepted Good Clinical Practice source documentation. Thus, the applicant removed the data collected from Site 461 in the efficacy analyses. Data from this site were included in safety and PK analyses.

Table 8 – Protocol Deviations (Vehicle-Controlled Period)

	Study 303			Study 304		
	Vehicle N=126	Ruxo 0.75% N=252	Ruxo 1.5% N=253	Vehicle N=124	Ruxo 0.75% N=248	Ruxo 1.5% N=246
Any protocol deviations	87 (69%)	184 (73%)	169 (67%)	72 (58%)	155 (63%)	145 (59%)
Concomitant medication	4 (3%)	6 (2%)	8 (3%)	4 (3%)	7 (3%)	--
Exclusion criteria	2 (2%)	8 (3%)	5 (2%)	1 (1%)	5 (2%)	4 (2%)
Inclusion criteria	4 (3%)	6 (2%)	5 (2%)	2 (2%)	3 (1%)	3 (1%)
Informed consent	1 (1%)	3 (1%)	2 (1%)	--	--	2 (1%)
Missing endpoint assessments	53 (42%)	83 (33%)	88 (35%)	29 (23%)	65 (26%)	64 (26%)
Study procedures/assessments	47 (37%)	89 (35%)	89 (35%)	49 (40%)	88 (36%)	87 (35%)
Study treatment administration/dispensing	16 (13%)	43 (17%)	36 (14%)	13 (11%)	34 (14%)	18 (7%)
Study treatment compliance	6 (5%)	12 (5%)	16 (6%)	8 (7%)	17 (7%)	17 (7%)
Study treatment randomization	--	1 (<1%)	1 (<1%)	2 (2%)	2 (1%)	1 (<1%)
Visit scheduling	24 (19%)	55 (22%)	40 (16%)	11 (9%)	35 (14%)	30 (12%)
Other protocol deviation	1 (1%)	2 (1%)	4 (2%)	--	1 (<1%)	--

Source: pg 44 of Study Report 303 and pg 44 of Study Report 304 and reviewer analysis.

Demographic Characteristics

The baseline demographics were generally balanced across the treatment groups in the two studies. See Table 9. The majority of subjects were female, white and not Hispanic or Latino. The mean age was 35-36 years and approximately 20% of subjects were age 12 to 17 years and approximately 9% of subjects were age 65 years or older.

Table 9 – Demographics

	Study 303			Study 304		
	Vehicle N=126	Ruxo 0.75% N=252	Ruxo 1.5% N=253	Vehicle N=124	Ruxo 0.75% N=248	Ruxo 1.5% N=246
Age (years)						
Mean	35.2	36.8	33.7	38.9	35.8	35.9
Range	12-82	12-85	12-77	12-82	12-81	12-85
12-17 years	23 (18%)	52 (21%)	57 (19%)	22 (18%)	55 (22%)	45 (18%)
18-64 years	92 (73%)	171 (68%)	187 (74%)	87 (70%)	171 (69%)	181 (74%)
≥ 65 years	11 (9%)	28 (11%)	19 (7%)	15 (12%)	22 (9%)	20 (8%)
Gender						
Female	79 (63%)	154 (61%)	158 (63%)	80 (65%)	150 (61%)	150 (61%)
Male	47 (37%)	98 (39%)	95 (38%)	44 (36%)	98 (40%)	96 (39%)
Race						
White	85 (68%)	171 (68%)	177 (70%)	85 (69%)	174 (70%)	178 (72%)
Black or Afric.-Amer.	29 (23%)	55 (22%)	56 (22%)	32 (26%)	63 (25%)	57 (23%)
Asian	8 (6%)	10 (4%)	14 (6%)	2 (2%)	6 (2%)	6 (2%)
Am. Ind./ AK Native	--	2 (1%)	--	--	--	1 (<1%)
Native HI/ Pac. Isl.	--	3 (1%)	--	2 (2%)	--	--
Other	4 (3%)	11 (4%)	6 (2%)	3 (2%)	5 (2%)	4 (2%)
Ethnicity						
Hispanic or Latino	21 (17%)	30 (12%)	37 (15%)	17 (14%)	31 (13%)	30 (12%)
Not Hispanic or Latino	104 (83%)	218 (87%)	212 (84%)	107 (86%)	217 ((88%)	216 (88%)
Missing	1 (1%)	4 (2%)	4 (2%)	--	--	--
Region						
North America	88 (70%)	176 (79%)	176 (70%)	84 (68%)	166 (67%)	165 (67%)
Europe	38 (30%)	76 (30%)	77 (30%)	40 (32%)	82 (33%)	81 (33%)

Percentages may not sum to 100% due to rounding.
Source: pg 44 of Study Report 303 and pg 44 of Study Report 304 and reviewer analysis.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The baseline disease characteristics were balanced across treatment arms. Approximately 75% of subjects had moderate disease at baseline and approximately 63% to 65% of subjects had Itch NRS scores of at least 4 at baseline, with approximately 6% of subjects with missing Itch NRS scores at baseline (7-day average). See Table 10.

Table 10 – Baseline Disease Characteristics

	Study 303			Study 304		
	Vehicle N=126	Ruxo 0.75% N=252	Ruxo 1.5% N=253	Vehicle N=124	Ruxo 0.75% N=248	Ruxo 1.5% N=246
Total %BSA						
Mean (SD)	9.2 (5.1)	9.9 (5.4)	9.3 (5.2)	10.1 (5.8)	10.1 (5.3)	9.9 (5.4)
Range	3-20	3-20	3-20	3-20	3-20	3-22
IGA Score						
Mild (2)	31 (25%)	61 (24%)	60 (24%)	33 (27%)	64 (26%)	63 (26%)
Moderate (3)	95 (75%)	191 (76%)	193 (76%)	92 (73%)	184 (74%)	183 (74%)
EASI Score						
Mean (SD)	7.4 (4.3)	8.1 (4.8)	7.9 (4.6)	8.2 (5.2)	8.1 (5.0)	7.8 (4.9)
Range	1.2 - 23.6	0.6 - 24.2	0.8 - 24.8	0.6 - 26.0	1.0 - 30.6	0.8 - 27.4
Itch NRS Score						
Mean (SD)	5.1 (2.5)	5.1 (2.3)	5.2 (2.5)	5.1 (2.4)	5.2 (2.5)	4.9 (2.5)
Range	0 - 9.9	0 - 10	0 – 10	0 - 10	0 – 10	0 – 10
Baseline ≤ 4	40 (32%)	77 (31%)	84 (33%)	36 (29%)	66 (27%)	79 (32%)
Baseline > 4	78 (62%)	156 (62%)	161 (64%)	81 (65%)	168 (68%)	154 (63%)
Missing	8 (6%)	19 (8%)	8 (3%)	7 (6%)	14 (6%)	13 (5%)
PROMIS Sleep Disturbance						
Mean (SD)	18.1 (5.3)	19.1 (5.9)	19.0 (5.8)	19.2 (6.2)	19.0 (6.2)	19.0 (6.4)
Range	8.9 – 37.9	8 – 38.7	8 – 39	8 – 38.7	8 – 38.6	8 – 37.9
Baseline ≤ 14	26 (21%)	46 (18%)	48 (19%)	22 (18%)	51 (21%(	52 (21%)
Baseline > 14	90 (71%)	187 (74%)	190 (75%)	94 (76%)	179 (72%)	177 (72%)
Missing	10 (8%)	19 (8%)	15 (6%)	8 (6%)	18 (7%)	17 (7%)

Percentages may not sum to 100% due to rounding.
Source: pg 41-42 of Study Report 303 and pg 41-42 of Study Report 304 and reviewer analysis.

Efficacy Results – Primary Endpoint

The primary efficacy endpoint was treatment success on the IGA at Week 8, defined as a score of 0 or 1 with at least 2 grades reduction from baseline. Each dose was compared to vehicle using two-sided α=0.025 to account for the multiplicity due to two doses. The protocol specified that the primary endpoint would be analyzed with logistic regression with terms for treatment group, baseline IGA, and region, based on the Wald test. Exact logistic regression was to be used if any of the dose levels have an expected cell count less than 5. The applicant presented p-values and 95% confidence intervals for the odds ratio based on exact logistic regression. The primary method of handling missing data was non-responder imputation. This reviewer also calculated 95% confidence intervals based on the treatment difference using Mantel-Haenszel weighting and the stratification factors, because treatment differences may be easier to interpret than odds ratios. In Study 304, subjects at Site 461 were excluded from the analysis for the reasons discussed above. Ruxolitinib 0.75% and 1.5% were superior to placebo for the primary endpoint of treatment success at Week 8 (Table 11).

Table 11 – IGA Success at Week 8 (Non-Responder Imputation)

	Study 303			Study 304		
	Vehicle N=126	Ruxo 0.75% N=252	Ruxo 1.5% N=253	Vehicle N=118	Ruxo 0.75% N=231	Ruxo 1.5% N=228
IGA Success	19 (15.1%)	126 (50.0%)	136 (53.8%)	9 (7.6%)	90 (39.0%)	117 (51.3%)
p-value		<0.0001	<0.0001		<0.0001	<0.0001
Odds ratio (95% CI)		6.4 (3.6, 11.9)	7.5 (4.2, 14.0)		8.8 (4.1, 21.2)	15.8 (7.4, 38.1)
Treatment difference (95% CI)		35.1% (26.5%, 43.7%)	38.9% (30.3%, 47.4%)		31.6% (23.8%, 39.4%)	44.1% (36.2%, 52.0%)

CI = Confidence interval
Study 304 results exclude subjects from Site 461
Source: pg 63 of Study Report 303 and pg 63 of Study Report 304 and reviewer analysis.

As supportive and sensitivity analyses, the applicant conducted a longitudinal repeated measures logistic regression, and two alternate ways of handling missing data: multiple imputation and LOCF. The multiple imputation analysis used a fully conditional specification method. The applicant also conducted a tipping point analysis. For the tipping point analysis presented in Table 12, the results presented are for the case where all subjects with missing data on the vehicle arm are imputed as successes and all subjects on the ruxolitinib arms are imputed as non-responders, as this most extreme case in the tipping point analysis still leads to nominally statistically significant results. The results of these supportive and sensitivity analyses are similar to the primary analysis. All p-values for these analyses were <0.002. See Table 12.

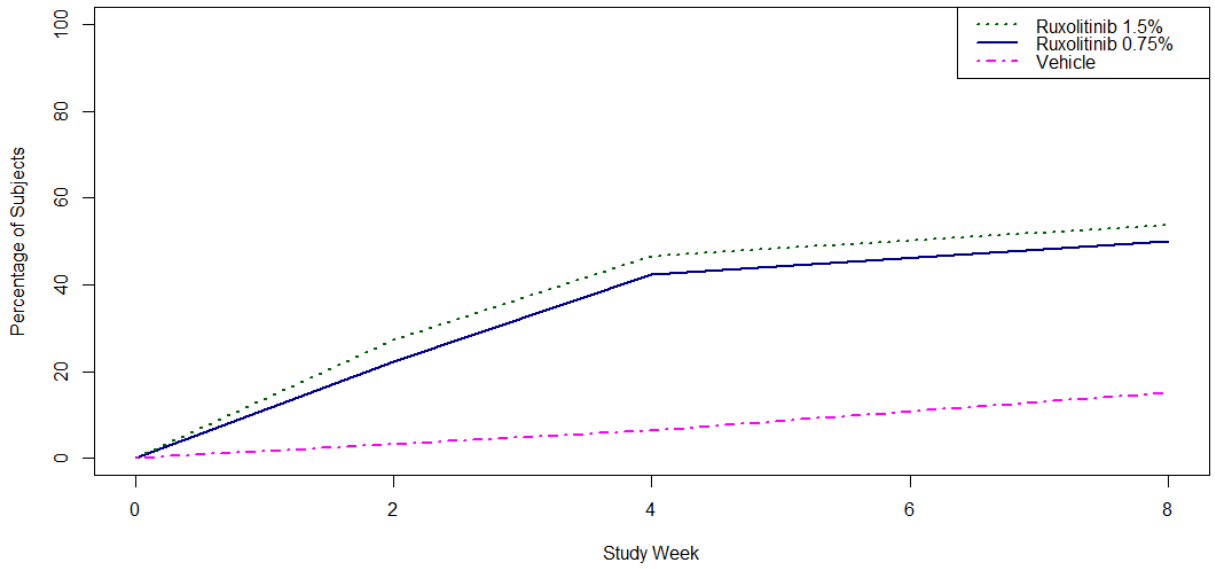
Table 12 – IGA Success at Week 8 (Sensitivity and Supportive Analyses)

	Study 303			Study 304		
	Vehicle N=126	Ruxo 0.75% N=252	Ruxo 1.5% N=253	Vehicle N=118	Ruxo 0.75% N=231	Ruxo 1.5% N=228
Percent missing data	19.8%	10.7%	8.3%	14.4%	11.7%	4.4%
Longitudinal logistic	11.3%	53.9%	57.0%	5.3%	36.1%	51.8%
p-value		<0.0001	<0.0001		<0.0001	<0.0001
Multiple imputation	16.4%	52.2%	56.3%	8.4%	40.4%	51.9%
p-value		<0.0001	<0.0001		<0.0001	<0.0001
LOCF	17.2%	53.7%	58.0%	8.9%	41.3%	53.2%
p-value		<0.0001	<0.0001		<0.0001	<0.0001
Tipping point (worst case)	34.9%	50.0%	53.8%	22.0%	39.0%	51.3%
p-value		0.0055	0.0005		0.0015	<0.0001

Study 304 results exclude subjects from Site 461
Source: pg 63 and 331 of Study Report 303 and pg 63 and 359 of Study Report 304 and reviewer analysis.

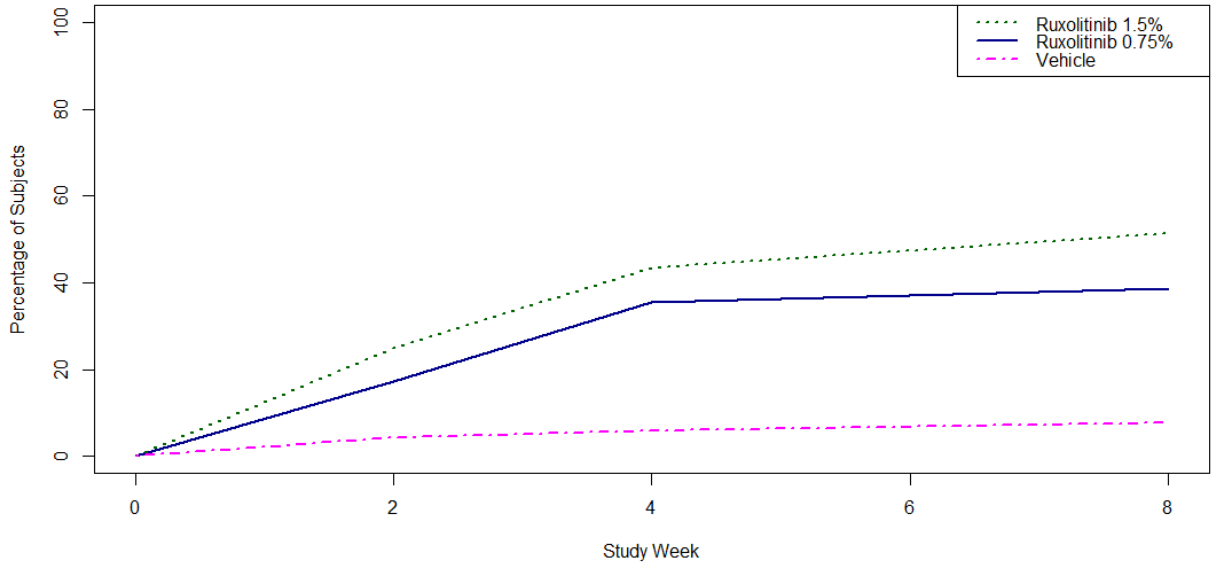
Efficacy over Time
The primary efficacy results for IGA success for the ruxolitinib arms separated from the vehicle arm over the treatment period (Weeks 2, 4, and 8). See Figure 5 and Figure 6.

Figure 5 – IGA Success over Time (Study 303)



Source: Reviewer analysis.

Figure 6 – IGA Success over Time (Study 304)

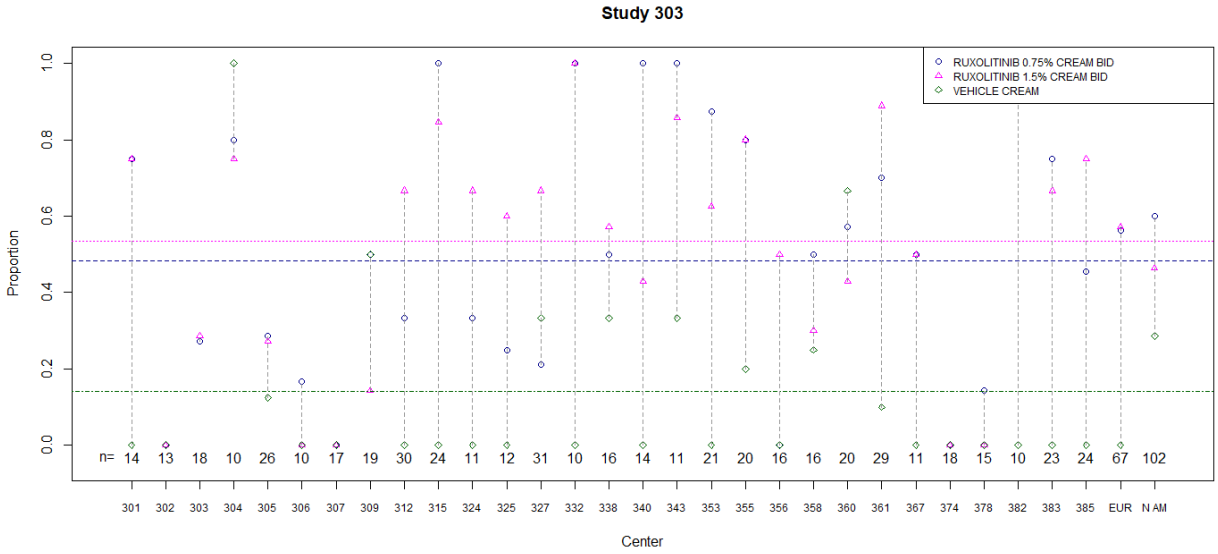


Source: Reviewer analysis.

Efficacy By Center

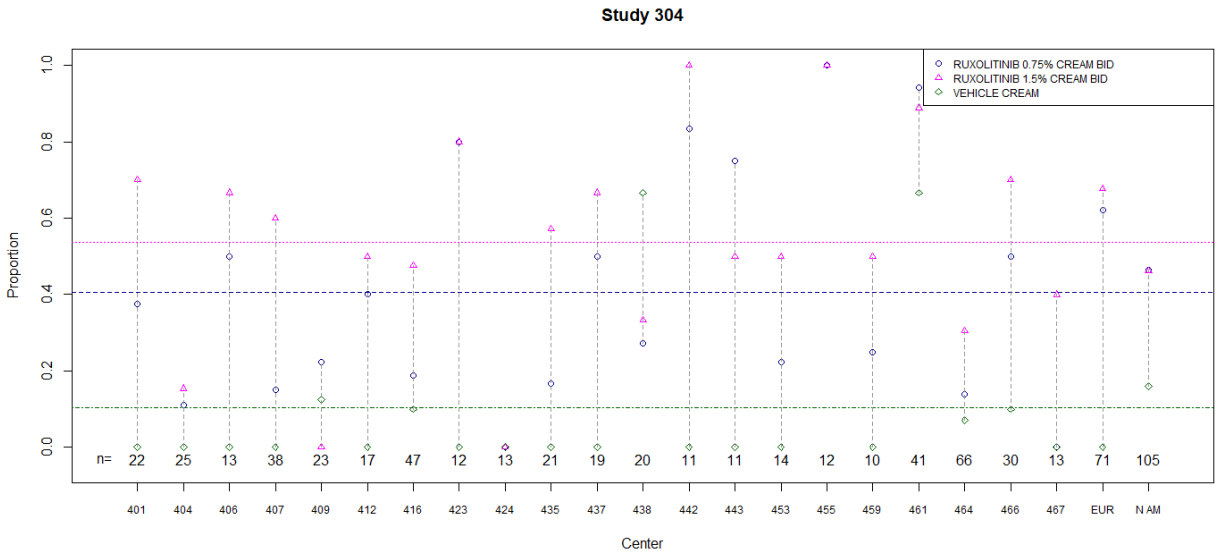
Study 303 enrolled 631 subjects at 78 sites, including 48 sites in North America and 30 in Europe. Study 304 enrolled 618 subjects at 65 sites, included 37 sites in North America and 28 in Europe. Because many of the sites in the two studies enrolled relatively few subjects, Figure 7 and Figure 8 present the primary endpoint results by site for the sites that enrolled at least 10 subjects. The smaller sites are pooled by region (North America (N AM) and Europe (EUR)). The results were generally consistent across sites in the two studies.

Figure 7 – IGA Success at Week 8 by Site in Study 303 (Sites with ≥10 Subjects)



n=Total number of subjects per center
Source: Reviewer analysis

Figure 8 - IGA Success by Site in Study 304 (Sites with ≥10 Subjects)



n=Total number of subjects per center
Source: Reviewer analysis

Findings in Subgroup Populations
Treatment effects were generally consistent across age, gender, race, ethnicity, and geographic region subgroups. The studies enrolled few subjects in the American Indian/Alaskan native and Native Hawaiian/Pacific Islander groups. See Table 13.

Table 13 – IGA Success at Week 8 by Demographic Subgroups

	Study 303			Study 304		
	Vehicle N=126	Ruxo 0.75% N=252	Ruxo 1.5% N=253	Vehicle N=118	Ruxo 0.75% N=231	Ruxo 1.5% N=228
Age (years)						
12-17 years	5/23 (21.7%)	29/53 (54.7%)	24/47 (51.1%)	1/20 (5.0%)	21/53 (39.6%)	20/40 (50.0%)
18 – 64 years	11/92 (12.0%)	87/171 (50.9%)	99/187 (52.9%)	7/83 (8.4%)	63/156 (40.4%)	87/169 (51.5%)
≥ 65 years	3/11 (27.3%)	10/28 (35.7%)	13/19 (68.4%)	1/15 (6.7%)	6/22 (27.3%)	10/19 (52.6%)
Gender						
Female	6/79 (7.6%)	84/154 (54.6%)	82/158 (51.9%)	6/75 (8.0%)	59/138 (42.8%)	66/135 (48.9%)
Male	13/47 (27.7%)	42/98 (42.9%)	54/95 (56.8%)	3/43 (7.0%)	31/93 (33.3%)	51/93 (54.8%)
Race						
White	15/85 (17.7%)	93/171 (54.4%)	101/177 (57.1%)	5/79 (6.3%)	70/157 (44.6%)	92/160 (57.5%)
Black or Afric.-Amer.	3/29 (10.3%)	21/55 (38.2%)	26/56 (46.4%)	4/32 (12.5%)	16/63 (25.4%)	17/57 (29.8%)
Asian	0/8 (0%)	6/10 (60.0%)	5/14 (35.7%)	0/2 (0%)	2/6 (33.3%)	4/6 (66.7%)
Am. Ind./ AK Native	--	0/2 (0%)	--	--	--	1/1 (100%)
Native HI/ Pac. Isl.	--	1/3 (33.3%)	--	0/2 (0%)	--	--
Other	1/4 (25.0%)	5/11 (45.5%)	4/6 (66.7%)	0/3 (0%)	2/5 (40.0%)	3/4 (75.0%)
Ethnicity						
Hispanic or Latino	4/21 (19.1%)	10/30 (33.3%)	17/37 (46.0%)	1/17 (5.9%)	7/30 (23.3%)	14/29 (48.3%)
Not Hispanic or Latino	15/104 (14.4%)	114/218 (52.3%)	116/212 (54.7%)	8/101 (7.9%)	83/201 (41.3%)	103/199 (51.8%)
Missing	0/1 (0%)	2/4 (50.0%)	3/4 (75.0%)	--	--	--
Region						
North America	13/88 (14.8%)	74/176 (42.1%)	85/176 (48.3%)	8/84 (9.5%)	49/166 (29.5%)	75/165 (45.5%)

Europe	6/38 (15.8%)	52/76 (68.4%)	51/77 (66.2%)	1/34 (2.9%)	41/65 (63.1%)	42/63 (66.7%)

Source: reviewer analysis

Data Quality and Integrity

The applicant identified one site in Study 304 (Site 461; 41 subjects) as having serious noncompliance with the protocol and accepted Good Clinical Practice source documentation. Thus, the applicant removed the data from Site 461 in the efficacy analyses. Data from this site were included in safety and PK analyses. The removal of this site from the efficacy analyses did not impact the conclusions of the primary endpoint.

Efficacy Results – Secondary and other relevant endpoints

The protocol specified three key secondary endpoints (EASI 75, ≥4-point improvement on Itch NRS, ≥6-point improvement on PROMIS Sleep Disturbance). The applicant specified a fourth secondary endpoint in the SAP (PROMIS Sleep Impairment). See the Statistical Analysis Plan section above for a description of how multiplicity was controlled across the secondary endpoints. The Itch NRS success endpoint was analyzed among subjects who had a baseline score ≥4, in order to include only subjects capable of demonstrating at least a 4-point improvement from baseline. Similarly, the PROMIS endpoints were intended to include only subjects capable of demonstrating at least a 6-point improvement from baseline. However, the SAP noted that subjects with baseline ≥6 would be included, which fails to take into account that because the PROMIS scores range from 8 to 40 (sum of 8 items measured from 1 to 5), rather than having a minimum score of 0, the applicant's analysis includes subjects who were not capable of demonstrating a 6-point improvement. To include only subjects capable of demonstrating a 6-point improvement, this reviewer conducted analyses using only subjects with baseline scores ≥14. Missing data was imputed using non-responder imputation for all key secondary endpoints. The results for Study 304 exclude the subjects from Site 461.

The results for EASI 75 were similar to the results for the IGA success endpoint, and the results were statistically significant for both doses in both studies. However, the protocols did not require a minimum value for the EASI scale at baseline, and subjects had EASI scores as low as 0.6 at baseline. It may be difficult to interpret a 75% reduction for such small baseline values. However, because this endpoint was statistically significant, the endpoints further down the hierarchy can also be evaluated.

The improvement on the Itch NRS endpoint also demonstrated statistical significance for both doses in both studies, and the results were similar to the results for the IGA success endpoint.

Considering the analysis for the improvement on the PROMIS sleep scales, the results for the 6-point improvement on the PROMIS Sleep Disturbance were similar for both the

analysis provided by the applicant (using all subjects with a recorded baseline score) and the probable intended analysis (using subjects with a baseline scores ≥14). The results were statistically significant in Study 303 for both doses (p<0.025), but neither dose was statistically significant for the endpoint in Study 304. See Table 14. Thus, the PROMIS Sleep Impairment endpoint could be evaluated in Study 303, but not Study 304. Improvement in the PROMIS Sleep Impairment endpoint was not statistically significant in Study 303 (the p-values for both doses would need to be <0.05 or the smaller p-value would need to be <0.025). (b) (4)

(b) (4)

Table 14 –Secondary Endpoint Results

	Study 303			Study 304		
	Vehicle N=126	Ruxo 0.75% N=252	Ruxo 1.5% N=253	Vehicle N=118	Ruxo 0.75% N=231	Ruxo 1.5% N=228
EASI75	13 (24.6%)	141 (56.0%)	157 (62.1%)	17 (14.4%)	119 (51.5%)	141 (61.8%)
p-value		<0.0001	<0.0001		<0.0001	<0.0001
Treatment diff. (95% CI)		31.3% (21.7%, 41.0%)	37.5% (28.0%, 47.0%)		37.3% (28.3%, 46.3%)	47.5% (38.6%, 56.4%)
≥4 imp. on itch NRS[a]	N=78 12 (15.4%)	N=156 63 (40.4%)	N=161 84 (52.2%)	N=80 13 (16.3%)	N=157 67 (42.7%)	N=146 74 (50.7%)
p-value		0.0002	<0.0001		<0.0001	<0.0001
Treatment diff. (95% CI)		24.2% (13.0%, 35.4%)	36.7% (25.5%, 48.0%)		27.7% (16.6%, 38.3%)	35.8% (24.4%, 47.2%)
≥6 imp. on PROMIS Sleep Disturbance	N=116 11 (9.5%)	N=233 49 (21.0%)	N=238 53 (22.3%)	N=110 21 (19.1%)	N=213 44 (20.7%)	N=211 54 (25.6%)
Applicant's analysis[b] p-value		0.0081	0.0039		0.8553	0.2539
Probable Intended analysis[c] p-value	(b) (4)			(b) (4)		
≥6 imp. on PROMIS Sleep Impairment	N=114 15 (13.2%)	N=233 47 (20.2%)	N=245 53 (21.6%)	N=111 15 (13.5%)	N=215 43 (20.0%)	N=212 49 (23.1%)
Applicant's analysis[b] p-value		0.1421	0.0746		0.1784	0.0472
Probable Intended analysis[c] p-value	(b) (4)			(b) (4)		

[a] Among subjects with baseline ≥4
[b] Among subjects with baseline ≥6
[c] Among subjects with baseline ≥14
CI = Confidence interval
Study 304 results exclude subjects from Site 461

Source: pg 64 and 65 of Study Report 303 and pg 64 and 65 of Study Report 304 and reviewer analysis.

Dose/Dose Response

Both the 0.75% and 1.5% doses of ruxolitinib demonstrated efficacy relative to vehicle. Efficacy results were either similar on the two doses or slightly better on the 1.5% dose for the primary and secondary endpoints in the two studies. The applicant is seeking approval for the 1.5% dose only.

Additional Analyses Conducted on the Individual Trial

Approximately 20% of subjects enrolled in Studies 303 and 304 were age 12 to 17 years, 123 subjects in Study 303 (including 47 subjects on the ruxolitinib 1.5% arm) and 122 subjects in Study 304 (including 45 subjects on the ruxolitinib 1.5% arm). Because the long-term safety study is still ongoing, there are limited long-term data available. Efficacy results by age group (12 to 17 years and 18 years and older) are presented in Table 15. The results in adult subjects are similar to the results in the overall population.

Table 15 – Efficacy Endpoints by Age Group

	Study 303			Study 304		
	Vehicle N=126	Ruxo 0.75% N=252	Ruxo 1.5% N=253	Vehicle N=118	Ruxo 0.75% N=231	Ruxo 1.5% N=228
IGA Success						
12- 17 years Treatment diff. (95% CI)	5/23 (21.7%)	29/53 (54.7%) 33.4% (11.5%, 55.4%)	24/47 (51.1%) 29.7% (7.2%, 52.1%)	1/20 (5.0%)	21/53 (39.6%) 33.2% (17.1%, 49.3%)	20/40 (50.0%) 42.7% (24.6%, 60.9%)
≥18 years Treatment diff. (95% CI)	14/103 (13.6%)	97/199 (48.7%) 35.8% (26.6%, 45.0%)	11/206 (54.4%) 41.0% (31.8%, 50.2%)	8/98 (8.2%)	69/178 (38.8%) 31.1% (22.2%, 39.9%)	97/188 (51.6%) 44.0% (35.2%, 52.8%)
EASI 75						
12- 17 years Treatment diff. (95% CI)	12/23 (52.2%)	30/47 (63.8%) 11.5% (-12.3%, 35.3%)	34/53 (64.2%) 12.4% (-11.2%, 36.0%)	3/20 (15.0%)	24/53 (45.3%) 28.7% (8.1%, 49.2%)	23/40 (57.5%) 39.1% (16.6%, 61.7%)
≥18 years Treatment diff. (95% CI)	19/103 (18.5%)	107/199 (53.77%) 35.3% (25.1%, 45.6%)	127/206 (61.7%) 43.2% (33.3%, 53.2%)	14/98 (14.3%)	95/178 (53.4%) 39.3% (29.2%, 49.3%)	118/188 (62.8%) 48.8% (39.0%, 58.5%)
Itch NRS						
12- 17 years Treatment diff. (95% CI)	3/12 (25.0%)	11/30 (36.7%) 0.6% (-29.7%, 30.9%)	16/28 (57.1%) 32.6% (0.4%, 64.7%)	1/11 (9.1%)	13/28 (46.4%) 33.2% (10.1%, 56.4%)	9/20 (45.0%) 37.7% (9.4%, 66.0%)
≥18 years Treatment diff. (95% CI)	9/66 (15.4%)	52/126 (41.3%) 26.9% (14.7%, 39.1%)	68/133 (51.1%) 37.3% (25.2%, 49.5%)	12/69 (17.4%)	54/129 (41.9%) 25.6% (13.2%, 38.0%)	65/126 (51.6%) 35.3% (22.8%, 47.9%)

CI = Confidence interval

Study 304 results exclude subjects from Site 461
Source: reviewer analysis.

8.1.3. Integrated Assessment of Effectiveness

Efficacy results for the primary endpoint of IGA success and the secondary endpoints of EASI 75 and ≥4-point improvement on the Itch NRS were consistent across Studies 303 and 304. The treatment effects were robust across different ways of handling missing data. Efficacy was not demonstrated for the secondary endpoints based on the PROMIS Short Form- Sleep Disturbance (8b) and Sleep Impairment (8a) scales. See Table 16.

Table 16 – Primary and Key Secondary Efficacy Results

	Study 303			Study 304		
	Vehicle N=126	Ruxo 0.75% N=252	Ruxo 1.5% N=253	Vehicle N=118	Ruxo 0.75% N=231	Ruxo 1.5% N=228
IGA Success p-value	19 (15.1%)	126 (50.0%) <0.0001	136 (53.8%) <0.0001	9 (7.6%)	90 (39.0%) <0.0001	117 (51.3%) <0.0001
EASI75 p-value	13 (24.6%)	141 (56.0%) <0.0001	157 (62.1%) <0.0001	17 (14.4%)	119 (51.5%) <0.0001	141 (61.8%) <0.0001
≥4 imp. on itch NRS p-value	N=78 12 (15.4%)	N=156 63 (40.4%) 0.0002	N=161 84 (52.2%) <0.0001	N=80 13 (16.3%)	N=157 67 (42.7%) <0.0001	N=146 74 (50.7%) <0.0001

Source: Reviewer analysis.

8.1.4 Clinical Outcomes Assessments Findings

8.1.4.1 EXECUTIVE SUMMARY

In this submission, the applicant is seeking approval of ruxolitinib for the treatment of atopic dermatitis (AD). The Applicant proposes specific targeted clinical outcome assessment (COA)-related labeling claims from two double-blind, randomized, vehicle-controlled pivotal trials of identical design (Studies INCB 18424-303 and 18424-304; from here on referred to as Studies 303 and -304) in adolescent and adult patients with AD. To support these claims, the applicant submitted a COA evidence dossier. The primary objective of this review is to evaluate from a COA perspective if the submitted information supports the COA-related labeling claims.

The ranked secondary efficacy patient-reported outcome (PRO) endpoints proposed for labeling are:

- Proportion of participants with a ≥ 4-point improvement in the Itch-Numeric Rating Scale (NRS) score from baseline to Week 8 (A copy of the instrument is in Appendix A)

- (b) (4)

The data from Studies 303 and -304 demonstrated that ruxolitinib had statistically significant improvements in itch as measured by the Itch-NRS compared with vehicle. (b) (4)

From a COA perspective, the Itch NRS is adequate to support labeling claims.

(b) (4)

(b) (4)

8.1.4.2 **REVIEW CONCLUSIONS**

Itch NRS

The Itch NRS was reviewed for content validity and the other measurement properties. The Itch NRS is adequate to support labeling claims in this context of use as the instrument is:

- appropriate for measurement of itch (at its worst);
- validly and reliably measures itch (a clinically relevant and important concept to patients);
- and data can be communicated in labeling in a way that is accurate, interpretable and not misleading.

Further, the magnitude of the statistically significant treatment effect appears clinically meaningful to patients. A 4-point improvement in the 11-point Itch NRS has been documented to be a meaningful improvement to patients.

(b) (4)

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(b) (4)

8.1.4.3 RECOMMENDATIONS FOR FUTURE STUDIES

(b) (4)

8.2. Review of Safety

8.2.1. Safety Review Approach

The Applicant provided integrated safety analyses from 3 data pools:

- Pool 1: The *"Phase 3, Atopic Dermatitis Vehicle-Controlled Population" (Phase 3 VC population)* was the primary safety analysis pool and consisted of data from the Phase 3 AD trials (303 and 304) through Week 8, the vehicle-controlled (VC) period. The 2 identical Phase 3 trials enrolled 1249 subjects, and during the VC period, 500 subjects received the 0.75% concentration, 499 received the 1.5% concentration, and 250 received vehicle. Subjects applied study treatment twice daily (BID).

- Pool 2: The *"Phase 2/3 Atopic Dermatitis Population" (Phase 2/3 population)* consisted of pooled safety data through Week 52 from the Phase 3 studies (303 and 304), during which subjects applied study treatment intermittently (i.e., as needed) and from the Phase 2 dose-ranging study (206). This pool consisted of 1544 subjects, 857 of whom applied ruxolitinib cream 1.5% BID.

Study 206 enrolled adults and was a randomized, double-blind, vehicle- and active (triamcinolone acetonide cream, 0.1%)-controlled study which evaluated ruxolitinib cream 0.15%, 0.5%, and 1.5% applied once daily (QD) and 0.75% and 1.5% applied

BID. Subjects in the ruxolitinib and the vehicle treatment groups applied study product for 8 weeks. Subjects in the 1.5% BID group applied product for an additional 4 weeks as needed (open-label). The triamcinolone acetonide cream group applied product BID for 4 weeks then vehicle for 4 weeks.

The Applicant did not include a pool that consisted only of data through week 52 from the Phase 3 studies.

- Pool 3: The *"All Ruxolitinib Cream Population"* was the largest pool, consisting of data from 1942 subjects. Pool 3 was comprised of safety data pooled across clinical development programs i.e., all indications (AD, psoriasis, alopecia areata, and vitiligo) and all ruxolitinib cream concentrations and dosing regimens. However, this pool did not include data from the maximum use study (103) or the local safety studies (104, 105, 106, 107, and 108).

  See Table 17 for the pooled populations and treatment groups.

  Per the note attached to Table 4 of the Integrated Summary of Safety, the "*safety population* (emphasis added) includes all participants who applied the study drug at least once. Treatment groups for the safety population were determined according to the actual treatment the participant applied on Day 1 regardless of the treatment assignment at randomization. For participants who crossed over to different treatment group(s), Day 1 is the first application date in the specific period."

Table 17 Pooled Populations and Treatment Groups*

Pooled Population	Studies	Treatment Groups/Columns (No. of Participants)	Comments
Pool 1: Phase 3 Atopic Dermatitis Vehicle-Controlled Population (N = 1249)	INCB 18424-303 and -304	• Vehicle Cream BID (250) • Ruxolitinib 0.75% Cream BID (500) • Ruxolitinib 1.5% Cream BID (499) • Ruxolitinib Cream Total (999)	Safety data are summarized for the VC period (Day 1 through Week 8) only.
Pool 2: Phase 2/3 Atopic Dermatitis Population (N = 1544)	INCB 18424-206, -303, and -304	• Vehicle cream BID (302) • Ruxolitinib 0.15% Cream QD (51) • Ruxolitinib 0.5% Cream QD (51) • Ruxolitinib 0.75% Cream BID (601) • Ruxolitinib 1.5% Cream QD (51) • Ruxolitinib 1.5% Cream BID (857) • Ruxolitinib Cream Total (1483)	Safety data are summarized for all study periods. • For participants who crossed over from active control to ruxolitinib cream, only the data from the period with ruxolitinib cream are included. • For participants who crossed over from vehicle cream to ruxolitinib cream, safety data from each period are presented by the treatment regimen for each respective period. • For participants who applied ruxolitinib cream at different strengths and/or application frequencies in different periods of a study (eg, ruxolitinib 0.15% cream QD during the VC and ruxolitinib 1.5% cream BID during the open-label period), safety data from each period are presented by ruxolitinib treatment regimen for each respective period.
Pool 3: All Ruxolitinib Cream Population (N = 1942)	INCB 18424-102 (Cohorts 1 and 2 only), -201, -202, -203, -204, -206, -211, -303, and -304	• Ruxolitinib 0.15% Cream QD (82) • Ruxolitinib 0.5% Cream QD (153) • Ruxolitinib 0.5% Cream BID (10) • Ruxolitinib 1.0% Cream QD (55) • Ruxolitinib 0.75% Cream BID (601) • Ruxolitinib 1.5% Cream QD (149) • Ruxolitinib 1.0% Cream BID (5) • Ruxolitinib 1.5% Cream BID (1113) • Ruxolitinib Cream Total (1942)	Safety data are summarized for all study periods. • For participants who crossed over from vehicle or active control to ruxolitinib cream, only the data from the period(s) with ruxolitinib cream are included. • For participants who applied ruxolitinib cream at different strengths and/or application frequencies in different periods of a study (eg, ruxolitinib 0.15% cream QD during the VC period and ruxolitinib 1.5% cream BID during the open-label period), safety data from each period are presented by ruxolitinib treatment regimen for each respective period.

*Source: Table 4 Integrated Summary of Safety
Notes: All of the analyses were conducted using the safety population, which includes all participants who applied the study drug at least once. Treatment groups for the safety population were determined according to the actual treatment the participant applied on Day 1 regardless of the treatment assignment at randomization. For participants who crossed over to different treatment group(s), Day 1 is the first application date in the specific period.

Although pooling data from any exposed subjects (irrespective of concentration, frequency, or duration of exposure) may increase the potential for signal detection, it does not allow assessment for correlating potential signals with dose or duration of exposure.

The Applicant also provided analyses of adverse events of interest for oral ruxolitinib and for other JAK inhibitors.

8.2.2. Review of the Safety Database

Overall Exposure

At the time of data cutoff for the NDA (06/22/2020), all subjects in the Phase 3 trials (303 and 304) had either completed the VC period (1119 subjects, 90%) or had discontinued study drug early (130 subjects, 10%). A total of 535 subjects were ongoing in the long-term safety (LTS) phase of the studies (through Week 52), and 321 subjects had completed the studies.

At data cut-off date for the NDA, 597 subjects were ongoing in clinical studies: 303, 304 and 211 (vitiligo).

Table 18 presents the exposures for the Phase 3 VC population through Week 8.

Table 18 Summary of Exposure (Phase 3 Atopic Dermatitis Vehicle-Controlled Population)*

Variable	Vehicle Cream BID (N = 250)	Ruxolitinib Cream Regimen		Total (N =1249)
		0.75% BID (N = 500)	1.5% BID (N = 499)	
Duration of treatment (days)				
Mean (SD)	51.12 (13.889)	54.48 (11.357)	55.34 (9.816)	54.15 (11.443)
Median	56.00	56.00	56.00	56.00
Min, max	1.0, 76.0	1.0, 151.0	1.0, 100.0	1.0, 151.0
Total weight of medication applied (grams)				
Mean (SD)	252.19 (219.393)	251.69 (201.950)	232.94 (189.809)	244.30 (200.930)
Median	192.63	194.07	172.86	186.30
Min, max	-78.3, 1020.4	-163.3, 998.1	-136.5, 956.5	-163.3, 1020.4

Average weight of medication applied daily (grams)				
Mean (SD)	8.13 (27.379)	7.64 (31.542)	6.83 (22.243)	7.41 (27.296)
Median	3.84	3.60	3.13	3.45
Min, max	-1.1, 293.2	-2.8, 503.9	-2.4, 222.0	-2.8, 503.9

*Source: Table 6 of Summary of Clinical Safety

Table 19 presents the longer exposures for study subjects in the AD program (Phase 2/3 Population). The exposures for ≥ 24 weeks reflect the Phase 3 studies, as subjects in study 206 who were treated with the 1.5% strength had a maximum exposure of 12 weeks. At the time of submission of the NDA, the numbers of subjects exposed to the 1.5% product was somewhat above the minimum number recommended in ICH E1A for the 6 months and one-year time periods.

Table 19 Summary of Ruxolitinib Cream Exposure (Phase 2/3 Atopic Dermatitis Population)*

Variable	Vehicle Cream BID (N =	Ruxolitinib Cream Regimen					Total[a] (N =1544)
		0.15% QD (N = 51)	0.5% QD (N = 51)	0.75% BID (N = 601)	1.5% QD (N = 51)	1.5% BID (N = 857)	
Duration of treatment (days)[b]							
N	302	51	51	601	51	857	1544
Mean (SD)	50.85	54.88	51.61	250.57	55.51	197.09	222.31
Median	56.00	56.00	56.00	288.00	56.00	251.00	271.00
Min, max	1.0, 76.0	9.0, 83.0	1.0, 65.0	1.0, 419.0	29.0, 69.0	0, 403.0	1.0, 419.0
Categorical summary duration of treatment (weeks)							
< 8 weeks	64 (21.2)	6 (11.8)	11 (21.6)	50 (8.3)	7 (13.7)	240 (28.0)	170 (11.0)
≥ 8 to < 24 weeks	238 (78.8)	45 (88.2)	40 (78.4)	86 (14.3)	44 (86.3)	127 (14.8)	410 (26.6)
≥ 24 to < 52 weeks	0	0	0	353 (58.7)	0	365 (42.6)	674 (43.7)
≥ 52 to < 104 weeks	0	0	0	112 (18.6)	0	125 (14.6)	290 (18.8)
Total weight of medication applied (g)							
N	302	51	51	601	51	857	1544
Mean (SD)	264.50 (237.151)	366.22 (324.630)	333.36 (271.974)	785.31 (615.032)	388.83 (339.171)	594.45 (544.346)	723.31 (597.433)
Median	197.88	259.50	262.00	596.50	229.70	441.23	542.63
Min, max	-78.3,	24.4,	0, 1197.5	-148.7,	23.8,	0, 3307.6	-148.7,
Person-years of	42.04	7.66	7.21	412.30	7.75	462.44	897.34

*Source: Table 7 of Summary of Clinical Safety

[a] Participants who switched treatments are counted once in each treatment group. The total column presents exposure to any study drug treatment including vehicle.

[b] Duration of treatment is defined as the duration from the first application of study drug to the last application of study drug. Scheduled visit windows were applied in mapping cutoff visits.

With submission of the 4-month safety update, the numbers of subjects for the referenced time periods (6 months and one year) were 203 and 285, respectively; see Table 20.

Table 20 Summary of Ruxolitinib Cream Exposure from 4-Month Safety Update (Phase 2/3 Atopic Dermatitis Population)*

Variable	Vehicle Cream BID (N = 302)	Ruxolitinib Cream Regimen					Total[a] (N = 1544)
		0.15% QD (N = 51)	0.5% QD (N = 51)	0.75% BID (N = 601)	1.5% QD (N = 51)	1.5% BID (N = 857)	
Duration of treatment (days)[b]							
n	302	51	51	601	51	857	1544
Mean (SD)	50.85 (14.190)	54.88 (10.033)	51.61 (13.967)	268.56 (123.562)	55.51 (5.416)	210.22 (148.447)	236.61 (140.431)
Median	56.00	56.00	56.00	327.00	56.00	268.00	315.50
Min, max	1.0, 76.0	9.0, 83.0	1.0, 65.0	1.0, 419.0	29.0, 69.0	0, 434.0	1.0, 469.0
Categorical summary duration of treatment (n [%])							
< 8 weeks	64 (21.2)	6 (11.8)	11 (21.6)	50 (8.3)	7 (13.7)	240 (28.0)	170 (11.0)
≥ 8 to < 24 weeks	238 (78.8)	45 (88.2)	40 (78.4)	90 (15.0)	44 (86.3)	129 (15.1)	415 (26.9)
≥ 24 to < 52 weeks	0	0	0	190 (31.6)	0	203 (23.7)	286 (18.5)
≥ 52 to < 104 weeks	0	0	0	271 (45.1)	0	285 (33.3)	673 (43.6)
Total weight of medication applied (g)							
n	302	51	51	601	51	857	1544
Mean (SD)	264.50 (237.151)	366.22 (324.630)	333.36 (271.974)	750.46 (653.325)	388.83 (339.171)	569.72 (563.435)	696.02 (622.973)
Median	197.88	259.50	262.00	542.46	229.70	385.99	487.00
Min, max	−78.3, 1281.0	24.4, 1657.1	0, 1197.5	−148.7, 4872.5	23.8, 1261.4	0, 3411.9	−148.7, 4872.5
Person-years of exposure	42.04	7.66	7.21	441.91	7.75	493.25	957.76

*Source: Table 6 of 4-Month Safety Update
[a] Participants who switched treatments are counted once in each treatment group. The total column presents exposure to any study drug treatment including vehicle. b Duration of treatment is defined as the duration from the first application of study drug to the last application of study drug. Scheduled visit windows were applied in mapping cutoff visits.

Relevant characteristics of the safety population:

Baseline demographic and disease characteristics of the Phase 3 population were generally similar cross treatment groups. See Tables 21 and 22.

Table 21 Summary of Demographic Characteristics (Phase 3 Atopic Dermatitis Vehicle-Controlled Population)*

Variable	Vehicle Cream BID (N = 250)	Ruxolitinib Cream Regimen		Total (N =1249)
		0.75% BID (N = 500)	1.5% BID (N = 499)	
Age (years)				
n	250	500	499	1249
Mean (SD)	37.0 (18.56)	36.3 (18.75)	34.7 (17.60)	35.8 (18.27)
Median	34.0	33.0	31.0	32.0
Min, max	12, 82	12, 85	12, 85	12, 85
Age group, n (%)				
12-17 years	45 (18.0)	108 (21.6)	92 (18.4)	245 (19.6)
18-64 years	179 (71.6)	342 (68.4)	368 (73.7)	889 (71.2)
≥ 65 years	26 (10.4)	50 (10.0)	39 (7.8)	115 (9.2)
Sex, n (%)				
Male	91 (36.4)	196 (39.2)	191 (38.3)	478 (38.3)
Female	159 (63.6)	304 (60.8)	308 (61.7)	771 (61.7)
Race, n (%)				
White/Caucasian	170 (68.0)	345 (69.0)	355 (71.1)	870 (69.7)
Black or African American	61 (24.4)	118 (23.6)	113 (22.6)	292 (23.4)
Asian	10 (4.0)	16 (3.2)	20 (4.0)	46 (3.7)
American Indian/Alaska Native	0	2 (0.4)	1 (0.2)	3 (0.2)
Native Hawaiian/Pacific Islander	2 (0.8)	3 (0.6)	0	5 (0.4)
Other	7 (2.8)	16 (3.2)	10 (2.0)	33 (2.6)
Ethnicity, n (%)				
Hispanic or Latino	38 (15.2)	61 (12.2)	67 (13.4)	166 (13.3)
Not Hispanic or Latino	211 (84.4)	435 (87.0)	428 (85.8)	1074 (86.0)
Missing	1 (0.4)	4 (0.8)	4 (0.8)	9 (0.7)
Region, n (%)				
North America	172 (68.8)	342 (68.4)	341 (68.3)	855 (68.5)
Europe	78 (31.2)	158 (31.6)	158 (31.7)	394 (31.5)
BMI (kg/m^2)				
N	250	499	499	1248
Mean (SD)	27.33 (6.494)	27.47 (6.913)	27.74 (7.792)	27.55 (7.196)
Median	26.51	26.18	26.25	26.29
Min, max	13.5, 52.8	15.4, 56.6	15.7, 65.7	13.5, 65.7

*Source: Table 8 of Summary of Clinical Safety

Table 22 Summary of Baseline Disease Characteristics (Phase 3 Atopic Dermatitis Vehicle-Controlled Population)*

Variable	Vehicle Cream BID (N = 250)	Ruxolitinib Cream Regimen		Total (N =1249)
		0.75% BID (N = 500)	1.5% BID (N = 499)	
Years since initial diagnosis of atopic dermatitis				
n	250	500	499	1249
Mean (SD)	20.90 (16.478)	20.02 (15.180)	19.46 (14.332)	19.97 (15.118)
Median	16.5	15.1	16.1	15.8
Min, max	0.8, 79.1	0.1, 68.8	0, 69.2	0, 79.1
Years since onset of current atopic dermatitis episode				
n	249	498	497	1244
Mean (SD)	3.77 (9.314)	3.59 (8.502)	3.27 (7.410)	3.50 (8.256)
Median	0.4	0.4	0.5	0.4
Min, max	0, 78.9	0, 68.8	0, 54.8	0, 78.9
Number of atopic dermatitis episodes/flare-ups over the last 12 months				
n	249	498	498	1245
Mean (SD)	7.28 (25.698)	5.2 (6.661)	5.97 (17.589)	5.93 (16.540)
Median	3.0	3.0	3.0	3.0
Min, max	0, 365.0	0, 60.0	0, 365.0	0, 365.0
Facial involvement of atopic dermatitis, n (%)				
Yes	93 (37.2)	195 (39.0)	197 (39.5)	485 (38.8)
No	157 (62.8)	305 (61.0)	302 (60.5)	764 (61.2)
Total % BSA involvement in current atopic dermatitis episode				
n	250	500	499	1249
Mean (SD)	9.64 (5.470)	9.99 (5.335)	9.62 (5.331)	9.77 (5.360)
Median	8.0	9.0	8.0	8.0
Min, max	3.0, 20.0	3.0, 20.0	3.0, 22.0	3.0, 22.0

Variable	Vehicle Cream BID (N = 250)	Ruxolitinib Cream Regimen		Total (N =1249)
		0.75% BID (N = 500)	1.5% BID (N = 499)	
Itch NRS score				
n	235	467	478	1180
Mean (SD)	5.10	5.16	5.05	5.10
Median	5.20	5.29	5.14	5.20
Min, max	0, 10.0	0, 10.0	0, 10.0	0, 10.0
IGA score, n (%)				
Mild: 2	64 (25.6)	125 (25.0)	123 (24.6)	312 (25.0)

Moderate: 3	186 (74.4)	375 (75.0)	376 (75.4)	937 (75.0)
EASI score				
n	250	500	499	1249
Mean (SD)	7.82 (4.776)	8.11 (4.881)	7.84 (4.765)	7.95 (4.812)
Median	6.9	7.2	7.2	7.1
Min, max	0.6, 26.0	0.6, 30.6	0.8, 27.4	0.6, 30.6
EASI score category, n (%)				
≤ 7	127 (50.8)	249 (49.8)	244 (48.9)	620 (49.6)
> 7	123 (49.2)	251 (50.2)	255 (51.1)	629 (50.4)
History of asthma, n (%)				
Yes	71 (28.4)	137 (27.4)	148 (29.7)	356 (28.5)
No	179 (71.6)	363 (72.6)	351 (70.3)	893 (71.5)
History of allergies, n (%)				
Yes	156 (62.4)	318 (63.6)	314 (62.9)	788 (63.1)
No	94 (37.6)	182 (36.4)	185 (37.1)	461 (36.9)
History of contact dermatitis, n (%)				
Yes	37 (14.8)	57 (11.4)	57 (11.4)	151 (12.1)
No	213 (85.2)	443 (88.6)	442 (88.6)	1098 (87.9)
Common complications of atopic dermatitis, n (%)				
Skin infections requiring antibiotic	31 (12.4)	65 (13.0)	71 (14.2)	167 (13.4)
Eczema herpeticum	4 (1.6)	7 (1.4)	6 (1.2)	17 (1.4)
Other	11 (4.4)	12 (2.4)	13 (2.6)	36 (2.9)
None/NA	208 (83.2)	418 (83.6)	417 (83.6)	1043 (83.5)

*Source: Table 9 of Summary of Clinical Safety

Adequacy of the safety database:

The safety database was adequate in size and extent of drug exposures to permit an assessment of the safety of ruxolitinib 1.5% cream in subjects ≥ 12 years of age with mild-to-moderate AD.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

No issues were identified regarding data integrity or the overall quality of the submission that impacted the safety review.

Categorization of Adverse Events

For the pooled safety analyses, the Applicant coded adverse events (AEs) using MedDRA v 21.1. The Applicant assessed severity of AEs using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.03 in the pivotal Phase 3 studies (303 and 304) and the dose-ranging study (206) i.e., the studies that constituted Pool 2. If a toxicity was not in the CTCAE, the Applicant categorized the AE using the criteria in Table 23.

Table 23 Severity Grades*

Grade	CTCAE Version 3.0	CTCAE Version 4.03
1	Mild	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate activities of daily living.
3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
4	Life-threatening	Life-threatening consequences; urgent intervention indicated.
5[a]	Death related to AE	Death related to AE

*Source: Section 1.3.1 of the Summary of Clinical Safety
[a]There were no on-study deaths in the development program.

The Applicant limited the analyses of AEs to treatment-emergent AEs (TEAEs), defined as any AE that was initially reported between the first application date and 30 days after last application date or worsening of a pre-existing AE during this timeframe. For subjects who crossed over treatments, the end date was 30 days following the date of last application in a period or the date of first application in a subsequent period (whichever came first). The Applicant tabulated TEAEs by MedDRA preferred term (PT) and system organ class (SOC). The Applicant recorded relationship to study treatment as suspected or not suspected in the Phase 3 studies (303 and 304) and the dose-ranging study (206).

Routine Clinical Tests

In the Phase 3 studies, the Applicant conducted testing of serum chemistries and hematology at screening, Day 1 (baseline), and Weeks 2, 4, and 8 during the VC period. During the LTS period, lab testing was done monthly beginning at Week 12 through Week 54 and 30 days after the last dose of study drug. This schedule of testing was acceptable.

8.2.4. **Safety Results**

Deaths

No on-study deaths were reported across the clinical development program.

Serious Adverse Events

A total of 7 serious adverse events (SAEs) occurred in ruxolitinib-treated subjects during the VC period. In the Phase 3 VC population, SAEs were reported as follows:

- vehicle cream- 2 subjects (0.8%),
- ruxolitinib 0.75% cream BID- 4 (0.8%), and
- ruxolitinib 1.5% cream BID- 3 (0.6%).

Pneumonia was the only SAE for which there was more than one report in a treatment group, and both events occurred in the 0.75% group. The other SAE for which there was more than one report was cerebrovascular accident (CVA), and there were 2 reports of this event: one in the 0.75% arm and the other in the 1.5% arm.

See Table 24.

Table 24 Summary of Serious Treatment-Emergent Adverse Events (Phase 3 Atopic Dermatitis Vehicle-Controlled Population)*

MedDRA PT, n (%)	Vehicle Cream BID (N = 250)	Ruxolitinib Cream Regimen		Ruxolitinib Cream Total (N = 999)
		0.75% BID (N = 500)	1.5% BID (N = 499)	
Subjects with any serious TEAE	*2 (0.8)*	*4 (0.8)*	*3 (0.6)*	*7 (0.7)*
Pneumonia	0	2 (0.4)	0	2 (0.2)
Cerebrovascular accident	0	1 (0.2)	1 (0.2)	2 (0.2)
Arrhythmia	0	0	1 (0.2)	1 (0.1)
Acute abdomen	0	0	1 (0.2)	1 (0.1)
Cholangitis	0	0	1 (0.2)	1 (0.1)
Jaundice cholestatic	0	0	1 (0.2)	1 (0.1)
Tooth infection	0	1 (0.2)	0	1 (0.1)
Nasal sinus cancer	1 (0.4)	0	0	0
Dermatitis atopic	1 (0.4)	0	0	0

*Source: Table 15 of the Summary of Clinical Safety
[a]Reported term: atopic dermatitis flare

Generally:

- A causative role for study treatment in the event was not apparent or seemed unlikely due to timing of onset of event relative to onset of study treatment, the nature of the event (e.g., bile duct stent), and/or confounders in the medical history (e.g., the CVAs).
- The SAEs did not result in long or complicated courses or long-term sequelae.
- No action was taken with study treatment or any interruption was short-term e.g., one day.

Information regarding the SAEs that occurred in ruxolitinib-treated subjects is presented below:

- A 53 y/o White male (ruxolitinib 1.5% cream) experienced the SAEs of **cholangitis** and **cholestatic jaundice** on Day 21 (last application of study drug was Day 20). On that day, he had had a bile duct stent removed. That evening he developed fever, chills, and abdominal pain and was transported to the hospital by ambulance. He was admitted on Day 22. On Day 24, a new stent was placed. Study treatment was interrupted that day (Day 24) and resumed on Day 25. He was considered recovered from the SAEs of ascending cholangitis and obstructive jaundice on Day 25.

- A 66 y/o Black female (ruxolitinib 0.75% cream) presented to the emergency department on Day 30 with coughing and left rib pain and was admitted for **pneumonia** the same day (last dose of study drug had been Day 29). Chest x-ray revealed pneumonia and left rib fracture. No additional information was provided regarding the pneumonia. She was treated and was discharged on Day 31. The SAE was reported as resolved on Day 34. No action was taken with study drug.

- A 29 y/o White female (ruxolitinib 1.5% cream) experienced the SAE of **acute abdomen** on Day 10. She had had dull lower abdominal pains for 3 months, with a significant increase apparently in the 3 weeks before the recorded onset of the SAE and was admitted for acute abdomen. She was treated; work-up was apparently negative. She was discharged on Day 12, and the SAE was considered resolved on Day 15. Study treatment was not interrupted, as she continued treatment during her hospitalization.

- 52 y/o White female (ruxolitinib 0.75% cream BID) with obesity (BMI 40.3), hypercholesterolemia, hypertension, and she was a smoker. She had been experiencing dizziness and headache since Day 25. On Day 54, she experienced intermittent dizziness/vertigo, visual changes, and a severe headache and presented to the emergency department and was determined to have experienced a right occipital lobe **cerebrovascular accident (CVA)** that day. Her last application of study drug was Day 32. Workup also revealed bilateral carotid artery stenosis. She was discharged on Day 58, and the SAE was reported as

resolved on Day 86. Note: Per the narrative, she was lost to follow-up on Day 32.

- A 71 y/o White female (ruxolitinib 1.5% cream BID) had a history of hyperlipidemia, type 2 diabetes mellitus, and hypertension. On Day 57, the subject experienced a **CVA**, diagnosed after she lost consciousness (last application of study drug was Day 56). The SAE was reported as resolved with sequelae on Day 60. She also experienced the SAE of "arrhythmia" (not otherwise specified) on an unknown day, but between Days 68 and 81. She discontinued the study on Day 86 due to the CVA.

- A 54 y/o Black female (ruxolitinib 0.75% cream BID) experienced the SAE of **pneumonia**. On Day 30, she developed a severe cough. On Day 31 she "developed pneumonia" and presented to the emergency department and was admitted. No organism was reported. A urine legionella screen was negative. A Gram stain was "suggestive of poor quality," and no culture was done. The only inpatient medical treatments described in the narrative were codeine/guaifenesin and ipratropium-albuterol inhalation therapy. It appears that she was discharged on Day 35. She began oral levofloxacin on Day 36, which was discontinued on Day 42. The SAE was reported as resolved on Day 42. No action was taken with study drug.

- A 33 y/o White female (ruxolitinib 0.75% cream) experienced the SAE of **tooth infection** on Day 42. She developed tooth pain (wisdom tooth) on Day 36, and the tooth was extracted without complications on Day 37. She presented to the dentist on Day 39 with post-extraction pain and was diagnosed with "inflammation and infection." She was prescribed antibiotics, but did not improve and was hospitalized on Day 42, where she received intravenous antibiotics. She improved and was discharged on Day 44. The SAE was considered resolved on Day 50. Study drug application was "unchanged," she ultimately withdrew consent (Day 248) and was discontinued from the study on Day 274.

  The pattern in occurrence of SAEs in the Phase 2/3 population raised no new safety concerns relative to the shorter-term exposure in the Phase 3 VC population. There was one SAE in study 206: a myocardial infarction that occurred in a subject in the triamcinolone/vehicle treatment group. That SAE is not among the SAEs reported for the Phase 2/3 population i.e., all of the SAEs in this pool are from the pivotal studies, 303 and 304. See Table 25.

Table 25 Summary of Serious Treatment-Emergent Adverse Events (Phase 2/3 Atopic Dermatitis Population)*

MedDRA PT, n (%)	Vehicle Cream BID (N = 302)	Ruxolitinib Cream Regimen					Ruxolitinib Cream Total[a] (N = 1483)
		0.15% QD (N = 51)	0.5% QD (N = 51)	0.75% BID (N = 601)	1.5% QD (N = 51)	1.5% BID (N = 857)	
Participants with any serious TEAE	*2 (0.7)*	*0*	*0*	*17 (2.8)*	*0*	*10 (1.2)*	*27 (1.8)*
Pneumonia	0	0	0	3 (0.5)	0	0	3 (0.2)
Cerebrovascular accident	0	0	0	1 (0.2)	0	1 (0.1)	2 (0.1)
Acute abdomen	0	0	0	0	0	1 (0.1)	1 (0.1)
Anaemia postoperative	0	0	0	1 (0.2)	0	0	1 (0.1)
Ankle fracture	0	0	0	1 (0.2)	0	0	1 (0.1)
Arrhythmia	0	0	0	0	0	1 (0.1)	1 (0.1)
Bronchitis	0	0	0	0	0	1 (0.1)	1 (0.1)
Central nervous system lesion	0	0	0	1 (0.2)	0	0	1 (0.1)
Cholangitis	0	0	0	0	0	1 (0.1)	1 (0.1)
Cholecystitis infective	0	0	0	0	0	1 (0.1)	1 (0.1)
Cholelithiasis	0	0	0	0	0	1 (0.1)	1 (0.1)
Chronic tonsillitis	0	0	0	0	0	1 (0.1)	1 (0.1)
Colitis	0	0	0	0	0	1 (0.1)	1 (0.1)
Deep vein thrombosis	0	0	0	0	0	1 (0.1)	1 (0.1)
Dyspnoea	0	0	0	0	0	1 (0.1)	1 (0.1)
Femur fracture	0	0	0	1 (0.2)	0	0	1 (0.1)
Humerus fracture	0	0	0	1 (0.2)	0	0	1 (0.1)
Hypovolaemia	0	0	0	0	0	1 (0.1)	1 (0.1)
Jaundice cholestatic	0	0	0	0	0	1 (0.1)	1 (0.1)
Meniscus injury	0	0	0	1 (0.2)	0	0	1 (0.1)
Myocardial infarction	0	0	0	1 (0.2)	0	0	1 (0.1)
Ovarian cyst ruptured	0	0	0	1 (0.2)	0	0	1 (0.1)
Pelvic fracture	0	0	0	1 (0.2)	0	0	1 (0.1)
Pulmonary embolism	0	0	0	0	0	1 (0.1)	1 (0.1)
Pyelonephritis	0	0	0	1 (0.2)	0	0	1 (0.1)
Pyrexia	0	0	0	0	0	1 (0.1)	1 (0.1)
Radius fracture	0	0	0	1 (0.2)	0	0	1 (0.1)
Rib fracture	0	0	0	1 (0.2)	0	0	1 (0.1)
Sepsis	0	0	0	1 (0.2)	0	0	1 (0.1)
Serositis	0	0	0	0	0	1 (0.1)	1 (0.1)
Small intestinal obstruction	0	0	0	1 (0.2)	0	0	1 (0.1)
Substance-induced psychotic disorder	0	0	0	1 (0.2)	0	0	1 (0.1)
Tooth infection	0	0	0	1 (0.2)	0	0	1 (0.1)
Type 2 diabetes mellitus	0	0	0	1 (0.2)	0	0	1 (0.1)
Ulna fracture	0	0	0	1 (0.2)	0	0	1 (0.1)
Dermatitis atopic[b]	1 (0.3)	0	0	0	0	0	0
Nasal sinus cancer	1 (0.3)	0	0	0	0	0	0

*Source: Table 32 Integrated Summary of Safety

In the context of what is known regarding the safety profile of oral ruxolitinib and other JAK inhibitors, additional information is provided below regarding some of SAEs of note that were reported in the Phase 2/3 population:

- An 82 y/o White male who applied vehicle cream BID during the VC period crossed over to ruxolitinib 1.5% cream BID on Day 57. No action was taken with the study drug due to the SAEs of **pyrexia** and **hypovolemia**. On Day 268, the

participant experienced fever of 102.7, shortness of breath (SOB) and weakness after walking to the post office mid-afternoon. The outside temperature was 99 degrees F. On the same day he experienced fever and volume contraction. He was brought to the emergency department and was found to be tachycardic. He was treated for possible sepsis. On Day 270, he was discharged with the diagnoses of pyrexia and hypovolemia. The outcome of the events was recovered/resolved apparently on the same day. The investigator attributed the SAEs to the subject's walking outside when the temperature was 99 degrees F.

- An additional SAE of **pneumonia** was reported during the long-term phase of a Phase 3 study: a 68 y/o male in the 0.75% BID group experienced pneumonia on Day 190. He presented to the emergency department on that day with coughing and shortness of breath and was hospitalized. He was treated and discharged on Day 193. Study treatment was stopped on Day 190 and resumed on Day 194. He was considered recovered from the event on Day 207.

- A 67 y/o White female who used ruxolitinib 1.5% cream BID during the VC and LTS periods experienced the SAE of **acute bronchitis** on Day 89. She had had shortness of breath that same day, and on an unspecified day presented to the emergency department and was admitted the same day. Treatment included antibiotics, oral steroids, and inhalants. She was discharged (day not specified), and the SAE was considered resolved on Day 98.

- A 20 y/o Black female (ruxolitinib 0.75% cream BID) experienced the SAEs of **pyelonephritis** and **sepsis** on Day 252. Her past medical history included Type 2 diabetes mellitus (last study drug application before onset of the SAEs was on Day 251). On Day 223, she experienced kidney stones, which resolved on Day 250. On Day 252, she experienced pyelonephritis and sepsis and was hospitalized due to pain related to the kidney stones. On Day 256, a ureteral stent was placed, and she was discharged the same day. Both SAEs were considered resolved on Day 257.

- A 26 y/o White male (ruxolitinib 1.5% cream BID) with "prolonged" **chronic tonsillitis** experienced worsening of the condition and had a tonsillectomy, both on Day 65. The SAE was considered resolved on Day 67. No action was taken with the study drug.

- A 50 y/o male ("Native Hawaiian or other Pacific Islander") in the vehicle cream to ruxolitinib 0.75% cream BID group experienced a **myocardial infarction** on Day 203 and was hospitalized. His past medical history included "blood cholesterol Increased," type 2 diabetes mellitus, and hypertension. His BMI was 33.4 kg/m^2 at baseline. On Day 205, he underwent successful coronary artery bypass graft surgery and the myocardial infarction was considered resolved the same day. He withdrew consent on Day 356 and was discontinued on Day 399 (his last application of study drug was on Day 175).

- A 61 y/o male White (ruxolitinib 1.5% cream BID) with a history of **deep vein thrombosis** (DVT) experienced the SAEs of DVT on Day 145 and **pulmonary embolism** (PE) on Day 156. On an unspecified date, he had pain in the left leg (popliteal region). He presented to his physician on Day 154 with leg pain and leg edema. On Day 155, venous Doppler ultrasound of the left leg showed DVT of the femoral and popliteal veins. He experienced "multiple bilateral emboli" on Day 156. He received anticoagulant therapy, but refused hospitalization. He was still recovering from the SAEs as of Day 367. No action was taken with the study drug due to either of the SAEs.

Dropouts and/or Discontinuations Due to Adverse Effects

The highest incidence of discontinuations due to TEAEs in the Phase 3 VC population was in the vehicle group (8 subjects; 3.2%), and the most commonly TEAE reported was "dermatitis atopic," which seemingly represents worsening of the disease state. The proportions of subjects who discontinued from the ruxolitinib treatment groups were the same between the 0.75% and 1.5% arms at 0.8% (4 subjects in each group), and no TEAE was reported in more than one subject as the event leading to discontinuation in either active treatment arm. The cerebrovascular accident was the only SAE that led to discontinuation of study treatment. All TEAEs that led to discontinuation of treatment were reported as resolved or recovered except for "dry skin," and the outcome for this event was unknown. See Table 26.

Table 26 Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of Study Drug (Phase 3 Atopic Dermatitis Vehicle-Controlled Population)*

MedDRA PT, n (%)	Vehicle Cream BID (N =	Ruxolitinib Cream Regimen		Ruxolitinib Cream Total (N = 999)
		0.75% BID (N = 500)	1.5% BID (N = 499)	
Participants with any TEAE leading to discontinuation	*8 (3.2)*	*4 (0.8)*	*4 (0.8)*	*8 (0.8)*
Colitis ulcerative	0	1 (0.2)	0	1 (0.1)
Cerebrovascular accident	0	0	1 (0.2)	1 (0.1)
Asthma	0	1 (0.2)	0	1 (0.1)
Dermatitis atopic[a]	5 (2.0)	0	1 (0.2)	1 (0.1)
Dry skin	0	1 (0.2)	0	1 (0.1)
Papule	0	0	1 (0.2)	1 (0.1)
Pruritus generalized	0	0	1 (0.2)	1 (0.1)
Rash macular	0	1 (0.2)	0	1 (0.1)
Urticaria	0	0	1 (0.2)	1 (0.1)
Application site pain[b]	2 (0.8)	0	0	0
Application site swelling	1 (0.4)	0	0	0
Hepatic enzyme increased	1 (0.4)	0	0	0

Nasal sinus cancer	1 (0.4)	0	0	0

* Source: Table 34 Integrated Summary of Safety
[a] Reported terms of atopic dermatitis flare, atopic dermatitis exacerbation, exacerbation of atopic dermatitis, worsening of atopic dermatitis.
[b] Event LLT included application site burning.

The incidence of TEAEs leading to treatment interruption in the VC period of the Phase 3 trials was highest in the vehicle group, at 3.6% (9 subjects). Between the active treatment groups, the incidence was higher in the 1.5% group (8 subjects; 1.6%) compared to the 0.75% group (4 subjects; 0.8%). Cholangitis and cholestatic jaundice were the only SAEs that resulted in interruption of treatment. Urticaria and application site irritation were the only TEAES that were reported in more than one subject. The 2 reports of urticaria were both reported in ruxolitinib groups, one report each in the 0.75% group and 1.5% group (0.2% each). Two of the 3 reports of application site irritation occurred in the 1.5% ruxolitinib group (0.4%), and the 3rd report was in the vehicle arm (0.4%). The reports of neutropenia, herpes simplex and herpes zoster all occurred in the 1.5% group. Neutrophil count decreased was reported in the 0.75% arm. All events that led to interruption of treatment were reported as recovered or resolved, except for hepatocellular injury. See Table 27.

Table 27 Summary of TEAEs Leading to Interruption of Study Drug (Phase 3 Atopic Dermatitis Vehicle-Controlled Population)*

MedDRA PT, n (%)	Vehicle Cream BID (N = 250)	Ruxolitinib Cream Regimen		Ruxolitinib Cream Total (N = 999)
		0.75% BID (N = 500)	1.5% BID (N = 499)	
Number (%) of participants with any TEAE leading to dose interruption	*9 (3.6)*	*4 (0.8)*	*8 (1.6)*	*12 (1.2)*
Application site irritation	1 (0.4)	0	2 (0.4)	2 (0.2)
Urticaria	0	1 (0.2)	1 (0.2)	2 (0.2)
Neutropenia	0	0	1 (0.2)	1 (0.1)
Application site folliculitis	0	1 (0.2)	0	1 (0.1)
Application site papules	0	1 (0.2)	0	1 (0.1)
Cholangitis	0	0	1 (0.2)	1 (0.1)
Differential white blood cell count	0	0	1 (0.2)	1 (0.1)
Hepatocellular injury	0	1 (0.2)	0	1 (0.1)
Herpes simplex	0	0	1 (0.2)	1 (0.1)
Herpes zoster	0	0	1 (0.2)	1 (0.1)
Jaundice cholestatic	0	0	1 (0.2)	1 (0.1)
Neutrophil count decreased	0	1 (0.2)	0	1 (0.1)
White blood cell count increased	0	0	1 (0.2)	1 (0.1)
Dermatitis atopic[a]	3 (1.2)	0	0	0
Application site pruritus	2 (0.8)	0	0	0

Application site pain[b]	1 (0.4)	0	0	0
Dry skin	1 (0.4)	0	0	0
Eczema	1 (0.4)	0	0	0
Erythema	1 (0.4)	0	0	0
Headache	1 (0.4)	0	0	0
Pruritus	1 (0.4)	0	0	0

*Source: Table 35: Integrated Summary of Safety
[a] Reported terms of atopic dermatitis exacerbation worsening of atopic dermatitis.
[b]Event LLTs: application site burning, pain after application

Significant Adverse Events

Adverse events that were assessed as Grade 3 or higher in the Phase 3 VC population are presented in Table 28. The Applicant assessed AE severity using the CTCAE criteria. If the toxicity was not listed in those criteria, the Applicant applied the definition of Grade 3 severity from CTCAE v.4.03: "Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care (activities of daily living)" and other definitions from the CTCAE criteria. See the "Categorization of Adverse Events" section above. Of the TEAEs that were assessed as ≥ Grade 3 severity, two were reported in more than one ruxolitinib-treated subject: Cerebrovascular accident and pneumonia (each reported in two subjects). Investigators considered the following events to be related to study treatment: atopic dermatitis (in the vehicle arm), herpes zoster (1.5% arm), and "papule" (1.5% arm).

Table 28 Summary of Treatment-Emergent Adverse Events of Grade 3 or Higher Severity (Phase 3 Atopic Dermatitis Vehicle-Controlled Population)*

MedDRA PT, n (%)	Vehicle Cream BID (N =	Ruxolitinib Cream Regimen		Ruxolitinib Cream Total (N = 999)
		0.75% BID (N = 500)	1.5% BID (N = 499)	
Participants with any ≥ Grade 3	*3 (1.2)*	*7 (1.4)*	*9 (1.8)*	*16 (1.6)*
Cerebrovascular accident	0	1 (0.2)	1 (0.2)	2 (0.2)
Pneumonia	0	2 (0.4)	0	2 (0.2)
Acute abdomen	0	0	1 (0.2)	1 (0.1)
Anaphylactic shock	0	0	1 (0.2)	1 (0.1)
Arrhythmia	0	0	1 (0.2)	1 (0.1)
Bronchitis	0	0	1 (0.2)	1 (0.1)
Carotid artery stenosis	0	1 (0.2)	0	1 (0.1)
Cholangitis	0	0	1 (0.2)	1 (0.1)
Dermatitis atopic[a]	2 (0.8)	1 (0.2)	0	1 (0.1)
Diabetes mellitus	0	1 (0.2)	0	1 (0.1)
Herpes zoster	0	0	1 (0.2)	1 (0.1)

Jaundice cholestatic	0	0	1 (0.2)	1 (0.1)
Muscle rupture	0	0	1 (0.2)	1 (0.1)
Papule	0	0	1 (0.2)	1 (0.1)
Syncope	0	0	1 (0.2)	1 (0.1)
Tooth infection	0	1 (0.2)	0	1 (0.1)
Upper limb fracture	0	1 (0.2)	0	1 (0.1)
Nasal sinus cancer	1 (0.4)	0	0	0

*Source: Table 14 Summary of Clinical Safety

In the Phase 2/3 population, 65 subjects (4.4%) experienced a TEAE ≥ Grade 3 severity. The 3 reports of bronchitis occurred in ruxolitinib-treated subjects: one in the 0.75% group and 2 in the 1.5% group, and one of these was an SAE. A total of 8 subjects experienced TEAEs ≥ Grade 3 severity that investigators considered to be related to ruxolitinib treatment: herpes zoster, herpes ophthalmic, herpes virus infection, hordeolum, hypertriglyceridemia, and papule (all in one subject each in the ruxolitinib 1.5% cream BID group) and neutropenia (one subject in 0.75% BID group).Table 29 presents those events that occurred in 2 or more subjects.

Table 29 Summary of Treatment-Emergent Adverse Events of Grade 3 or Higher Severity in ≥ 2 Participants in any Treatment Group (Phase 2/3 Atopic Dermatitis Population)*

MedDRA PT, n (%)	Vehicle Cream BID (N = 302)	Ruxolitinib Cream Regimen					Ruxolitinib Cream Total[a] (N = 1483)
		0.15% QD (N = 51)	0.5% QD (N = 51)	0.75% BID (N = 601)	1.5% QD (N = 51)	1.5% BID (N = 857)	
Participants with any ≥ Grade 3 TEAE	*3 (1.0)*	*0*	*1 (2.0)*	*33 (5.5)*	*0*	*31 (3.6)*	*65 (4.4)*
Bronchitis	0	0	0	1 (0.2)	0	2 (0.2)	3 (0.2)
Dermatitis atopic[b]	2 (0.7)	0	0	2 (0.3)	0	1 (0.1)	3 (0.2)
Pneumonia	0	0	0	3 (0.5)	0	0	3 (0.2)
Cerebrovascular accident	0	0	0	1 (0.2)	0	1 (0.1)	2 (0.1)
Diabetes mellitus	0	0	0	2 (0.3)	0	0	2 (0.1)
Influenza	0	0	0	0	0	2 (0.2)	2 (0.1)
Pyelonephritis	0	0	0	1 (0.2)	0	1 (0.1)	2 (0.1)
Syncope	0	0	0	1 (0.2)	0	1 (0.1)	2 (0.1)

*Source: Table 29 Integrated Summary of Safety
[a] Participants who switched to another treatment during the study were only counted once in Total.
[b] Reported terms of atopic dermatitis flare, atopic dermatitis exacerbation, atopic dermatitis aggravated, atopic dermatitis worsening

In the All Ruxolitinib Cream Population, the pattern of TEAEs ≥ Grade 3 in severity was similar to what was observed in the Phase 2/3 Population. The overall frequency of TEAEs in this analysis was higher in the 0.75% group compared to the 1.5% BID; however, the frequency of individual TEAEs was similar between the 2 treatment groups. See Table 30.

Table 30 Summary of Treatment-Emergent Adverse Events of Grade 3 or Higher Severity Occurring in ≥ 2 Participants (All Ruxolitinib Cream Population)*

MedDRA PT, n (%)	Ruxolitinib Cream Regimen								Ruxolitinib Cream Total[a] (N = 1942)
	0.15% QD (N = 82)	0.5% QD (N = 153)	0.5% BID (N = 10)	1.0% QD (N = 55)	0.75% BID (N = 601)	1.5% QD (N = 149)	1.0% BID (N = 5)	1.5% BID (N = 1113)	
Participants with any ≥ Grade 3 TEAE	*0*	*4 (2.6)*	*0*	*0*	*33 (5.5)*	*7 (4.7)*	*0*	*41 (3.7)*	*85 (4.4)*
Bronchitis	0	0	0	0	1 (0.2)	0	0	2 (0.2)	3 (0.2)
Dermatitis atopic[b]	0	0	0	0	2 (0.3)	0	0	1 (0.1)	3 (0.2)
Pneumonia	0	0	0	0	3 (0.5)	0	0	0	3 (0.2)
Syncope	0	0	0	0	1 (0.2)	0	0	2 (0.2)	3 (0.2)
Arthralgia	0	0	0	0	0	0	0	2 (0.2)	2 (0.1)
Cerebrovascular accident	0	0	0	0	1 (0.2)	0	0	1 (0.1)	2 (0.1)
Cholelithiasis	0	0	0	0	0	1 (0.7)	0	1 (0.1)	2 (0.1)
Coronary artery occlusion	0	2 (1.3)	0	0	0	0	0	0	2 (0.1)
Diabetes mellitus	0	0	0	0	2 (0.3)	0	0	0	2 (0.1)
Influenza	0	0	0	0	0	0	0	2 (0.2)	2 (0.1)
Pyelonephritis	0	0	0	0	1 (0.2)	0	0	1 (0.1)	2 (0.1)
Sepsis	0	0	0	0	1 (0.2)	0	0	1 (0.1)	2 (0.1)

*Source: Table 30 Integrated Summary of Safety
[a] Participants who switched to another treatment during the study were only counted once in Total.
[b] Reported terms of atopic dermatitis flare, atopic dermatitis exacerbation, atopic dermatitis aggravated, atopic dermatitis worsening

Treatment Emergent Adverse Events and Adverse Reactions

In the Phase 3 VC Population, 277 subjects (27.7%) experienced at least one AE: 83 (33.2%) in the vehicle group, 145 (29%) in the 0.75% group, and 132 (26.5%) in the 1.5% group.

TEAEs were most frequently reported in the Infections and infestations SOC: vehicle- 17 subjects (6.8%), ruxolitinib 0.75% cream - 68 (13.6%), and ruxolitinib 1.5% cream- 55 (11.0%). Nasopharyngitis was the commonly reported TEAE in this SOC (and overall): vehicle- 2 subjects (0.8%), ruxolitinib 0.75% cream - 15 (3.0%), and ruxolitinib 1.5% cream - 13 (2.6%). Upper respiratory tract infection was the second most commonly reported TEAE in this SOC: vehicle- 5 subjects (2.0%), ruxolitinib 0.75% cream - 7 (1.4%), ruxolitinib 1.5% cream - 12 (2.4%)

TEAES were next most commonly reported in the Skin and subcutaneous disorders SOC: vehicle- 25 subjects (10.0%), ruxolitinib 0.75% cream - 21 (4.2%), and ruxolitinib 1.5% cream - 25 (5.0%). Urticaria was the most commonly reported TEAE in this SOC in ruxolitinib groups: vehicle- 0, ruxolitinib 0.75% cream - 4 (0.8%), and ruxolitinib 1.5% cream - 4 (0.8%).

See Table 31.

Table 31 Adverse Reactions Occurring in ≥ 1% of Subjects Treated with Ruxolitinib 1.5% and at Higher Incidence than Vehicle in the Phase 3 Studies through Week 8*

Adverse Reaction	Vehicle (N=250) n (%)	Ruxolitinib cream	
		0.75% N= 500	1.5% N= 499
*Subjects with any TEAE**	*83 (33)*	*145 (29)*	*132 (27)*
Nasopharyngitis	2 (1)	15 (3)	13 (3)
Diarrhea	1 (< 1)	2(<1)	3 (1)
Bronchitis	0 (0)	3 (1)	4 (1)
Ear infection	0 (0)	1 (< 1)	4 (1)
Eosinophil count increased	0 (0)	0 (0)	4 (1)
Urticaria	0 (0)	4 (1)	4 (1)
Folliculitis	0 (0)	0 (0)	3 (1)
Tonsillitis	0 (0)	1 (< 1)	3 (1)
Rhinorrhea	1 (< 1)	1 (< 1)	3 (1)

*Source: Table 3.2.2.1 Integrated Summary of Safety
Note: Numbers are rounded up, as for presentation in product labeling.

Adverse reactions that occurred in the Phase 3 VC Population in < 1% of subjects in the ruxolitinib 1.5% cream group and none in the vehicle group included: neutropenia, allergic conjunctivitis, pyrexia, seasonal allergy, herpes zoster, otitis externa, Staphylococcal infection, and acneiform dermatitis.

Application Site Reactions

In the Phase 3 VC Population, the overall incidence of application site reactions (ASRs) was highest in the vehicle arm and similar between the 2 ruxolitinib arms. This pattern also applies when individual TEAEs are considered. With the possible exception of folliculitis, all of the ASRs may be disease manifestations of AD. The lower incidences in the active arms may be attributed to drug effect. The overall incidence of ASRs in the active arms was low, and irritancy was not suggested as a significant issue under the intended conditions of use.

Table 32 Summary of Application Site Reactions (Phase 3 Atopic Dermatitis Vehicle-Controlled Population)*

Category MedDRA PT, n (%)	Vehicle Cream BID (N =	Ruxolitinib Cream		Ruxolitinib Cream Total (N = 999)
		0.75% BID (N = 500)	1.5% BID (N = 499)	
Any application site TEAE	*18 (7.2)*	*11 (2.2)*	*8 (1.6)*	*19 (1.9)*
Application site pain[a]	12 (4.8)	3 (0.6)	4 (0.8)	7 (0.7)
Application site pruritus	7 (2.8)	5 (1.0)	1 (0.2)	6 (0.6)
Application site folliculitis	0	2 (0.4)	0	2 (0.2)
Application site irritation	2 (0.8)	0	2 (0.4)	2 (0.2)
Application site dryness	0	0	1 (0.2)	1 (0.1)
Application site erythema	2 (0.8)	1 (0.2)	0	1 (0.1)
Application site exfoliation	0	1 (0.2)	0	1 (0.1)
Application site papules	0	1 (0.2)	0	1 (0.1)
Application site swelling	1 (0.4)	0	0	0

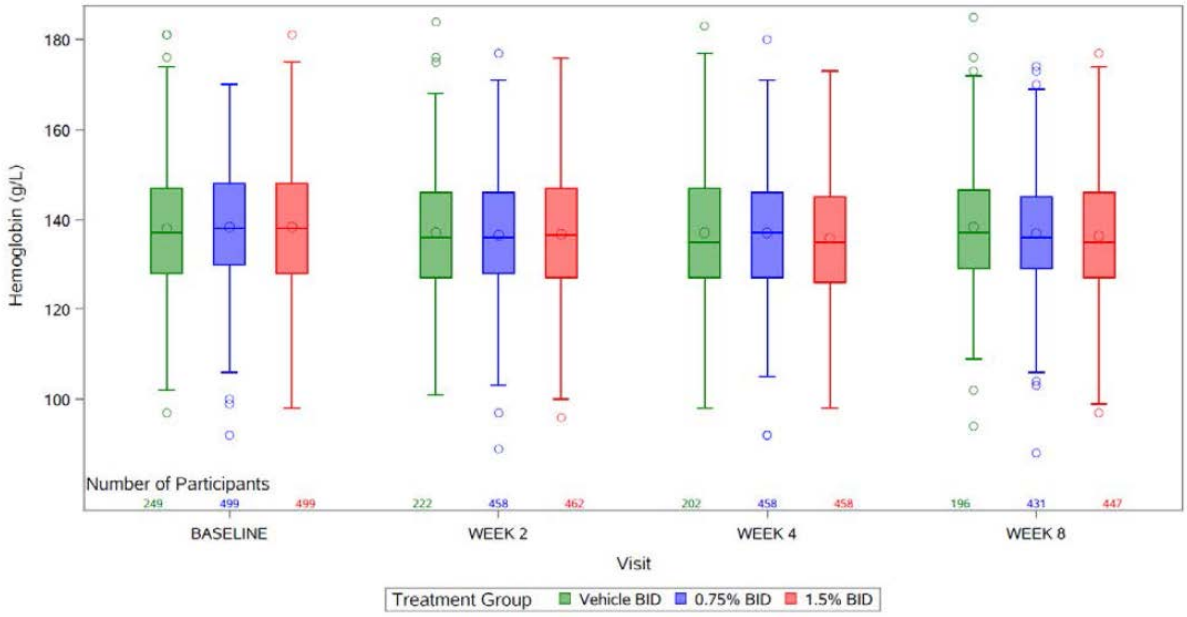
*Source: Table 17 Summary of Clinical Safety
TEAEs were defined as any AE reported for the first time or worsening of a pre-existing event after first application of study drug. Participants were counted only once under each MedDRA PT.
[a] Event LLTs included application site burning, application site stinging, and pain after application

Laboratory Findings

Hemoglobin Levels

Mean hemoglobin levels were similar between the vehicle and both ruxolitinib groups at all visits through Week 8 in the Phase 3 VC population, and a similar pattern was noted in the Phase 2/3 Population, which included evaluation through Week 52. The percent changes in hemoglobin in the Phase 2/3 pool, were similar to what was observed through Week 8, and hemoglobin levels generally remained in the normal range. Additionally, mean hemoglobin levels were similar between the 0.75% and 1.5% BID treatment groups. See Figure 9 regarding hemoglobin levels in the Phase 3 VC population.

Figure 9 Box Plot of Hemoglobin Levels by Visit and Treatment Group (Phase 3 Atopic Dermatitis Vehicle-Controlled Population)*



*Source: Figure 3 Integrated Summary of Safety
Mean values are denoted by the larger "o" symbol.

Through Week 8 i.e., the Phase 3 VC Population, most subjects (~ 95% in all 3 treatment groups) were Grade 0 at baseline. For subjects in the ruxolitinib groups who were categorized as Grade 0 at baseline, ≥ 92% remained Grade 0 post baseline, when the worst post-baseline value was considered. For subjects in the ruxolitinib groups who were categorized as Grade 0 at baseline, the worst post-baseline values resulted in shifts to Grade 1, and this shift was noted in ~ 5% of subjects in each ruxolitinib treatment group. No subjects, in any treatment arm, experienced a post-baseline shift in hemoglobin levels to Grade 3. See Table 33.

Table 33 Shift Summary of Hemoglobin Concentration Values in CTC Grade to the Worst (Low) Abnormal Value (Phase 3 Atopic Dermatitis Vehicle-Controlled Population)*

	Baseline[a]		Worst Postbaseline Value[b]				
	Grade	n (%)	Grade 0	Grade 1	Grade 2	Grade 3	Missing
Vehicle cream BID (N = 250)	Grade 0	238 (95.2)	221 (92.9)	7 (2.9)	3 (1.3)	0	7 (2.9)
	Grade 1	10 (4.0)	4 (40.0)	6 (60.0)	0	0	0
	Grade 2	1 (0.4)	0	0	1 (100.0)	0	0
	Grade 3	0	0	0	0	0	0
	Missing	1 (0.4)	1 (100.0)	0	0	0	0
	Total	250 (100.0)	226 (90.4)	13 (5.2)	4 (1.6)	0	7 (2.8)
Ruxolitinib 0.75% cream BID (N = 500)	Grade 0	475 (95.0)	442 (93.1)	23 (4.8)	0	0	10 (2.1)
	Grade 1	22 (4.4)	4 (18.2)	16 (72.7)	1 (4.5)	0	1 (4.5)
	Grade 2	2 (0.4)	1 (50.0)	0	1 (50.0)	0	0
	Grade 3	0	0	0	0	0	0
	Missing	1 (0.2)	0	0	0	0	1 (100.0)
	Total	500 (100.0)	447 (89.4)	39 (7.8)	2 (0.4)	0	12 (2.4)
Ruxolitinib 1.5% cream BID (N = 499)	Grade 0	477 (95.6)	439 (92.0)	25 (5.2)	0	0	13 (2.7)
	Grade 1	21 (4.2)	2 (9.5)	17 (81.0)	2 (9.5)	0	0
	Grade 2	1 (0.2)	0	1 (100.0)	0	0	0
	Grade 3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	499 (100.0)	441 (88.4)	43 (8.6)	2 (0.4)	0	13 (2.6)

*Source: Table 42 Summary of Clinical Safety

Notes: Grade 0 = Below Grade 1 and any grade in the other direction; Grade 1 = Increase in > 0 to 20 g/L above ULN or above baseline if baseline is above ULN; Grade 2 = Increase in > 20 to 40 g/L above ULN or above baseline if baseline is above

ULN; Grade 3 = Increase in > 40 g/L above ULN or above baseline if baseline is above ULN.

[a] The percentages were calculated using the baseline total as the denominator.

[b] For each row, the percentages were calculated using the number of participants with given grade at baseline as the denominator; worst value on study is the worst grade observed postbaseline for a given participant.

In the Phase 2/3 Population (includes data through Week 52), ~93-95% of subjects across all 3 treatment arms were Grade 0, and for ~90% of subjects in both ruxolitinib groups and ~93% of subjects in the vehicle group, the worst post-baseline value remained in the Grade 0 category. One subject (0.2%) in the ruxolitinib 0.75% group who was Grade 0 at baseline experienced a shift to worst postbaseline value in the Grade 3 category; no subjects in the ruxolitinib 1.5% group or vehicle group experienced this type of shift. However, one subject in the ruxolitinib 1.5% group who was Grade 2 at baseline had a worst post-baseline value in the Grade 3 category. See Table 34.

Table 34 Shift Summary of Hemoglobin Concentration Values in CTC Grade to the Worst (Low) Abnormal Value (Phase 2/3 Atopic Dermatitis Population)*

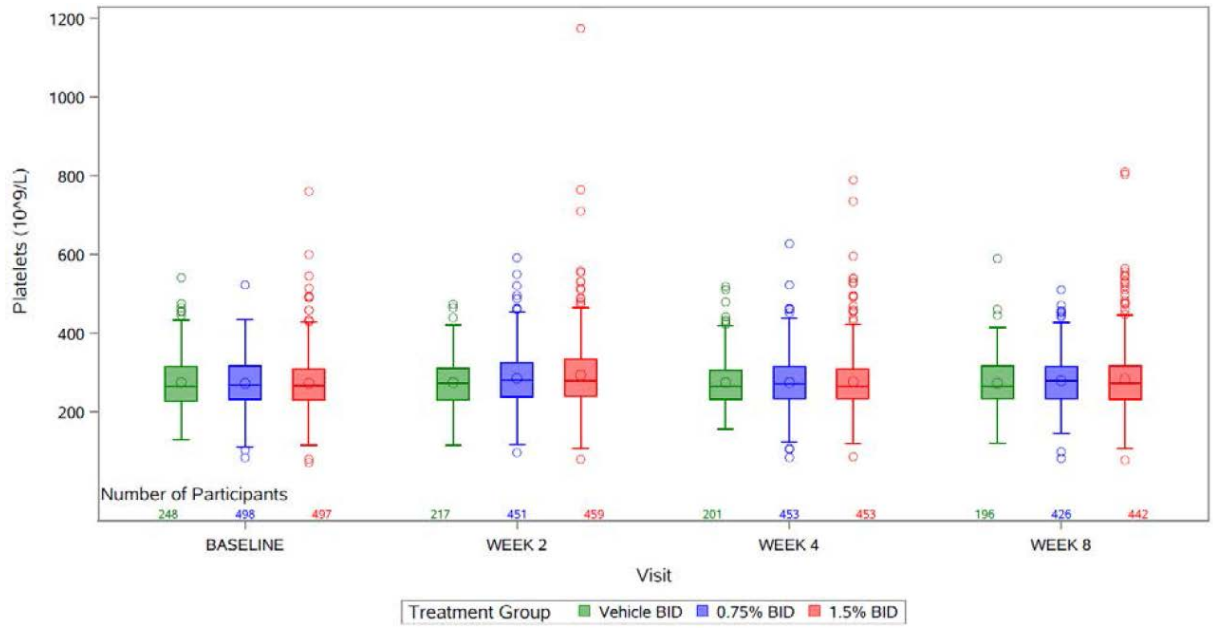
	Baseline[a]		Worst Postbaseline Value[b]				
	Grade	n (%)	Grade 0	Grade 1	Grade 2	Grade 3	Missing
Vehicle cream BID (N = 302)	Grade 0	285 (94.4)	264 (92.6)	10 (3.5)	3 (1.1)	0	8 (2.8)
	Grade 1	15 (5.0)	6 (40.0)	9 (60.0)	0	0	0
	Grade 2	1 (0.3)	0	0	1 (100.0)	0	0
	Grade 3	0	0	0	0	0	0
	Missing	1 (0.3)	1 (100.0)	0	0	0	8 (2.6)
	Total	302 (100.0)	271 (89.7)	19 (6.3)	4 (1.3)	0	0
Ruxolitinib 0.75% cream BID (N = 601)	Grade 0	569 (94.7)	512 (90.0)	46 (8.1)	2 (0.4)	1 (0.2)	8 (1.4)
	Grade 1	25 (4.2)	3 (12.0)	18 (72.0)	3 (12.0)	0	1 (4.0)
	Grade 2	3 (0.5)	1 (33.3)	0	2 (66.7)	0	0
	Grade 3	0	0	0	0	0	0
	Missing	4 (0.7)	1 (25.0)	0	0	0	3 (75.0)
	Total	601 (100.0)	517 (86.0)	64 (10.6)	7 (1.2)	1 (0.2)	12 (2.0)
Ruxolitinib 1.5% cream BID (N = 857)	Grade 0	795 (92.8)	717 (90.2)	66 (8.3)	1 (0.1)	0	11 (1.4)
	Grade 1	57 (6.7)	5 (8.8)	40 (70.2)	11 (19.3)	1 (1.8)	0
	Grade 2	1 (0.1)	0	1 (100.0)	0	0	0
	Grade 3	0	0	0	0	0	0
	Missing	4 (0.5)	0	0	0	0	4 (100.0)
	Total	857 (100.0)	722 (84.2)	107 (12.5)	12 (1.4)	1 (0.1)	15 (1.8)

*Source: Table 43 Summary of Clinical Safety
Notes: Grade 0 = Below Grade 1 and any grade in the other direction; Grade 1 = Increase in > 0 to 20 g/L above ULN or above baseline if baseline is above ULN; Grade 2 = Increase in > 20 to 40 g/L above ULN or above baseline if baseline is above ULN; Grade 3 = Increase in > 40 g/L above ULN or above baseline if baseline is above ULN.
[a] The percentages were calculated using the baseline total as the denominator.
[b] For each row, the percentages were calculated using the number of participants with given grade at baseline as the denominator; worst value on-study is the worst grade observed postbaseline for a given participant.

Platelet Counts

Mean platelet counts were similar across all 3 treatment groups at all visits through Week 8 (Phase 3 VC Population), and a similar pattern was noted in the Phase 2/3 Population, which included evaluation through Week 52. The Applicant observed "small, transient increases in platelet counts" at Week 2 in the ruxolitinib groups in the Phase 3 studies. However, counts remained within the normal range. No trends were noted in platelet counts in the Phase 2/3 Population, and platelet counts generally remained stable and in the normal range. See Figure 10 regarding changes in platelets in the Phase 3 VC Population.

Figure 10 Box Plot of Platelet Counts by Visit and Treatment Group (Phase 3 Atopic Dermatitis Vehicle-Controlled Population)*



*Source: Figure 4 Integrated Summary of Safety
Mean values are denoted by the larger "o" symbol.

Through Week 8, most subjects (~ 97% in all 3 treatment groups) were Grade 0 at baseline. No subjects in any of the 3 treatment groups experienced a shift to a worst post-baseline value greater than Grade 1. The shift from baseline Grade 0 to a worst post-baseline value in the Grade 1 category occurred for 6 subjects in the vehicle group (2.5%), 8 subjects in the 0.75% ruxolitinib group (1.7%), and 3 subjects in the 1.5% ruxolitinib group (0.6%). For subjects in the ruxolitinib groups who were categorized as Grade 0 at baseline, ~96-97%% remained Grade 0 post baseline, when the worst post-baseline value was considered, and this occurred for ~95% of subjects in the vehicle group. See Table 35.

Table 35 Shift Summary of Platelet Count Values in CTC Grade to the Worst (Low) Abnormal Value (Phase 3 Atopic Dermatitis Vehicle-Controlled Population)*

	Baseline[a]		Worst Postbaseline Value[b]					
	Grade	**n (%)**	**Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Missing**
Vehicle cream BID (N = 250)	Grade 0	244 (97.6)	231 (94.7)	6 (2.5)	0	0	0	7 (2.9)
	Grade 1	4 (1.6)	0	3 (75.0)	0	0	0	1 (25.0)
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	2 (0.8)	2 (100.0)	0	0	0	0	0
	Total	250 (100.0)	233 (93.2)	9 (3.6)	0	0	0	8 (3.2)
Ruxolitinib 0.75% cream BID (N = 500)	Grade 0	484 (96.8)	466 (96.3)	8 (1.7)	0	0	0	10 (2.1)
	Grade 1	14 (2.8)	4 (28.6)	9 (64.3)	0	0	0	1 (7.1)
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	2 (0.4)	1 (50.0)	0	0	0	0	1 (50.0)
	Total	500 (100.0)	471 (94.2)	17 (3.4)	0	0	0	12 (2.4)
Ruxolitinib 1.5% cream BID (N = 499)	Grade 0	483 (96.8)	468 (96.9)	3 (0.6)	0	0	0	12 (2.5)
	Grade 1	13 (2.6)	4 (30.8)	8 (61.5)	0	0	0	1 (7.7)
	Grade 2	1 (0.2)	0	1 (100.0)	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	2 (0.4)	1 (50.0)	0	0	0	0	1 (50.0)
	Total	499 (100.0)	473 (94.8)	12 (2.4)	0	0	0	14 (2.8)

*Source: Table 44 Summary of Clinical Safety
[a] The percentages were calculated using the baseline total as the denominator.
[b] For each row, the percentages were calculated using the number of participants with given grade at baseline as the denominator; worst value on study is the worst grade observed postbaseline for a given participant.

In the Phase 2/3 Population (includes data through Week 52), ~97-98% of subjects across all 3 treatment arms were Grade 0 at baseline, and for ~95-96% of subjects in all 3 treatment groups, the worst post-baseline value remained in the Grade 0 category. One subject experienced a post-baseline shift from Grade 0 at baseline to worst post-baseline shift to Grade 3 (0.1%), and that subject was in the ruxolitinib 1.5% group. Otherwise, no subjects in any of the 3 treatment groups experienced a shift to a worst post-baseline value greater than Grade 1. See Table 36.

Table 36 Shift Summary of Platelet Count Values in CTC Grade to the Worst (Low) Abnormal Value (Phase 2/3 Atopic Dermatitis Population)*

	Baseline[a]		Worst Postbaseline Value[b]					
	Grade	n (%)	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Missing
Vehicle cream BID (N = 302)	Grade 0	296 (98.0)	282 (95.3)	6 (2.0)	0	0	0	8 (2.7)
	Grade 1	4 (1.3)	0	3 (75.0)	0	0	0	1 (25.0)
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	2 (0.7)	2 (100.0)	0	0	0	0	0
	Total	302 (100.0)	284 (94.0)	9 (3.0)	0	0	0	9 (3.0)
Ruxolitinib 0.75% cream BID (N = 601)	Grade 0	580 (96.5)	548 (94.5)	24 (4.1)	0	0	0	8 (1.4)
	Grade 1	16 (2.7)	5 (31.3)	10 (62.5)	0	0	0	1 (6.3)
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	5 (0.8)	2 (40.0)	0	0	0	0	3 (60.0)
	Total	601 (100.0)	555 (92.3)	34 (5.7)	0	0	0	12 (2.0)
Ruxolitinib 1.5% cream BID (N = 857)	Grade 0	834 (97.3)	803 (96.3)	20 (2.4)	0	1 (0.1)	0	10 (1.2)
	Grade 1	16 (1.9)	3 (18.8)	11 (68.8)	1 (6.3)	0	0	1 (6.3)
	Grade 2	1 (0.1)	0	1 (100.0)	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	6 (0.7)	1 (16.7)	0	0	0	0	5 (83.3)
	Total	857 (100.0)	807 (94.2)	32 (3.7)	1 (0.1)	1 (0.1)	0	16 (1.9)

*Source: Table 45 Summary of Clinical Safety

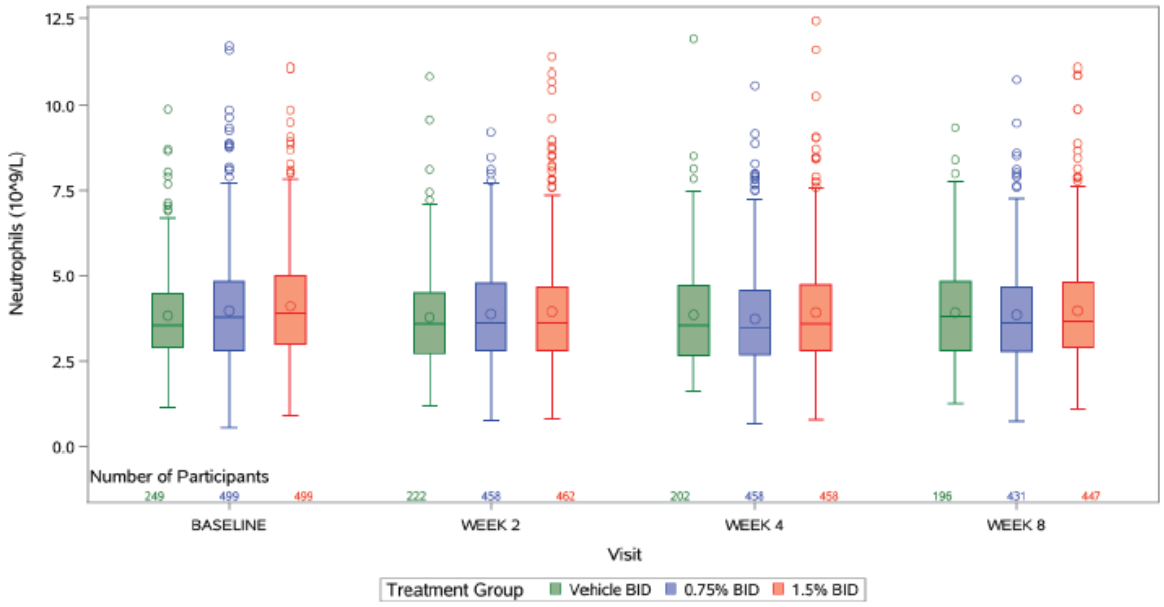
[a] The percentages were calculated using the baseline total as the denominator.

[b] For each row, the percentages were calculated using the number of participants with given grade at baseline as the denominator; worst value on study is the worst grade observed postbaseline for a given participant.

Neutrophils

Mean neutrophil counts were similar across the 3 treatment groups at all visits through Week 8, with no trends noted. A similar pattern was noted in the Phase 2/3 pool, and mean counts generally were within the normal range through Week 52.

Figure 11 Box Plot of Neutrophil Counts by Visit and Treatment Group (Phase 3 Atopic Dermatitis Vehicle-Controlled Population)*



*Source: Figure 5 Integrated Summary of Safety
Mean values are denoted by the larger "o" symbol

Across all 3 treatment groups, ~ 97% of subjects had baseline neutrophil counts assessed as Grade 0. In the ruxolitinib groups, 94% of these subjects had worst post-baseline values of Grade 0 through Week 8, and this was observed in ~92% of subjects in the vehicle group. One subject who had Grade 0 neutrophil counts at baseline experienced a decrease in counts to a worst post-baseline shift to Grade 3, and that subject was in the ruxolitinib 1.5% group. Of subjects with baseline counts in the Grade 0 category, 1-2% across the 3 treatment groups had decreases in counts and shifted to Grade 2 as worst post-baseline values. See Table 37.

Table 37 Shift Summary of Neutrophil Count Values in CTC Grade to the Worst (Low) Abnormal Value (Phase 3 Atopic Dermatitis Vehicle-Controlled Population)*

	Baseline[a]		Worst Postbaseline Value[b]					
	Grade	**n (%)**	**Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Missing**
Vehicle cream BID (N = 250)	Grade 0	244 (97.6)	224 (91.8)	8 (3.3)	5 (2.0)	0	0	7 (2.9)
	Grade 1	4 (1.6)	1 (25.0)	1 (25.0)	2 (50.0)	0	0	0
	Grade 2	1 (0.4)	0	0	1 (100.0)	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	1 (0.4)	1 (100.0)	0	0	0	0	0
	Total	250 (100.0)	226 (90.4)	9 (3.6)	8 (3.2)	0	0	7 (2.8)
Ruxolitinib 0.75% cream BID (N = 500)	Grade 0	481 (96.2)	453 (94.2)	10 (2.1)	9 (1.9)	0	0	9 (1.9)
	Grade 1	5 (1.0)	2 (40.0)	2 (40.0)	0	0	0	1 (20.0)
	Grade 2	12 (2.4)	3 (25.0)	3 (25.0)	4 (33.3)	1 (8.3)	0	1 (8.3)
	Grade 3	1 (0.2)	0	0	0	1 (100.0)	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	1 (0.2)	0	0	0	0	0	1 (100.0)
	Total	500 (100.0)	458 (91.6)	15 (3.0)	13 (2.6)	2 (0.4)	0	12 (2.4)
Ruxolitinib 1.5% cream BID (N = 499)	Grade 0	487 (97.6)	456 (93.6)	10 (2.1)	7 (1.4)	1 (0.2)	0	13 (2.7)
	Grade 1	5 (1.0)	4 (80.0)	0	1 (20.0)	0	0	0
	Grade 2	6 (1.2)	0	1 (16.7)	4 (66.7)	1 (16.7)	0	0
	Grade 3	1 (0.2)	0	0	0	1 (100.0)	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Total	499 (100.0)	460 (92.2)	11 (2.2)	12 (2.4)	3 (0.6)	0	13 (2.6)

*Source: Table 46 Summary of Clinical Safety

[a] The percentages were calculated using the baseline total as the denominator.

[b] For each row, the percentages were calculated using the number of participants with given grade at baseline as the denominator; worst value on study is the worst grade observed postbaseline for a given participant.

In the Phase 2/3 population, 95-98% of subjects across all treatment groups had baseline neutrophil counts of Grade 0. For these subjects, through Week 52, the worst post-baseline shift experienced by subjects was a decrease in neutrophil counts to Grade 2 for 5 subjects (1.7%) in the vehicle group and 22 subjects (3.8%) in the ruxolitinib 0.75% group. A total of 24 subjects (2.9%) in the ruxolitinib 1.5% group experienced a shift from Grade 0 to Grade 2, and 5 subjects (0.6%) in this treatment group experienced a shift from Grade 0 to Grade 3. Also, 3 additional subjects in the 1.5% group shifted to Grade 3: one who was in Grade 1 at baseline and 2 who were Grade 2.

Table 38 Shift Summary of Neutrophil Count Values in CTC Grade to the Worst (Low) Abnormal Value (Phase 2/3 Atopic Dermatitis Population)*

	Baseline[a]		Worst Postbaseline Value[b]					
	Grade	n (%)	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Missing
Vehicle cream BID (N = 302)	Grade 0	296 (98.0)	273 (92.2)	10 (3.4)	5 (1.7)	0	0	8 (2.7)
	Grade 1	4 (1.3)	1 (25.0)	1 (25.0)	2 (50.0)	0	0	0
	Grade 2	1 (0.3)	0	0	1 (100.0)	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	1 (0.3)	1 (100.0)	0	0	0	0	0
	Total	302 (100.0)	275 (91.1)	11 (3.6)	8 (2.6)	0	0	8 (2.6)
Ruxolitinib 0.75% cream BID (N = 601)	Grade 0	573 (95.3)	516 (90.1)	28 (4.9)	22 (3.8)	0	0	7 (1.2)
	Grade 1	10 (1.7)	2 (20.0)	3 (30.0)	4 (40.0)	0	0	1 (10.0)
	Grade 2	13 (2.2)	1 (7.7)	4 (30.8)	4 (30.8)	3 (23.1)	0	1 (7.7)
	Grade 3	1 (0.2)	0	0	0	1 (100.0)	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	4 (0.7)	1 (25.0)	0	0	0	0	3 (75.0)
	Total	601 (100.0)	520 (86.5)	35 (5.8)	30 (5.0)	4 (0.7)	0	12 (2.0)
Ruxolitinib 1.5% cream BID (N = 857)	Grade 0	832 (97.1)	758 (91.1)	34 (4.1)	24 (2.9)	5 (0.6)	0	11 (1.3)
	Grade 1	11 (1.3)	3 (27.3)	3 (27.3)	4 (36.4)	1 (9.1)	0	0
	Grade 2	9 (1.1)	0	1 (11.1)	6 (66.7)	2 (22.2)	0	0
	Grade 3	1 (0.1)	0	0	0	1 (100.0)	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	4 (0.5)	0	0	0	0	0	4 (100.0)
	Total	857 (100.0)	761 (88.8)	38 (4.4)	34 (4.0)	9 (1.1)	0	15 (1.8)

*Source: Table 47 Summary of Clinical Safety

[a] The percentages were calculated using the baseline total as the denominator.

[b] For each row, the percentages were calculated using the number of participants with given grade at baseline as the denominator; worst value on study is the worst grade observed postbaseline for a given participant.

The Applicant identified no consistent patterns in changes in chemistry parameters, including liver, renal, or lipid tests.

Liver Function Tests

The Applicant reported that alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin percent changes were similar across all treatment groups through Week 8 and through Week 52, with no trends identified and no clinically significant variations and with values generally remaining stable and within normal ranges through the long-term period.

The Applicant reported post-baseline shifts in the Phase 3 VC Population in ALT, AST, and bilirubin were generally to Grade 1 or 2. Two subjects in the ruxolitinib 1.5% group

experienced Grade 1 to Grade 3 post-baseline shifts, and the shifts were in the ALT and bilirubin (one subject for each of these shifts). Most shifts in the Phase 2/3 Atopic Dermatitis Population in the 3 parameters were also to Grade 1 or 2. The Applicant reported Grade 0 to Grade 3 shifts for 4 subjects for ALT and 3 subjects for AST in the ruxolitinib 0.75% cream group and in the ruxolitinib 1.5% cream BID group: 1 subject had a Grade 0 to Grade 3 shift in ALT shift; 1 subject had a Grade 1 to Grade 3 ALT shift; 1 subject had a Grade 0 to Grade 4 shift in AST; 1 subject had a Grade 1 to Grade 3 shift in bilirubin; and 2 subjects had Grade 2 to Grade 3 shifts in bilirubin.

Lipid Panel (Non-Fasting)

Fasting assessments were not done. The Applicant reported that percent changes in cholesterol, low-density lipoproteins (LDL), very-low-density lipoproteins (VLDL), high-density lipoproteins (HDL), and triglycerides were similar across all treatment groups at all visits through Week 8 and through Week 52. No trends were identified and no clinically significant variations through Week 8, and with values generally remaining stable and within normal ranges through the long-term period (through Week 52).

Vital Signs

The Applicant did not summarize vital signs for the pooled populations. In referencing individual study reports from the AD program, the Applicant reported that most subjects had normal vital signs at baseline and at post dose assessments. Vital sign readings that met alert criteria were transient and infrequent, and increases in blood pressure was the most common.

Electrocardiograms (ECGs)

Three studies in the psoriasis program (201, 202, and 203) included frequent ECGs, as these studies were conducted prior to the thorough QT study with oral ruxolitinib. In those studies, the Applicant reported transient, minor variations in ECG intervals, but that there were generally no clinically meaningful ECG changes.

QT

The Applicant reported the following regarding the thorough QT study conducted with oral ruxolitinib (p. 168 of Integrated Summary of Safety):

> A thorough QT study of oral ruxolitinib at a supratherapeutic dose (200 mg), which produced plasma concentrations well above those observed for ruxolitinib 1.5% cream BID, was negative for QT-prolongation according to the International Council for Harmonisation E14 Guidance…In addition, for ruxolitinib, the hERG IC50 is 131.6 μM… The highest mean (SD) concentrations seen in humans to date have been 7.1 (1.35) μM following a single 200 mg oral dose of ruxolitinib. When adjusted for protein binding (3.3% unbound), this equates to 0.234 (0.045) μM, which is approximately 1/550th of the hERG IC50.

Immunogenicity

This section is not applicable.

8.2.5. Analysis of Submission-Specific Safety Issues

Oral ruxolitinib is indicated for treatment of myelofibrosis, polycythemia vera, and acute graft-versus-host disease (see Section 1.1 of this review for the full indication statements). The label for oral ruxolitinib includes Warnings and Precautions pertaining to:

- Thrombocytopenia, anemia and neutropenia
- Risk of infection: tuberculosis, progressive multifocal leukoencephalopathy (PML), herpes zoster, hepatitis B
- Non-melanoma skin cancer: basal cell, squamous cell, and Merkel cell carcinoma
- Lipid elevations

The Applicant performed safety analyses which evaluated subjects treated with topical ruxolitinib for the occurrence of adverse reactions reported with oral ruxolitinib. Additionally, the Applicant performed safety analyses which evaluated subjects for risks associated with other oral JAK inhibitors. Specifically, they evaluated the clinical database for the thromboembolic risk described with oral JAK inhibitors approved for treatment of rheumatoid arthritis e.g., tofacitinib, but a risk that has not been reported in association with oral ruxolitinib to date. The Applicant also assessed AEs in the Infections and infestation SOC, due to increased risk of skin infection in patients with AD related to their underlying disease.

8.2.5.1. Cytopenias

Overall, the Applicant identified no trends in decreases in hematological parameters. The Applicant also identified no correlation between overall mean steady state plasma concentration (C_{ss}) quartiles and decreases in hematological parameters i.e., hemoglobin, absolute neutrophils, mean platelet volumes (MPVs), and platelet counts.

Phase 3 VC Population

Through week 8, the incidences of erythropenia were similar between vehicle and ruxolitinib treatment groups. All TEAEs related to neutropenia were reported in the ruxolitinib groups, and the overall incidence was low. See Table 39.

Table 39 Summary of Erythropenia and Neutropenia Treatment-Emergent Adverse Events in Decreasing Order of Frequency (Phase 3 Atopic Dermatitis Vehicle-Controlled Population)*

Category MedDRA PT, n (%)	Vehicle Cream BID (N = 250)	Ruxolitinib Cream Regimen		Ruxolitinib Cream Total (N = 999)
		0.75% BID (N = 500)	1.5% BID (N = 499)	
Any erythropenia TEAE	*1 (0.4)*	*2 (0.4)*	*0*	*2 (0.2)*
Anemia	1 (0.4)	2 (0.4)	0	2 (0.2)
Any neutropenia TEAE	*0*	*3 (0.6)*	*2 (0.4)*	*5 (0.5)*
Neutropenia	0	2 (0.4)	2 (0.4)	4 (0.4)
Neutrophil count decreased	0	1 (0.2)	0	1 (0.1)

*Source: Table 20 Summary of Clinical Safety

Through Week 8, the VC period, one subject in the 0.75% group experienced a decrease in platelet count at Week 4. This subject had a low baseline platelet count (128 x 10^9/L).

All but 2 subjects had ruxolitinib trough concentrations below 25 nM at all visits during the 8-week VC period. Each of these 2 subjects had “an isolated spike” (unspecified) that was less than half of the ruxolitinib IC_{50} for JAK2 inhibition in whole blood assays (281 nM), per the Applicant, the minimum level relevant for systemic pharmacological effects on bone marrow.

Table 39 presents details of all subjects who experienced cytopenias through Week 8 in the Phase 3 studies. All of the events were of Grade 1 or 2 severity, and none of the events was a SAE. For 3 subjects (including the subject in the vehicle group), the cytopenia was present on Day 1, prior to application of study treatment. Study treatment was interrupted for 2 subjects, including one of the subjects who had evidence of a cytopenia (neutropenia) on Day 1. For the remaining subjects, study treatment was unchanged.

Table 40 Participants With Cytopenias in the Phase 3 Atopic Dermatitis Vehicle-Controlled Population*

Study Age/Sex	PT	Severity Serious (Y/N)	Onset Duration	Laboratory Value at Baseline	Laboratory Value at Onset	Worst Laboratory Value During the 8-Week VC Period	Action Taken With the Study Drug Investigator Assessment of Relationship to Study Drug
Vehicle cream BID							
INCB 18424-304 46/F	Anaemia	Grade 1 N	Day 1[a] 89 days	Hemoglobin: 102 g/L	Hemoglobin: 102 g/L	Hemoglobin: 102 g/L	No change Not related
Ruxolitinib 0.75% cream BID							
INCB 18424-303 14/F	Neutropenia	Grade 1 N	Day 29 28 days	Neutrophils: 2.28×10^9/L	Neutrophils: 1.65×10^9/L	Neutrophils: 1.65×10^9/L	No change Related
INCB 18424-304 52/F	Neutropenia (worsening)	Grade 2 N	Day 1[a] 15 days	Neutrophils: 1.46×10^9/L	Neutrophils: 1.46×10^9/L	Neutrophils: 1.40×10^9/L	No change Not related
INCB 18424-304 20/F	Neutrophil count decreased	Grade 2 N	Day 1[a] 17 days	Neutrophils: 1.40×10^9/L	Neutrophils: 1.40×10^9/L	Neutrophils: 1.40×10^9/L	Drug interrupted (study drug application restarted: yes) Not related
INCB 18424-303 51/F	Anaemia	Grade 1 N	Day 17 211 days	Hemoglobin: 110 g/L	Hemoglobin: 108 g/L	Hemoglobin: 103 g/L	No change Not related
INCB 18424-304 54/F	Anaemia	Grade 2 N	Day 31 Ongoing	Hemoglobin: 109 g/L	Hemoglobin: 109 g/L	Hemoglobin: 109 g/L	No change Not related
INCB 18424-304 78/M	Platelet count decreased	Grade 1 N	Day 28 316 days	Platelets: 128×10^9/L	Platelets: 104×10^9/L	Platelets: 98×10^9/L	No change Not related
Ruxolitinib 1.5% cream BID							
INCB 18424-303 23/F	Neutropenia	Grade 1 N	Day 16 14 days	Neutrophils: 3.28×10^9/L	Neutrophils: 1.41×10^9/L	Neutrophils: 1.41×10^9/L	No change Not related
INCB 18424-304 28/F	Neutropenia	Grade 1 N	Day 29 85 days	Neutrophils: 1.95×10^9/L	Neutrophils: 1.43×10^9/L	Neutrophils: 1.32×10^9/L	Drug interrupted (study drug application restarted: yes) Related

*Source: Table 21 Summary of Clinical Safety

[a] Participants had their baseline assessment on Day 1, prior to the first study drug application.

Phase 2/3 Atopic Dermatitis Population

In the Phase 2/3 population (data through Week 52), the incidence of erythropenia events was highest in the 0.75% ruxolitinib group. The incidence of neutropenia events was generally similar between the 0.75% and 1.5% BID arms, but higher in the 0.75% ruxolitinib group, with no events reported in the vehicle arm. There were no SAEs related to cytopenias (except for post-operative anemia, which was attributed to the subject's surgery). Most events resolved without action taken with study treatment (including the Grade 3 neutropenia).

Table 41 Summary of Erythropenia and Neutropenia Treatment-Emergent Adverse Events in Decreasing Order of Frequency (Phase 2/3 Atopic Dermatitis Population)*

Category MedDRA PT, n (%)	Vehicle Cream BID (N = 302)	Ruxolitinib Cream Regimen					Ruxolitinib Cream Total (N = 1483)[a]
		0.15% QD (N = 51)	0.5% QD (N = 51)	0.75% BID (N = 601)	1.5% QD (N = 51)	1.5% BID (N = 857)	
Any erythropenia TEAE	*1 (0.3)*	*0*	*0*	*9 (1.5)*	*0*	*3 (0.4)*	*12 (0.8)*
Anaemia	1 (0.3)	0	0	7 (1.2)	0	3 (0.4)	10 (0.7)
Haemoglobin decreased	0	0	0	1 (0.2)	0	0	1 (0.1)
Microcytic anaemia	0	0	0	1 (0.2)	0	0	1 (0.1)
Any neutropenia TEAE	*0*	*0*	*0*	*11 (1.8)*	*0*	*12 (1.4)*	*23 (1.6)*
Neutropenia	0	0	0	7 (1.2)	0	12 (1.4)	19 (1.3)
Neutrophil count	0	0	0	4 (0.7)	0	1 (0.1)	5 (0.3)

*Source: Table 22 Summary of Clinical Safety
a Participants who switched to another treatment during the study were only counted once in Total.

8.2.5.2. Infection

Herpes Zoster

Across clinical development programs for all indications (1942 subjects who had at least one application of cream, the All Ruxolitinib Population), the Applicant identified 12 subjects who experienced 13 herpes zoster events (includes one subject who experienced herpes zoster and postherpetic neuralgia). All 12 subjects had been treated with ruxolitinib cream. All events were of Grade 1 or 2 severity, except for one event that was Grade 3. For one subject, the event occurred at the application site, and for 6 other subjects the herpes zoster was not an application site. For the remaining 5 subjects, the location of the eruption was not reported or was “not applicable” (one subject). Study treatment was interrupted for one subject. For the remaining subjects, study treatment was unchanged (for 3 subjects, the herpes zoster occurred after the last application of ruxolitinib cream).

Of the 12 subjects who had herpes zoster, 8 (66.6%) were in the AD studies, including the 2 pediatric subjects who experienced this event: a 13 y/o male and a 17 y/o male. Additionally, a 26 y/o female and a 30 y/o male in the AD program experienced herpes zoster. The Applicant reported that the plasma ruxolitinib levels, for the 6 AD subjects with available data, were “substantially less than the IC50 for JAK2 inhibition in whole blood assays,” referring to the levels prior to onset of the event (p. 120, Integrated Summary of Safety). The incidence of herpes zoster in the Phase 3 AD studies was 0.2%.

See Table 42 for details of all subjects who experienced herpes zoster across clinical development programs for all indications.

Table 42 Treatment-Emergent Adverse Events of Herpes Zoster (Safety Population)*

Study Age/Sex	Treatment Group	PT	Grade	Serious (Y/N)	Related (Y/N)	At Application Site (Y/N)	Action Taken With the Study Drug	Study Day Start	Duration (days)
Participants with atopic dermatitis									
INCB 18424-206 26/F	Ruxolitinib 0.15% cream QD (DB period)/ruxolitinib 1.5% cream BID (OLE)	Herpes zoster	1	N	N	NR	NA: onset 19 days after last ruxolitinib application	110	8
INCB 18424-304 13/M	Ruxolitinib 0.75% cream BID	Herpes zoster	2	N	N	N	No change	170	15
INCB 18424-304 80/M	Ruxolitinib 0.75% cream BID	Herpes zoster	2	N	N	N	No change	290	124
INCB 18424-304 65/F	Ruxolitinib 0.75% cream BID	Herpes zoster	2	N	N	N	No change	111	10
		Herpes zoster	2	N	N	N	No change	193	5
INCB 18424-303 55/F	Ruxolitinib 1.5% cream BID	Herpes zoster	3	N	Y	N	No change	11	26
INCB 18424-303 17/M	Ruxolitinib 1.5% cream BID	Herpes zoster	2	N	N	N	No change	283	34
INCB 18424-304 71/F	Ruxolitinib 1.5% cream BID	Herpes zoster	2	N	N	NR	Drug interrupted (from Day 3 to Day 15)	5	8
		Postherpetic neuralgia	2	N	N	NR	No change	13	28
INCB 18424-304 30/M	Ruxolitinib 1.5% cream BID	Herpes zoster	1	N	N	N	No change	318	19
Participants with psoriasis									
INCB 18424-203 55/M	Ruxolitinib 0.5% cream QD	Herpes zoster	1	N	N	NR	NA: onset 10 days after last ruxolitinib application	91	Ongoing
Participants with alopecia areata									
INCB 18424-204 31/M	Placebo/ruxolitinib 1.5% cream BID	Herpes zoster	2	N	N	NR	NA: onset 14 days after last ruxolitinib application	347	13
Participants with vitiligo									
INCB 18424-211 50/M	Ruxolitinib 1.5% cream BID	Herpes zoster	1	N	N	Y	No change	NR	Ongoing (recovering/ resolving)
INCB 18424-211 47/M	Ruxolitinib 1.5% cream BID	Herpes zoster	1	N	N	Not applicable[a]	No change	345	11

*Source: Table 45 Integrated Summary of Safety

DB = double-blind; NA = not applicable because participant was not on study drug at the time of event onset; NR = not reported; OLE = open-label extension.

[a] Per response on the electronic case report form

Other Viral Skin Infections

Herpes simplex was reported in 2 subjects in the Phase 3 VC Population, one subject in each of the ruxolitinib treatment groups, making for an incidence of 0.2% in each group. There was a single report of molluscum contagiosum, and it occurred in a subject in the 0.75% ruxolitinib group. These 3 viral skin infections were Grade 1 or 2 in severity. See Table 43.

Table 43 Summary of Skin and Subcutaneous Tissue Viral Infection Treatment-Emergent Adverse Events in Decreasing Order of Frequency (Phase 3 Atopic Dermatitis Vehicle-Controlled Population)*

MedDRA PT, n (%)	Vehicle Cream BID (N = 250)	Ruxolitinib Cream Regimen		Ruxolitinib Cream Total (N = 999)
		0.75% BID (N = 500)	1.5% BID (N = 499)	
Any skin and subcutaneous tissue viral infection TEAE	0	2 (0.4)	3 (0.6)	5 (0.5)
Herpes simplex	0	1 (0.2)	1 (0.2)	2 (0.2)
Herpes zoster	0	0	2 (0.4)	2 (0.2)
Molluscum contagiosum	0	1 (0.2)	0	1 (0.1)

*Source: Table 25 Summary of Clinical Safety

Additional TEAEs of herpes simplex were observed in the Phase 2/3 Population. The incidence of this event in the Phase 2/3 population was similar to that seen with the Phase 3 VC Population. There were no additional reports of molluscum contagiosum in the Phase 2/3 Population. See Table 44.

Table 44 Summary of Skin and Subcutaneous Tissue Viral Infection Treatment-Emergent Adverse Events in Decreasing Order of Frequency (Phase 2/3 Atopic Dermatitis Population)*

MedDRA PT, n (%)	Vehicle Cream BID (N = 302)	Ruxolitinib Cream Regimen					Ruxolitinib Cream Total (N = 1483)[a]
		0.15% QD (N = 51)	0.5% QD (N = 51)	0.75% BID (N =	1.5% QD (N = 51)	1.5% BID (N = 857)	
Any skin and subcutaneous tissue	*0*	*0*	*0*	*6 (1.0)*	*0*	*10 (1.2)*	*16 (1.1)*
Herpes zoster	0	0	0	3 (0.5)	0	5 (0.6)	8 (0.5)
Herpes simplex	0	0	0	2 (0.3)	0	5 (0.6)	7 (0.5)
Molluscum contagiosum	0	0	0	1 (0.2)	0	0	1 (0.1)

*Source: Table 26 Summary of Clinical Safety

[a] Participants who switched to another treatment during the study were only counted once in Total.

Infections and Infestations

Overall, subjects in the Phase 3 VC Population who experienced at least one TEAE in this SOC occurred as follows: 17 subjects (6.8%) in the vehicle cream group, 68 (13.6%) in the ruxolitinib 0.75% group, and 55 (11.0%) in the ruxolitinib 1.5% group. As previously discussed, nasopharyngitis and upper respiratory tract infections were the most frequently reported TEAEs (overall, not just in the Infections and infestations SOC). Bronchitis was the 3rd most frequently reported event in this SOC, and all 7 reports were in ruxolitinib treatment groups (0.7%). Other TEAEs in this SOC that were reported only in ruxolitinib treatment groups and at an overall incidence of ≥ 0.5% were conjunctivitis, ear infection, and gastroenteritis (all at 0.5% incidence). Sinusitis was the only other TEAE in this SOC that occurred at an overall incidence of 0.5% in ruxolitinib-

treated subjects, but the incidence was similar in the vehicle group (0.8%). All other TEAES that occurred only in ruxolitinib-treated subjects occurred at < 0.5% incidence. See Table 45.

The Applicant reported that all events in this SOC were Grade 1 or 2 and not SAEs except for the following 4 subjects (all have been previously discussed; see "Other Serious Adverse Events"):

- 2 subjects who experienced SAEs of pneumonia.
- a subject (ruxolitinib 1.5% group) who experienced bronchitis of Grade 3 severity.
- a subject (ruxolitinib 1.5% group) who experienced an SAE of tooth infection (Grade 3).

Table 45 Summary of Treatment-Emergent Adverse Events in the Infections and Infestations SOC in Decreasing Order of Frequency (Phase 3 Atopic Dermatitis Vehicle-Controlled Population)*

SOC MedDRA PT, n (%)	Vehicle Cream BID (N = 250)	Ruxolitinib Cream Regimen		Ruxolitinib Cream Total (N = 999)
		0.75% BID (N = 500)	1.5% BID (N = 499)	
Infections and infestations	17 (6.8)	68 (13.6)	55 (11.0)	123 (12.3)
Nasopharyngitis	2 (0.8)	15 (3.0)	13 (2.6)	28 (2.8)
Upper respiratory tract infection	5 (2.0)	7 (1.4)	12 (2.4)	19 (1.9)
Bronchitis	0	3 (0.6)	4 (0.8)	7 (0.7)
Conjunctivitis	0	4 (0.8)	1 (0.2)	5 (0.5)
Ear infection	0	1 (0.2)	4 (0.8)	5 (0.5)
Gastroenteritis	0	4 (0.8)	1 (0.2)	5 (0.5)
Sinusitis	2 (0.8)	4 (0.8)	1 (0.2)	5 (0.5)
Urinary tract infection	1 (0.4)	4 (0.8)	1 (0.2)	5 (0.5)
Otitis externa	0	2 (0.4)	2 (0.4)	4 (0.4)
Rhinitis	1 (0.4)	3 (0.6)	1 (0.2)	4 (0.4)
Tonsillitis	0	1 (0.2)	3 (0.6)	4 (0.4)
Viral upper respiratory tract infection	2 (0.8)	3 (0.6)	1 (0.2)	4 (0.4)
Folliculitis	0	0	3 (0.6)	3 (0.3)
Pharyngitis	0	3 (0.6)	0	3 (0.3)
Viral infection	1 (0.4)	2 (0.4)	1 (0.2)	3 (0.3)
Application site folliculitis	0	2 (0.4)	0	2 (0.2)
Gastroenteritis viral	0	1 (0.2)	1 (0.2)	2 (0.2)
Herpes simplex	0	1 (0.2)	1 (0.2)	2 (0.2)
Herpes zoster	0	0	2 (0.4)	2 (0.2)
Oral herpes	0	2 (0.4)	0	2 (0.2)
Pneumonia	1 (0.4)	2 (0.4)	0	2 (0.2)
Skin bacterial infection	0	1 (0.2)	1 (0.2)	2 (0.2)

Staphylococcal infection	0	0	2 (0.4)	2 (0.2)
Tinea pedis	0	2 (0.4)	0	2 (0.2)
Tooth infection	0	1 (0.2)	1 (0.2)	2 (0.2)
Abscess neck	0	1 (0.2)	0	1 (0.1)
Adenovirus infection	0	1 (0.2)	0	1 (0.1)
Cystitis	0	1 (0.2)	0	1 (0.1)
Herpes virus infection	0	0	1 (0.2)	1 (0.1)
Impetigo	0	1 (0.2)	0	1 (0.1)
Influenza	0	1 (0.2)	0	1 (0.1)
Molluscum contagiosum	0	1 (0.2)	0	1 (0.1)
Otitis media	0	1 (0.2)	0	1 (0.1)

SOC MedDRA PT, n (%)	**Vehicle Cream BID (N = 250)**	**Ruxolitinib Cream Regimen**		**Ruxolitinib Cream Total (N = 999)**
		0.75% BID (N = 500)	**1.5% BID (N = 499)**	
Pharyngitis streptococcal	0	0	1 (0.2)	1 (0.1)
Pharyngotonsillitis	0	0	1 (0.2)	1 (0.1)
Rash pustular	0	0	1 (0.2)	1 (0.1)
Respiratory tract infection	0	1 (0.2)	0	1 (0.1)
Roseola	0	1 (0.2)	0	1 (0.1)
Superinfection bacterial	0	1 (0.2)	0	1 (0.1)
Tinea cruris	0	0	1 (0.2)	1 (0.1)
Urinary tract infection bacterial	0	1 (0.2)	0	1 (0.1)
Viral pharyngitis	0	0	1 (0.2)	1 (0.1)
Bacterial vaginosis	1 (0.4)	0	0	0
Tracheitis	1 (0.4)	0	0	0

*Source: Table 28 Summary of Clinical Safety

Because of the higher incidences of nasopharyngitis in ruxolitinib groups compared to vehicle, the Applicant further evaluated the TEAEs relating to upper respiratory tract infection. Under the analysis that included the PTs “nasopharyngitis,” “upper respiratory tract infection,” and “viral upper respiratory tract infection,” the overall incidences of events were similar between the 3 treatment groups.

Table 46 Summary of Nasopharyngitis and Upper Respiratory Tract Infection Treatment-Emergent Adverse Events (Phase 3 Atopic Dermatitis Vehicle-Controlled Population)*

MedDRA PT, n (%)	Vehicle Cream BID (N = 250)	Ruxolitinib Cream Regimen		Ruxolitinib Cream Total (N = 999)
		0.75% BID (N = 500)	1.5% BID (N = 499)	
Any nasopharyngitis/upper respiratory tract infection TEAE	9 (3.6)	25 (5.0)	26 (5.2)	51 (5.1)
Nasopharyngitis	2 (0.8)	15 (3.0)	13 (2.6)	28 (2.8)
Upper respiratory tract infection	5 (2.0)	7 (1.4)	12 (2.4)	19 (1.9)
Viral upper respiratory tract infection	2 (0.8)	3 (0.6)	1 (0.2)	4 (0.4)

*Source: Table 29 Summary of Clinical Safety

Phase 2/3 Population

Nasopharyngitis and upper respiratory tract infections remained the most frequently reported TEAEs. The general pattern of types of events appeared to be generally the same as with what was seen with the Phase 3 VC population. See Table 47. Most TEAEs continued to be of Grade 1 or 2 severity and not SAEs.

Table 47 Summary of Treatment-Emergent Adverse Events in the Infections and Infestations SOC Occurring in ≥ 1% of Participants in Any Treatment Group in Decreasing Order of Frequency (Phase 2/3 Atopic Dermatitis Population)

SOC MedDRA PT, n (%)	Vehicle Cream BID (N = 302)	Ruxolitinib Cream Regimen					Ruxolitinib Cream Total (N = 1483)[a]
		0.15% QD (N = 51)	0.5% QD (N = 51)	0.75% BID (N = 601)	1.5% QD (N = 51)	1.5% BID (N = 857)	
Infections and infestations	27 (8.9)	8 (15.7)	2 (3.9)	218 (36.3)	11 (21.6)	245 (28.6)	478 (32.2)
Nasopharyngitis	6 (2.0)	3 (5.9)	1 (2.0)	44 (7.3)	4 (7.8)	71 (8.3)	122 (8.2)
Upper respiratory tract infection	8 (2.6)	2 (3.9)	1 (2.0)	49 (8.2)	1 (2.0)	64 (7.5)	116 (7.8)
Bronchitis	0	0	0	16 (2.7)	0	20 (2.3)	36 (2.4)
Rhinitis	1 (0.3)	0	0	19 (3.2)	0	11 (1.3)	30 (2.0)
Influenza	0	1 (2.0)	0	8 (1.3)	0	18 (2.1)	27 (1.8)
Sinusitis	2 (0.7)	0	0	15 (2.5)	0	10 (1.2)	25 (1.7)
Urinary tract infection	3 (1.0)	0	0	11 (1.8)	1 (2.0)	11 (1.3)	23 (1.6)
Pharyngitis	0	0	0	12 (2.0)	1 (2.0)	9 (1.1)	22 (1.5)
Oral herpes	0	0	0	12 (2.0)	0	8 (0.9)	20 (1.3)
Viral upper respiratory tract	2 (0.7)	0	0	9 (1.5)	0	9 (1.1)	18 (1.2)
Conjunctivitis	0	0	0	14 (2.3)	0	3 (0.4)	17 (1.1)
Gastroenteritis	1 (0.3)	0	0	7 (1.2)	0	9 (1.1)	16 (1.1)
Pharyngitis	0	1 (2.0)	0	3 (0.5)	0	7 (0.8)	11 (0.7)
Tonsillitis	0	0	0	6 (1.0)	0	4 (0.5)	10 (0.7)
Viral infection	1 (0.3)	0	0	6 (1.0)	0	4 (0.5)	10 (0.7)

Respiratory tract infection	0	0	0	2 (0.3)	1 (2.0)	2 (0.2)	5 (0.3)
Bacterial vaginosis	1 (0.3)	1 (2.0)	0	0	0	1 (0.1)	2 (0.1)
Skin infection	0	0	0	0	1 (2.0)	1 (0.1)	2 (0.1)
Dermatophytosis	0	1 (2.0)	0	0	0	0	1 (0.1)
Lower respiratory tract infection	0	0	0	0	1(2.0)	0	1 (0.1)
Pulpitis dental	0	0	0	0	1 (2.0)	0	1 (0.1)

*Source: Table 30 Summary of Clinical Safety

[a] Participants who switched to another treatment during the study were only counted once in Total.

Table 48 Summary of Study Size- and Exposure-Adjusted Incidence Rates of Treatment-Emergent Adverse Events in the Infections and Infestations SOC Occurring in ≥ 1% of Participants in Any Treatment Group in Decreasing Order of Frequency (Phase 2/3 Atopic Dermatitis Population)*

SOC MedDRA PT, Study Size- and Exposure-Adjusted IR Per 100	Vehicle Cream BID (N = 302)	Ruxolitinib Cream Regimen					Ruxolitinib Cream Total[b] (N = 1483)
		0.15% QD (N = 51)	0.5% QD (N = 51)	0.75% BID (N = 601)	1.5% QD (N = 51)	1.5% BID (N = 857)	
Infections and infestations	NC	NC	NC	NC	NC	NC	NC
Nasopharyngitis	8.7	2.4	0.8	10.0	3.1	15.4	13.7
Upper respiratory tract infection	15.9	1.6	0.8	11.2	0.8	13.9	13.0
Bronchitis	0	0	0	3.6	0	4.3	4.0
Rhinitis	2.7	0	0	4.3	0	2.4	3.3
Influenza	0	0.8	0	1.8	0	3.9	3.0
Sinusitis	5.4	0	0	3.4	0	2.2	2.8
Urinary tract infection	4.4	0	0	2.5	0.8	2.4	2.6
Pharyngitis	0	0	0	2.7	0.8	1.9	2.5
Oral herpes	0	0	0	2.7	0	1.7	2.2
Viral upper respiratory tract	5.4	0	0	2.0	0	2.0	2.0
Conjunctivitis	0	0	0	3.2	0	0.7	1.9
Gastroenteritis	0.9	0	0	1.6	0	2.0	1.8
Pharyngitis streptococcal	0	0.8	0	0.7	0	1.5	1.2
Tonsillitis	0	0	0	NC	0	NC	NC
Viral infection	NC	0	0	NC	0	NC	NC
Respiratory tract infection viral	0	0	0	0.5	0.8	0.4	0.6
Bacterial vaginosis	2.7	0.8	0	0	0	0.2	0.2
Skin infection	0	0	0	0	0.8	0.2	0.2
Dermatophytosis	0	0.8	0	0	0	0	0.1
Lower respiratory tract infection	0	0	0	0	0.8	0	0.1
Pulpitis dental	0	0	0	0	0.8	0	0.1

*Source: Table 31 Summary of Clinical Safety

IR = incidence rate; NC = not calculated; PY = person-years.

[a] Study-size-adjusted and exposure-adjusted IR is a weighted average of exposure-adjusted IR based on PY from each study.

[b] Participants who switched to another treatment during the study were only counted once in Total.

8.2.5.3. Malignancy/Non-Melanoma Skin Cancer

Across clinical development programs for all indications (1942 subjects who had at least one application of ruxolitinib cream), 7 subjects had at least one nonmelanoma skin cancer (NMSC). Of these, 4 subjects were in the AD clinical trials, and these subjects ranged in age from 65 to 82 years. When location was reported (location was not reported for one subject), none of the tumors in the AD subjects occurred at application sites. All but one of the 4 subjects had a single NMSC. The subject who had multiple tumors had one basal cell carcinoma (BCC) and 2 squamous cell carcinoma (SCC), and all lesions were at different locations relating to the right upper extremity (wrist, arm, and shoulder), and all lesions were reported on Study Day 7. The NMSC for the other 3 subjects in the AD studies "started" on Days 27, 43, and 298. The NMSC for all 4 subjects were at sites that might reasonably be considered "sun-exposed," and all were Grade 2 severity except for one subject with SCC whose TEAE was considered Grade 1. No changes were made with study drug for these 4 subjects. The other 3 subjects were from the vitiligo program, and discussion of NMSC in that population is beyond the scope of this review, as there be factors related to this population that may require consideration in such a discussion. See Table 49 for details of NMSC.

Table 49 Nonmelanoma Skin Neoplasm Treatment-Emergent Adverse Events (Safety Population)*

Study Age/Sex, Race	Treatment Group	Relevant Medical History/Relevant Prior Medications or Therapies and Concomitant Medications	PT (Location)	Grade	Serious (Y/N)	Related (Y/N)	At Application Site (Y/N)	Action Taken With the Study Drug	Study Day Start	Duration (days)
Participants with atopic dermatitis										
INCB 18424-303 65/M, White	Ruxolitinib 0.75% cream BID	None/None	Basal cell carcinoma (left outer nose)	2	N	N	Not reported	No change	27	31
INCB 18424-303 74/M, White	Ruxolitinib 0.75% cream BID	None/None	Basal cell carcinoma (right wrist)	2	N	N	N	No change	7	1
			Squamous cell carcinoma of skin (right arm)	2	N	N	N	No change	7	1
			Squamous cell carcinoma of skin (right shoulder)	2	N	N	N	No change	7	1
INCB 18424-303 74/M, White	Ruxolitinib 1.5% cream BID	None/None	Squamous cell carcinoma of skin (chest)	1	N	N	N	No change	298	Ongoing at study completion
INCB 18424-304 82/F, White	Ruxolitinib 1.5% cream BID	None/None	Squamous cell carcinoma of skin (left leg)	2	N	N	N	No change	43	63
Participants with vitiligo										
INCB 18424-211 42/F, White (Fitzpatrick Type II skin type)	Ruxolitinib 0.15% cream QD	None/None	Basal cell carcinoma (mid chest)	2	N	N	Y	Drug interrupted (study drug application restarted: yes)	198	31
INCB 18424-211 68/M, White (Fitzpatrick Type II skin type)	Ruxolitinib 0.5% cream QD (VC and continued DB periods)/ ruxolitinib 1.5% cream BID (OLE period)	None/ Photochemotherapy (prior therapy), tacrolimus (topical, prior medication)	Basal cell carcinoma (left lower leg)[a]	2	N	Y	Y	Drug discontinued	680	134
INCB 18424-211 50/M, White (Fitzpatrick Type II skin type)	Ruxolitinib 1.5% cream BID	Skin lesion (reported term: red lesion on right shoulder)/ Phototherapy (prior therapy), tacrolimus (topical, prior medication)	Basal cell carcinoma (right shoulder)	2	N	N	N	Drug interrupted (study drug application restarted: yes)	203	120
			Basal cell carcinoma (left posterior shoulder)	2	N	N	N	Drug interrupted (study drug application restarted: no)	378	106
			Basal cell carcinoma (left upper arm)	2	N	N	N	Drug interrupted (study drug application restarted: no)	378	106
			Basal cell carcinoma (right neck)	2	N	N	Y	Drug interrupted (study drug application restarted: no)	378	106

*Source: Table 54 Integrated Summary of Safety
DB = double-blind; OLE = open-label extension.
a This event was preceded by nonserious TEAEs of actinic keratosis (Grade 2, right inferior leg) and lichenoid actinic keratosis (Grade 2, left wrist and right superior leg) with onset on Day 387. None of these events were considered related to the study drug by the investigator, and no action was taken with the study drug due to these events. The events resolved on Day 477.

8.2.5.4. Lipid Elevations

The Applicant identified no clinically relevant trends in changes in blood lipids in analyses of data from the Phase 3 VC Population or the Phase 2/3 Population. Subjects were not required to be fasting for lab testing. See Tables 50 and 51. Also see Laboratory Findings.

Table 50 Summary of Treatment-Emergent Adverse Events of Elevated Triglycerides, Cholesterol, and Low Density Lipoprotein in Decreasing Order of Frequency (Phase 3 Atopic Dermatitis Vehicle-Controlled Population)*

MedDRA PT, n (%)	Vehicle Cream BID (N = 250)	Ruxolitinib Cream Regimen		Ruxolitinib Cream Total (N = 999)
		0.75% BID (N = 500)	1.5% BID (N = 499)	
Any elevated triglycerides, cholesterol, or low density	*1 (0.4)*	*3 (0.6)*	*3 (0.6)*	*6 (0.6)*
Blood triglycerides increased	0	1 (0.2)	1 (0.2)	2 (0.2)
Hypercholesterolaemia	0	1 (0.2)	0	1 (0.1)
Hyperlipidaemia	0	1 (0.2)	0	1 (0.1)
Hypertriglyceridaemia	1 (0.4)	0	1 (0.2)	1 (0.1)
Low density lipoprotein increased	0	0	1 (0.2)	1 (0.1)

*Source: Table 36: Summary of Clinical Safety

Table 51 Summary of Treatment-Emergent Adverse Events of Elevated Triglycerides, Cholesterol, and Low Density Lipoprotein in Decreasing Order of Frequency (Phase 2/3 Atopic Dermatitis Population)*

MedDRA PT, n (%)	Vehicle Cream BID (N = 302)	Ruxolitinib Cream Regimen					Ruxolitinib Cream Total (N = 1483)[a]
		0.15% QD (N = 51)	0.5% QD (N = 51)	0.75% BID (N = 601)	1.5% QD (N = 51)	1.5% BID (N = 857)	
Any elevated triglycerides, cholesterol, or low density	*1 (0.3)*	*0*	*0*	*10 (1.7)*	*0*	*10 (1.2)*	*20 (1.3)*
Hypertriglyceridaemia	1 (0.3)	0	0	3 (0.5)	0	4 (0.5)	7 (0.5)
Blood triglycerides increased	0	0	0	3 (0.5)	0	1 (0.1)	4 (0.3)
Hypercholesterolaemia	0	0	0	2 (0.3)	0	2 (0.2)	4 (0.3)
Hyperlipidaemia	0	0	0	2 (0.3)	0	2 (0.2)	4 (0.3)
Low density lipoprotein increased	0	0	0	0	0	1 (0.1)	1 (0.1)

*Source: Table 37: Summary of Clinical Safety

[a] Participants who switched to another treatment during the study were only counted once in Total.

8.2.5.5. Thromboembolic and Thrombocytosis Events

Thromboembolic Events

Across clinical development programs for all indications (1942 subjects who had at least one application of ruxolitinib cream, the Safety Population), 7 subjects experienced a thrombotic or embolic TEAE, and all were using ruxolitinib cream at the time of onset of the event:

- 2 subjects had coronary artery occlusion
- 2 subjects had cerebrovascular accidents and have been previously discussed.
- Myocardial infarction
- Pulmonary embolism
- Deep vein thrombosis with pulmonary embolism

At all study visits prior to the onset of the event, all of these subjects had plasma ruxolitinib concentrations lower than the reported mean steady-state plasma concentration for the 1.5% BID cream (35.7 nM) in the pivotal AD studies, 303 and 304. All subjects had a medical history that placed them at increased risk for a thromboembolic event. See Table 52.

Table 52 Arterial and Venous Thromboembolic Events (Safety Population)*

Study Participant No. Age/Sex, BMI at Baseline	Treatment Group	Relevant Medical History/Relevant Prior and Concomitant Medications	PT	Grade	Serious (Y/N)	Related (Y/N)	Action Taken With the Study Drug C_{ss} Values	Study Day Start	Duration
INCB 18424-203 (b) (6) 59/M, 28.7 kg/m²	Ruxolitinib 0.5% cream QD	High blood pressure/methotrexate (concomitant medication for rheumatoid arthritis)	Coronary artery occlusion	4	Y	N	Drug discontinued Day 28: 21.20 nM Day 56: 8.33 nM	52	4 days
INCB 18424-211 (b) (6) 56/M, 29.7 kg/m²	Ruxolitinib 0.5% cream QD (VC & continued DB periods)	Hyperlipidemia, hypertension/None	Coronary artery occlusion	3	Y	N	No change Week 28: 11.8 nM (preapplication) and 20.8 nM (2 h postapplication) Week 52: 26.9 nM (preapplication) and 16.2 nM (2 h postapplication)	328	3 days
INCB 18424-303 (b) (6) 22/F, 23.7 kg/m²	Ruxolitinib 0.75% cream BID	None/Hormonal contraceptive pill (marvelon [WHO Drug Class: progestogens and estrogens, fixed combinations])	Pulmonary embolism	1	N	N	Drug discontinued Day 60 (Week 8): 3.40 nM Day 88 (early termination: BQL	75	1 day
INCB 18424-304 (b) (6) 52/F, 40.3 kg/m²	Ruxolitinib 0.75% cream BID	Hypertension, hypercholesterolemia, hypothyroidism, migraine, postmenopausal, smoker/None	Cerebrovascular accident	4	Y	N	Not applicable Day 32 (Week 4): 4.21 nM	54	33 days
INCB 18424-304 (b) (6) 50/M, 33.4 kg/m²	Vehicle cream BID (VC period)/ ruxolitinib 0.75% cream BID (LTS period)	Blood cholesterol increased, type 2 diabetes mellitus, hypertension/None	Myocardial infarction	2	Y	N	Not applicable Day 175 (Week 24): 13.0 nM	203	3 days

Study Participant No. Age/Sex, BMI at Baseline	Treatment Group	Relevant Medical History/Relevant Prior and Concomitant Medications	PT	Grade	Serious (Y/N)	Related (Y/N)	Action Taken With the Study Drug C_{ss} Values	Study Day Start	Duration
INCB 18424-304 (b) (6) 71/F, 27.6 kg/m^2	Ruxolitinib 1.5% cream BID	Hyperlipidemia, type 2 diabetes mellitus, hypertension, hydrocephalus/None	Cerebrovascular accident	4	Y	N	Drug discontinued Day 31 (Week 4): 2.31 nM	57	4 days
INCB 18424-304 (b) (6) 61/M, 27.6 kg/m^2	Ruxolitinib 1.5% cream BID	DVT of lower extremity, wrist surgery, and family history of hypertension and DVT (mother)/None	Deep vein thrombosis	2	Y	N	No change Day 142 (Week 20): 32.4 nM Day 170 (Week 24): 15.0 nM	145	Ongoing (recovering /resolving)
			Pulmonary embolism	2	Y	N	No change Day 142 (Week 20): 32.4 nM Day 170 (Week 24): 15.0 nM	156	Ongoing (recovering /resolving)

*Source: Table 55 Integrated Summary of Safety
BQL = below the lower limit of quantification; DB = double-blind.
Note: Not applicable = the participant was not on study drug at the time of event onset.

Thrombocytosis Events

The Applicant queried clinical databases across all indications (1942 subjects who had at least one application of cream) for the following TEAEs: platelet count increased, MPV increased, and thrombocytosis. They identified 5 subjects under this search: 3 subjects with a TEAE of thrombocytosis and 2 subjects with platelet count increased. All were using ruxolitinib cream at the time of onset of the event. A total of 4 events were Grade 1, and one was Grade 2. No events were SAEs. For one subject, the event was identified on Day 1 (the subject's baseline visit). No action was taken with study drug for any of the subjects.

Table 53 Treatment-Emergent Thrombocytosis Events (Safety Population)*

Study Age/Sex	Relevant Medical History/Relevant Prior and Concomitant Medications	PT	Severity Serious	Onset Duration	Laboratory Value at Baseline	Laboratory Value at Onset[a]	Worst Laboratory Value	Action Taken With the Study Drug Investigator Assessment of Relationship to Study Drug
Ruxolitinib 0.75% cream BID								
INCB 18424-304 53/M	None/None	Thrombocytosis	Grade 1 No	Day 16 Ongoing	Platelets: 431×10^9/L	Platelets: 592×10^9/L	Platelets: 592×10^9/L	No action Not related
Vehicle cream BID (VC period)/ruxolitinib 0.75% cream BID (LTS period)								
INCB 18424-304 29/F	None/None	Thrombocytosis	Grade 2 No	Day 211 Ongoing	Platelets: 543×10^9/L	Platelets: 523×10^9/L	Platelets: 645×10^9/L	No action Not related
Ruxolitinib 1.5% cream BID								
INCB 18424-303 19/F	Hypochromic anaemia/None	Platelet count increased	Grade 1 No	Day 1[b] Ongoing	Platelets: 760×10^9/L	Platelets: 760×10^9/L	Platelets: 1175×10^9/L	No action Not related
INCB 18424-303 23/F	None/None	Thrombocytosis	Grade 1 No	Day 16 Ongoing	Platelets: 393×10^9/L	Platelets: 466×10^9/L	Platelets: 625×10^9/L	No action Not related
Ruxolitinib 1.5% cream QD (VC and continued DB periods)								
INCB 18424-211 46/F	None/None	Platelet count increased	Grade 1 No	Day 169 1 day	Platelets: 301×10^9/L	Platelets: 428×10^9/L	Platelets: 428×10^9/L[c]	No action Not related

*Source: Table 56 Integrated Summary of Safety
[a] Laboratory result on the day of onset or the last result before onset.
[b] Participant had their baseline assessment on Day 1, prior to the first study drug application.
[c] Worst value through Week 52.

8.2.5.6 Elevations of Liver Function Tests

Elevations in liver function tests (LFTs) have been reported with oral ruxolitinib. The Applicant queried clinical databases for AEs in the liver-related investigations, signs and symptoms standardized MedDRA query (SMQ). The Applicant identified no clinically-relevant trends relating to changes in LFTs. The incidences of TEAEs reported under the liver-related investigations were low in the integrated clinical databases. There were no SAEs relating to elevations of LFTs, and the Applicant reported that all events were Grade 1 or 2 severity. The results for the Phase 3 VC and the Phase 2/3 populations are presented below. Also see Section 54.

Table 54 Summary of Liver-Related Investigations, Signs and Symptoms SMQ Treatment-Emergent Adverse Events in Decreasing Order of Frequency (Phase 3 Atopic Dermatitis Vehicle-Controlled Population)*

MedDRA PT, n (%)	Vehicle Cream BID (N = 250)	Ruxolitinib Cream Regimen		Ruxolitinib Cream Total (N = 999)
		0.75% BID (N = 500)	1.5% BID (N = 499)	
Any liver-related investigations, signs and symptoms TEAE	*2 (0.8)*	*3 (0.6)*	*2 (0.4)*	*5 (0.5)*
Liver function test increased	0	1 (0.2)	1 (0.2)	2 (0.2)
Alanine aminotransferase increased	0	0	1 (0.2)	1 (0.1)
Aspartate aminotransferase	1 (0.4)	0	1 (0.2)	1 (0.1)
Blood bilirubin increased	0	1 (0.2)	0	1 (0.1)
Hepatic enzyme increased	1 (0.4)	1 (0.2)	0	1 (0.1)

*Source: Table 39 Summary of Clinical Safety

Table 55 Summary of Liver-Related Investigations, Signs and Symptoms SMQ Treatment-Emergent Adverse Events in Decreasing Order of Frequency (Phase 2/3 Atopic Dermatitis Population)*

MedDRA PT, n (%)	Vehicle Cream BID (N = 302)	Ruxolitinib Cream Regimen					Ruxolitinib Cream Total[a] (N = 1483)
		0.15% QD (N = 51)	0.5% QD (N = 51)	0.75% BID (N = 601)	1.5% QD (N = 51)	1.5% BID (N = 857)	
Any liver-related investigations, signs and	*3 (1.0)*	*0*	*0*	*17 (2.8)*	*0*	*10 (1.2)*	*27 (1.8)*
Alanine aminotransferase	1 (0.3)	0	0	6 (1.0)	0	2 (0.2)	8 (0.5)
Aspartate aminotransferase	2 (0.7)	0	0	7 (1.2)	0	1 (0.1)	8 (0.5)
Transaminases increased	0	0	0	4 (0.7)	0	3 (0.4)	7 (0.5)
Blood bilirubin increased	0	0	0	3 (0.5)	0	2 (0.2)	5 (0.3)
Liver function test increased	0	0	0	1 (0.2)	0	2 (0.2)	3 (0.2)
Hepatic enzyme increased	1 (0.3)	0	0	1 (0.2)	0	1 (0.1)	2 (0.1)
Blood alkaline phosphatase	1 (0.3)	0	0	1 (0.2)	0	0	1 (0.1)

*Source: Table 40 Summary of Clinical Safety

[a] Participants who switched to another treatment during the study were only counted once in Total.

8.2.6. Safety Analyses by Demographic Subgroups

In the Phase 3 VC population, the overall incidence of TEAEs for subjects who applied ruxolitinib cream was lower in adolescents (21.5%) compared to those 18 to < 65 years of age (28.9%) and ≥ 65 years (32.6%). The types and frequencies of TEAEs in subjects who applied ruxolitinib were generally similar irrespective of age. No difference based on sex was apparent in the proportion of ruxolitinib-treated subjects with TEAEs. The overall incidence of TEAEs for ruxolitinib-treated subjects was lower in Black or African American participants (18.2%) compared with White (30.6%) and Asian and Other (30.9%).

Table 56 Overall Summary of Treatment-Emergent Adverse Events by Demographic Characteristic Subgroup (Phase 3 Atopic Dermatitis Vehicle-Controlled Population)*

Demographic Characteristic	Subgroup	Treatment Group	N	Treatment-Emergent Adverse Events, n (%)						
				All	Treatment-Related	≥ Grade 3	Serious	With Fatal Outcome	Leading to Study Drug Interruption	Leading to Study Drug Discontinuation
Age	12 to < 18 years	Vehicle cream BID	45	17 (37.8)	5 (11.1)	0	0	0	4 (8.9)	0
		Ruxolitinib 0.75% cream BID	108	27 (25.0)	5 (4.6)	1 (0.9)	0	0	0	0
		Ruxolitinib 1.5% cream BID	92	16 (17.4)	3 (3.3)	1 (1.1)	0	0	1 (1.1)	0
		Total ruxolitinib cream	200	43 (21.5)	8 (4.0)	2 (1.0)	0	0	1 (0.5)	0
	18 to < 65 years	Vehicle cream BID	179	59 (33.0)	22 (12.3)	3 (1.7)	2 (1.1)	0	5 (2.8)	8 (4.5)
		Ruxolitinib 0.75% cream BID	342	102 (29.8)	16 (4.7)	4 (1.2)	3 (0.9)	0	4 (1.2)	2 (0.6)
		Ruxolitinib 1.5% cream BID	368	103 (28.0)	19 (5.2)	7 (1.9)	2 (0.5)	0	6 (1.6)	3 (0.8)
		Total ruxolitinib cream	710	205 (28.9)	35 (4.9)	11 (1.5)	5 (0.7)	0	10 (1.4)	5 (0.7)
	≥ 65 years	Vehicle cream BID	26	7 (26.9)	1 (3.8)	0	0	0	0	0
		Ruxolitinib 0.75% cream BID	50	16 (32.0)	2 (4.0)	2 (4.0)	1 (2.0)	0	0	2 (4.0)
		Ruxolitinib 1.5% cream BID	39	13 (33.3)	2 (5.1)	1 (2.6)	1 (2.6)	0	1 (2.6)	1 (2.6)
		Total ruxolitinib cream	89	29 (32.6)	4 (4.5)	3 (3.4)	2 (2.2)	0	1 (1.1)	3 (3.4)
Sex	Male	Vehicle cream BID	91	20 (22.2)	7 (7.7)	3 (3.3)	2 (2.2)	0	1 (1.1)	4 (4.4)
		Ruxolitinib 0.75% cream BID	196	54 (27.6)	6 (3.1)	2 (1.0)	0	0	1 (0.5)	4 (2.0)
		Ruxolitinib 1.5% cream BID	191	47 (24.6)	10 (5.2)	3 (1.6)	1 (0.5)	0	2 (1.0)	1 (0.5)
		Total ruxolitinib cream	387	101 (26.1)	16 (4.1)	5 (1.3)	1 (0.3)	0	3 (0.8)	5 (1.3)
	Female	Vehicle cream BID	159	63 (39.6)	21 (13.2)	0	0	0	8 (5.0)	4 (2.5)
		Ruxolitinib 0.75% cream BID	304	91 (29.9)	17 (5.6)	5 (1.6)	4 (1.3)	0	3 (1.0)	0
		Ruxolitinib 1.5% cream BID	308	85 (27.6)	14 (4.5)	6 (1.9)	2 (0.6)	0	6 (1.9)	3 (1.0)
		Total ruxolitinib cream	612	176 (28.8)	31 (5.1)	11 (1.8)	6 (1.0)	0	9 (1.5)	3 (0.5)
Race	White	Vehicle cream BID	170	56 (32.9)	20 (11.8)	2 (1.2)	1 (0.6)	0	6 (3.5)	6 (3.5)
		Ruxolitinib 0.75% cream BID	345	115 (33.3)	17 (4.9)	4 (1.2)	2 (0.6)	0	3 (0.9)	2 (0.6)
		Ruxolitinib 1.5% cream BID	355	99 (27.9)	20 (5.6)	8 (2.3)	3 (0.8)	0	5 (1.4)	4 (1.1)
		Total ruxolitinib cream	700	214 (30.6)	37 (5.3)	12 (1.7)	5 (0.7)	0	8 (1.1)	6 (0.9)
	Black or African American	Vehicle cream BID	61	19 (31.1)	5 (8.2)	0	0	0	2 (3.3)	1 (1.6)
		Ruxolitinib 0.75% cream BID	118	17 (14.4)	4 (3.4)	2 (1.7)	2 (1.7)	0	0	1 (0.8)
		Ruxolitinib 1.5% cream BID	113	25 (22.1)	4 (3.5)	0	0	0	3 (2.7)	0
		Total ruxolitinib cream	231	42 (18.2)	8 (3.5)	2 (0.9)	2 (0.9)	0	3 (1.3)	1 (0.4)
	Asian and Others	Vehicle cream BID	19	8 (42.1)	3 (15.8)	1 (5.3)	1 (5.3)	0	1 (5.3)	1 (5.3)
		Ruxolitinib 0.75% cream BID	37	13 (35.1)	2 (5.4)	1 (2.7)	0	0	1 (2.7)	1 (2.7)
		Ruxolitinib 1.5% cream BID	31	8 (25.8)	0	1 (3.2)	0	0	0	0
		Total ruxolitinib cream	68	21 (30.9)	2 (2.9)	2 (2.9)	0	0	1 (1.5)	1 (1.5)

*Source: Table 73 Integrated Summary of Safety

8.2.7. **Specific Safety Studies/Clinical Trials**

The Applicant conducted 5 studies in healthy subjects to evaluate the potential with ruxolitinib 1.5% cream for cumulative irritancy (study 104), photoallergenicity (105), contact sensitization (106), phototoxicity (107), and a combined study that evaluated irritation and phototoxicity in Japanese subjects (108).

Studies 104, 105, 106, and 107 were conducted in standard manners for these dermal safety studies. Study 108 was an open-label study conducted "to assess the skin irritation and phototoxicity potential of ruxolitinib cream in healthy Japanese participants in order to allow the enrollment of Japanese patients in subsequent clinical trials" (per the study rationale in the study report synopsis). Study 108 will not be further discussed, as it is not a standard dermal safety study, from a regulatory perspective. Additionally, irritation and phototoxicity are assessed in studies 104 and 107, respectively. Per the study reports for studies 105 and 107, ruxolitinib cream absorb within the 290-400 nm range (UVB and UVA spectra).

The results for studies 104 – 107 are discussed at a high level below:

- *Study 104 (cumulative irritancy)*: Under the exaggerated study conditions, ruxolitinib 1.5% cream was slightly irritating; vehicle cream and 0.9% saline (negative control) were not irritating; 0.2% sodium lauryl sulfate (positive control) was highly irritating. No subjects discontinued patch applications due to irritation.

- *Study 105 (photoallergenicity)*: There was no evidence that ruxolitinib 1.5% cream or vehicle cream induces photosensitization.

- *Study 106 (contact sensitization)*: No subject showed evidence suggestive of contact sensitization when tested with ruxolitinib 1.5% cream, vehicle cream, or 0.9% saline.

- *Study 107 (phototoxicity)*: Irradiated sites (ruxolitinib 1.5% cream, vehicle cream, and untreated) had higher irritation scores than the non-irradiated sites (ruxolitinib 1.5% cream and vehicle cream). The irritation was assessed as being related to the light application and was not considered to represent phototoxicity. There was no evidence of phototoxicity for ruxolitinib 1.5% cream and vehicle cream.

  Conclusion: Provocative dermal safety studies did not yield evidence to indicate that ruxolitinib 1.5% cream is significantly irritating, a photosensitizer, a contact sensitizer, or a photoirritant.

8.2.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The label for oral ruxolitinib includes the following discussion in the "Warnings and Precautions" section:

> **5.4 Non-Melanoma Skin Cancer**
>
> Non-melanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have occurred in patients treated with Jakafi. Perform periodic skin examinations.

Basal cell and squamous cell carcinomas were observed in clinical trials with topical ruxolitinib.

Also see Section 8.2.5.3

Human Reproduction and Pregnancy

Pregnant women and women who were lactating were excluded from all clinical studies. A total of 8 pregnancies and 1 pregnancy of a partner occurred across the clinical development program for ruxolitinib cream. When known, the following outcomes were reported:

- 3 pregnancies resulted in a term birth and healthy infant
- 2 subjects had spontaneous abortions (assessed as unrelated to study treatment by investigators).

The Division of Pediatric and Maternal Health team recommends 3 PMRs:

1. a pregnancy exposure registry
2. an additional pregnancy study that uses a different design from the pregnancy registry
3. a lactation study (milk only) in women prescribed ruxolitinib who are willing to discontinue breastfeeding their infants

Pediatrics and Assessment of Effects on Growth

The Applicant included 245 adolescents (subjects ≥ 12 to 17 years) in the Phase 3 program, which constituted ~ 20% of the overall study population and aligned with the Agreed Initial Pediatric Study Plan (iPSP). Of those 245 adolescents, 108 (22%) were in the 0.75% BID group and 92 (18%) were in the 1.5% BID group, the concentration proposed for marketing.

The initial submission of the NDA reported the following long-term exposures to the 1.5% cream for subjects ≥ 12 to 17 years:

- 81 had been exposed for 24-52 weeks.
- 14 had been exposed for ≥ 52 - < 104 weeks.

With submission of the 4-month Safety Update (03/19/2021), the numbers of long-term exposures to the 1.5% cream for subjects ≥ 12 to 17 years were:

- 48 had been exposed to 1.5% ruxolitinib cream for 24-52 weeks
- 47 had been exposed to 1.5% ruxolitinib cream for ≥ 52 - < 104 weeks.

Safety Data from Phase 3

The safety profile of ruxolitinib 1.5% cream in subjects 12 to 17 years appears to be similar to that in adults. The one SAE that occurred in a pediatric subject in the Phase 3 trials was a 13 y/o male who was admitted and diagnosed with new onset type 2 diabetes. In this same population, TEAES leading to study drug discontinuation occurred in 3 subjects (all in study 303 and all in the 0.75% group):

- 13 y/o male for worsening of eczema
- 15 y/o female for application site pain
- 13 y/o male for 0.75% worsened AD

Pediatric subjects in the AD studies experienced the following AEs of interest for oral ruxolitinib and other JAK inhibitors; all resolved, and no action was taken with study treatment:

- 14 y/o female experienced Grade 1 neutropenia
- 13 y/o male experienced Grade 2 herpes zoster
- 17 y/o male experienced Grade 2 herpes zoster

Similar to the overall population in the Phase 3 trials, nasopharyngitis was the most commonly reported TEAE in adolescents: 2.8% and 2.5%, respectively. Review of TEAEs in adolescents raised no new safety concerns. The Applicant identified no differences in laboratory outcomes (hematology, chemistry) in the Phase 3 studies, when subgroup analyses were performed according to age.

The MUsT (Study 103)

This study enrolled subjects ≥ 12 to 65 years of age, with an IGA score of ≥ 2, and BSA of ≥ 25%. Subjects applied ruxolitinib 1.5% cream BID, to all affected areas identified at baseline for 4 weeks with serial blood sampling on study Days 1 and 28. After completion of the 28-day treatment period, subjects were allowed to continue ruxolitinib 1.5% cream BID to affected areas for an optional 28-day extension period (i.e., through Day 56) to benefit from the optimal level of clinical effect.

The study enrolled 41 subjects, 21 (51%) of whom were pediatric subjects 13-17 years of age. All 21 pediatric subjects continued into the optional 28-day treatment extension

period. Of the 21 pediatric subjects:

- 10 (48%) had Grade 2 (mild) AD
- 8 (38%) had Grade 3 (moderate) AD
- 3 (14%) had Grade 4 (severe) AD

A total of 13 subjects (31.7%) experienced at least 1 TEAE during the study. One subject experienced the only SAE and only Grade 3 event in the study: a 32 y/o female developed a limb abscess. A total of 5 pediatric subjects (12%) experienced AEs; all events were Grade 1:

- (b) (6) (14/M): neutropenia (Days 86-119; resolved/recovered)
- (b) (6) (13/M): "ALT & AST increased" (Days 15-30; no action taken with study drug; resolved/recovered)
- (b) (6) (15/F): allergic rhinitis
- (b) (6) (17/F): lower back pain/pulled hamstring/1st degree burn/bronchitis (all on Days 47-67; no action taken with study drug; bronchitis recovered/resolved with unspecified sequelae)
- (b) (6) (17/F): upper respiratory tract infection (Days 69-79; resolved/recovered)

The AEs were generally ones that may be seen with JAK inhibitors. For 3 subjects, the AEs had their onset after completion of the treatment period (i.e., after Day 56), on Day 69 (upper respiratory tract infection), Day 86 (neutropenia), and Day 88 (allergic rhinitis). For the remaining 2 subjects, no action was taken with study drug. The AEs were considered treatment-related for 2 subjects (neutropenia and "ALT & AST increased").

Of the 5 adolescent subjects who experienced AEs, 4 had moderate or severe AD (the remaining subject had mild AD, and the AE was allergic rhinitis). AEs in the adolescent subjects were generally seen in subjects with the higher C_{max} and AUC_{0-t} values on Day 1. The % BSA for 3 subjects (26%, 29%, and 30%) who experienced AEs was in the range of most other adolescent subjects in the study, since 17 of those subjects (81%) had % BSA involvement of 26-32%. However, there was one adolescent subject ((b) (6)) who had higher affected % BSA (31.5%) and higher C_{max} and AUC_{0-t} than those 3 subjects with AEs, and no AEs were reported for that subject. A total of 3 adolescent subjects had % BSA affected of ≥ 40%, and 2 of those subjects experienced AEs. See Table 57.

Table 57 Adolescents Individual and Summary of Plasma Ruxolitinib Pharmacokinetic Parameters on Day 1*

Subject	*% BSA/IGA*	*C_{max} Day 1*	*AUC_{0-t} Day 1*
(b) (6); 16/M	32.0/4	20.5	208
(b) (6) 13/F	32.0/3	30.3	291
(b) (6) 13/F	35.0/3	34.0	344
(b) (6) 15/M	30.0/3	4.84	43.8
(b) (6) 16/M	25.0/2	5.10	38.3
(b) (6); 14/M	29.4/3	50.8	321
(b) (6) 16/M	29.8/2	25.9	176
(b) (6); 15/M	29.0/2	113	487
(b) (6) 14/M	25.7/2	30.7	212
(b) (6) 15/M	26.9/2	35.3	186
(b) (6) 14/M	26.5/2	23.1	123
(b) (6) 14/M	31.2/2	8.12	68.5
(b) (6); 14/F	30.6/2	21.6	148
(b) (6) 15/M	26.5/3	52.8	282
(b) (6) 15/F	26.0/2	1.99	15.3
(b) (6) 17/F	30.0/3	85.5	796
(b) (6); 13/M	29.5/2	15.3	115
(b) (6) 16/F	31.5/3	270	1020
(b) (6) 16/M	43.0/4	34.7	383
(b) (6); 13/M	43.4/3	1170	9350
(b) (6);	54.5/4	273	2210

17/F			

Subjects with AEs are highlighted
*Source: Listing 2.4.2 Study 103; Table 12 DMB-20.55.3
BSA=body surface area; IGA= Investigator's Global Assessment; C_{max}= maximum observed plasma concentration; AUC_{0-tau}= area under the plasma or serum concentration-time curve from time = 0 to the last measurable concentration at time = t

Discussion: The AEs that were observed in adolescents in the MUsT study were generally ones that may be seen with JAK inhibitors. For 3 subjects, the onset of AEs was ~ 2-4 weeks after completion of the treatment period, which may raise a question of relatedness to treatment. For the remaining 2 adolescents, no action was taken with study medication. The AEs were not worrisome in type, severity, course, or frequency, particularly given the potential exposure from use in a population with extensive disease (as appropriate for a MUsT). A total of 11 adolescent subjects (52%) met the criteria for being potential candidates for systemic therapy by the definitions applied in development programs for such products e.g., dupilumab and upadacitinib required that subjects have moderate-to-severe disease affecting at least 10% BSA. Additionally, all 21 continued treatment into the extension period which made for a potential 8-week treatment period, which may exceed the possible labeled use of "short-term and non-continuous" treatment. The MUsT appears to have assessed ruxolitinib 1.5% cream in several ways that are more intensive than the likely labeled conditions of use, and the safety findings were not concerning, to this reviewer.

Conclusions on Adolescent Use:

Data from the Phase 3 program and the MUsT revealed a safety profile in adolescents that was similar to that seen in adults. These data adequately support the safety of ruxolitinib 1.5% cream in adolescents, a product that will be labeled for "short-term and non-continuous" use. At approval, the product will also have labeling that reflects the safety profile of JAK inhibitors approved for treatment of inflammatory conditions (b) (6) With this labeling, prescribers and users will be advised of the potential for adverse reactions, including serious adverse reactions, with systemic exposure. That the Applicant has provided long-safety data for 47 adolescents to date is not itself sufficient basis for delaying approval, in my opinion. The available data reveal a safety profile in adolescents that is similar to that in adults. The options for safe and effective nonsteroidal topical treatments for AD are very limited. Delaying approval of the product for adolescents would delay availability of a new safe and effective nonsteroidal product for topical treatment of mild to moderate AD for this population. Additional long-term safety data will be collected in a one-year, open-label safety study in subjects 12-17 years old as a PMR, and this seems reasonable.

Other Pediatric Assessments

The Applicant requests:

- A partial waiver for study of the 0 to < 3 months age group on the grounds that

studies are highly impracticable because of difficulties in establishing a definitive diagnosis of AD in this age group. The chronicity of the disease, a criterion for the diagnosis of AD, cannot be evaluated in infants < 3 months of age.

- A deferral of pediatric assessments in the ≥ 2 years to < 12 years age group until after the completion of the benefit/risk assessment from the studies in adolescents (≥ 12 to < 18 years age group) (b) (4)
- (b) (4)

The approach to the other pediatric assessments is reasonable and consistent with the Agreed iPSP.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There is no known drug abuse potential for ruxolitinib cream. The Applicant did not specifically assess the potential for withdrawal and rebound. However, the Applicant found no evidence of either of these phenomena with ruxolitinib cream.

8.2.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Ruxolitinib cream is not marketed.

Expectations on Safety in the Postmarket Setting

With sufficient systemic exposure, the safety profile could be similar to that of oral ruxolitinib or other JAK inhibitors. Local reactions are a possibility with topical products. However, there was no signal that ruxolitinib cream has the potential for significant irritancy, sensitization, phototoxicity, or photoallergy.

8.2.10. Integrated Assessment of Safety

The safety database included 857 subjects who were exposed to ruxolitinib 1.5% cream in 3 safety and efficacy studies. Although the Applicant and Agency discussed the safety database, the Agency did not recommend specific numbers of subjects to include in the database in the NDA. The numbers of adult subjects with AD with exposures to ruxolitinib 1.5% cream BID somewhat exceeded those recommended in the ICH E1A guideline for the 6 month (n= 365) and one year (n = 125) time points. See Section 8.2.9 for discussion of the pediatric assessment.

A total of 7 subjects (0.7%) treated with ruxolitinib cream experienced SAEs in the Phase 3 VC Population, 3 of whom were treated with the 1.5% concentration proposed for marketing. Pneumonia was the only SAE for which there was more than one report in a treatment group, and both events occurred in the 0.75% group. The other SAE for which there was more than one report was cerebrovascular accident (CVA), and there were 2 reports of this event: one in the 0.75% arm and the other in the 1.5% arm.

Generally:

- A causative role for study treatment in the SAE was not apparent or seemed unlikely due to timing of onset of the event relative to onset of study treatment, the nature of the event (e.g., bile duct stent), and/or confounders in the medical history (e.g., history of hypercholesterolemia and hypertension in the subjects who experienced CVAs).
- The SAEs did not result in long or complicated hospital courses or long-term sequelae.
- No action was taken with study treatment or any interruption was short-term e.g., one day.

The pattern of occurrence of SAEs in the Phase 2/3 Population raised no new safety concerns relative to the shorter-term exposure in the Phase 3 VC Population.

The highest incidence of discontinuations due to TEAEs in the Phase 3 VC Population was in the vehicle group (8 subjects; 3.2%), and the most commonly TEAE reported was “dermatitis atopic.” The proportions of subjects who discontinued from the ruxolitinib treatment groups were the same between the 0.75% and 1.5% arms at 0.8% (4 subjects in each group), and no TEAE was reported in more than one subject as the event leading to discontinuation in either active treatment arm. The cerebrovascular accident was the only SAE that led to discontinuation of study treatment.

TEAEs ≥ Grade 3 severity tended to correlate with SAEs, which is not unexpected.

In the Phase 3 VC Population, 277 subjects (27.7%) experienced at least one AE: 83 (33.2%) in the vehicle group, 145 (29%) in the 0.75% group, and 132 (26.5%) in the 1.5% group. TEAEs were most frequently reported in the Infections and infestations SOC. Nasopharyngitis was the commonly reported TEAE in this SOC (and overall): vehicle- 2 subjects (0.8%), ruxolitinib cream 0.75%- 15 (3.0%), and ruxolitinib cream 1.5%- 13 (2.6%). Upper respiratory tract infection was the second most commonly reported TEAE in this SOC: vehicle- 5 subjects (2.0%), ruxolitinib cream 0.75%- 7 (1.4%), ruxolitinib cream 1.5%- 12 (2.4%). TEAES were next most commonly reported in the Skin and subcutaneous disorders SOC. Urticaria was the most commonly reported TEAE in ruxolitinib groups in this SOC: vehicle- 0, ruxolitinib cream 0.75%- 4 (0.8%), and ruxolitinib cream 1.5%- 4 (0.8%).

In the Phase 3 studies, the incidence of any application site TEAE was low in the ruxolitinib 1.5% cream BID arm, at 1.6% (7.2% in the vehicle arm), and the most

commonly reported event was “application site pain,” reported in 4 subjects (0.8%) in the ruxolitinib 1.5% cream arm (12 subjects or 4.8% in the vehicle arm). The Applicant also conducted a battery of provocative dermal safety studies in healthy subjects to evaluate the product for the potential for cumulative irritancy, contact sensitization, phototoxicity, and photoallergenicity. These studies are designed to screen for local cutaneous safety signals with fewer subjects than would be needed in clinical trials that evaluate intended, non-occlusive product use. The cumulative evidence from the safety and efficacy studies and the dermal safety studies indicates that ruxolitinib 1.5% cream does not have significant potential for irritancy, and did not show evidence of it causing contact sensitization or photosensitivity reactions.

The systemic exposure from ruxolitinib 1.5% cream may overlap with that from orally administered ruxolitinib (see the Clinical Pharmacology review in Section 6). The following sections discuss TEAEs that may reflect systemic exposure to ruxolitinib or that may be seen with other JAK inhibitors that are indicated for treatment of inflammatory conditions:

1. Cytopenias

Overall, the Applicant identified no trends in decreases in hematological parameters. The Applicant also identified no correlation between overall mean steady state plasma concentration (C_{ss}) quartiles and decreases in hematological parameters i.e., hemoglobin, absolute neutrophils, mean platelet volumes (MPVs), and platelet counts. No cytopenia TEAE was reported as an SAE.

Hemoglobin

Mean hemoglobin levels were similar between the vehicle and both ruxolitinib groups at all visits through Week 8. In the VC period, for subjects in the ruxolitinib groups whose hemoglobin concentration values were categorized as Grade 0 at baseline, 92-93% remained Grade 0 post baseline, when the worst post-baseline value was considered, and this was similar to vehicle (93%).

Through week 8, the incidences of erythropenia events (anemia) were similar between vehicle and ruxolitinib treatment groups, at 0.4% in the vehicle and 0.75% groups and no events reported in the 1.5% group.

Platelets

The Applicant observed “small, transient increases in platelet counts” at Week 2 in the ruxolitinib groups in the Phase 3 studies. However, counts remained within the normal range. Mean platelet counts were similar across all 3 treatment groups at all visits through Week 8 (Phase 3 VC Population). Through Week 8, most subjects (~ 97% in all 3 treatment groups) were Grade 0 at baseline. No subjects in any of the 3 treatment groups experienced a shift to a worst post-baseline value greater than Grade 1. The shift from baseline Grade 0 to a worst post-baseline value in the Grade

1 category occurred for 6 subjects in the vehicle group (2.5%), 8 subjects in the 0.75% ruxolitinib group (1.7%), and 3 subjects in the 1.5% ruxolitinib group (0.6%). For subjects in the ruxolitinib groups who were categorized as Grade 0 at baseline, ~96-97%% remained Grade 0 post baseline, when the worst post-baseline value was considered, and this occurred for ~95% of subjects in the vehicle group. See Table 33.

Neutrophils

Mean neutrophil counts were similar across the 3 treatment groups at all visits through Week 8, with no trends noted. A similar pattern was noted in the Phase 2/3 pool, and mean counts generally were within the normal range through Week 52.

Across all 3 treatment groups, ~ 97% of subjects had baseline neutrophil counts assessed as Grade 0. In the ruxolitinib groups, 94% of these subjects had worst post-baseline values of Grade 0 through Week 8, and this was observed in ~92% of subjects in the vehicle group. One subject who had Grade 0 neutrophil counts at baseline experienced a decrease in counts to a worst post-baseline shift to Grade 3, and that subject was in the ruxolitinib 1.5% group. Through Week 52, Grade 0 to Grade 3 shifts were reported only in the ruxolitinib 1.5% (5 subjects, 0.6%).

Through week 8, all TEAEs related to neutropenia were reported in the ruxolitinib groups, and the overall incidence was low, 2 subjects in each group (0.4%).

2. Infections

TEAEs were most frequently reported in the Infections and infestations SOC and were reported at the following overall incidences through Week 8: vehicle- 17 subjects (6.8%), ruxolitinib 0.75% cream - 68 (13.6%), and ruxolitinib 1.5% cream- 55 (11.0%). Nasopharyngitis was the commonly reported TEAE in this SOC (and overall), followed by Upper respiratory tract infection. The incidences of these 2 TEAEs were low and generally similar between the 3 treatment groups (1-3%) through the vehicle-controlled period (through Week 8). In the reviewer's experience, TEAEs are generally most commonly reported in the Infections and infestations SOC, and Nasopharyngitis and Upper respiratory tract infection are among the most commonly reported events. Bronchitis was the 3rd most frequently reported event in this SOC, and all 7 reports were in ruxolitinib treatment groups (0.7%), and the incidences were similar between the 0.75% and 1.5% treatment groups. Other TEAEs in this SOC that were reported only in ruxolitinib treatment groups and at an overall incidence of ≥ 0.5% were conjunctivitis, ear infection, and gastroenteritis (all at 0.5% incidence). All other TEAES that occurred only in ruxolitinib-treated subjects occurred in 1-2 subjects per event (< 0.5% incidence) and were commonplace types of infections e.g., oral herpes, tinea pedis, cystitis, influenza.

Herpes Zoster

Across clinical development programs for all indications (1942 subjects who had at least one application of cream, the All Ruxolitinib Population), the Applicant identified 12 subjects who experienced 13 herpes zoster events (includes one subject who experienced herpes zoster and postherpetic neuralgia). All events were of Grade 1 or 2 severity, except for one event that was Grade 3. None of the events was reported as an SAE. Study treatment was interrupted for one subject, the subject who experienced postherpetic neuralgia. For the remaining subjects, study treatment was unchanged (for 3 subjects, the herpes zoster occurred after the last application of ruxolitinib cream).

Of the 12 subjects who experienced herpes zoster, 8 (66.6%) were in the AD studies, including the 2 pediatric subjects who experienced this event: a 13 y/o male and a 17 y/o male. Additionally, a 26 y/o female and a 30 y/o male in the AD program experienced herpes zoster. The Applicant reported that the plasma ruxolitinib levels, for the 6 AD subjects with available data, were "substantially less than the IC50 for JAK2 inhibition in whole blood assays," referring to the levels prior to onset of the event. The incidence of herpes zoster in the Phase 3 AD studies was 0.2%.

3. Malignancy/NMSC

Across clinical development programs for all indications (1942 subjects who had at least one application of ruxolitinib cream), 7 subjects had at least one NMSC. Of these, 4 subjects were in the AD clinical trials, and these subjects ranged in age from 65 to 82 years. When location was reported (location was not reported for one subject), none of the tumors in the AD subjects occurred at application sites. All but one of the 4 subjects had a single NMSC. The subject who had multiple tumors had 1 BCC and 2 SCC, and all lesions were at different locations relating to the right upper extremity (wrist, arm, and shoulder), and all lesions were reported on Study Day 7. The NMSC for the other 3 subjects in the AD studies "started" on Days 27, 43, and 298. The NMSC for all 4 subjects in the AD program were at sites that might reasonably be considered "sun-exposed," and all were Grade 2 severity except for one subject with SCC whose TEAE was considered Grade 1. No changes were made with study drug for these 4 subjects.

No other malignancies were reported in ruxolitinib-treated subjects with AD through Week 52 [Neoplasms benign, malignant and unspecified (incl cysts and polyps) SOC]. Across clinical development programs for all indications, the other malignancies that were reported in the ruxolitinib-treated subjects were lentigo maligna and prostate cancer (one report each).

4. ***Lipid Elevations***

There was no requirement for fasting for lab evaluations. In this context, reports of elevations of any lipid parameter were uncommon (3 events in each ruxolitinib group) and were reported at single digits for any parameter in ruxolitinib groups, with incidence of 0.2% per TEAE.

The Applicant reported that percent changes in cholesterol, LDL, VLDL, HDL, and triglycerides were similar across all treatment groups at all visits through Week 8 and through Week 52. No trends were identified and no clinically significant variations through Week 8 and through Week 52. There was no evidence of impact of ruxolitinib on lipid parameters.

5. ***Thromboembolic Events***

Across clinical development programs for all indications (1942 subjects who had at least one application of cream), 7 subjects experienced a thrombotic or embolic TEAE (6 were SAEs), and all were using ruxolitinib cream at the time of onset of the event: coronary artery occlusion (n=2), cerebrovascular accident (n=2), myocardial infarction, pulmonary embolism (the only nonserious event), and deep vein thrombosis with pulmonary embolism.

At all study visits prior to the onset of the event, all of these subjects were reported to have had plasma ruxolitinib concentrations lower than the reported mean steady-state plasma concentration for the 1.5% BID cream (35.7 nM) in the pivotal AD studies, 303 and 304. All subjects had medical histories that placed them at increased risk for a thromboembolic event, which confounds the interpretation of relatedness to treatment.

6. Liver Function Tests

The Applicant reported that ALT, AST, and bilirubin percent changes were similar across all treatment groups through Week 8 and through Week 52, with no trends identified and no clinically significant variations and with values generally remaining stable and within normal ranges through the long-term period.

The Applicant reported post-baseline shifts in the Phase 3 VC Population in ALT, AST, and bilirubin were generally to Grade 1 or 2. Two subjects in the ruxolitinib 1.5% group experienced Grade 1 to Grade 3 post-baseline shifts, and the shifts were in the ALT and bilirubin (one subject for each of these shifts).

<u>Safety Conclusions</u>

The Applicant comprehensively evaluated the safety of ruxolitinib 1.5% cream in subjects with mild-to-moderate AD. Ruxolitinib 1.5% cream was well tolerated in the study population.

The types and frequency of safety evaluations were adequate to identify local TEAEs that might be observed with ruxolitinib 1.5% cream. The safety data indicate that ruxolitinib 1.5% cream does not have significant potential for irritancy, and did not demonstrate that ruxolitinib 1.5% cream may be a contact sensitizer or induce photosensitivity reactions.

The types and frequency of safety evaluations were also adequate to evaluate for systemic TEAEs that might be seen with oral ruxolitinib or with oral JAK inhibitors that are approved for other inflammatory conditions. Regarding the latter, other JAK inhibitors may have safety profiles that include adverse reactions that have not been reported with oral ruxolitinib to date. The Applicant also performed safety analyses across indications to assess for the potential for systemic adverse reactions with use of topical ruxolitinib cream. TEAEs suggestive of systemic effect were infrequent, uncomplicated, and generally resolved without any action taken with study treatment.

Because of the potential for systemic exposure that overlaps with oral ruxolitinib, labeling of risks from ruxolitinib 1.5% cream should align with the label for the oral product and with JAK inhibitors approved for treatment of inflammatory conditions.

For adults and adolescents, potential risks from systemic exposure may be mitigated by labeling that advises of:

- limits to the definition of the target population (mild to moderate disease),
- limits in the extent of BSA for treatment (up to 20% BSA),
- limits in the parameters of treatment (short-term, noncontinuous),
- limits in the amount of product to use in a specified time frame (60 gm per week).

Also, such labeling reflects the AD population that provided the safety data to support the marketing application.

8.3. Statistical Issues

No significant statistical issues were identified regarding the primary efficacy endpoint of treatment success on the IGA; efficacy was demonstrated for IGA success in both studies. There was no baseline requirement for EASI (subjects had baseline scores as small as 0.6) and thus it may be difficult to interpret for subjects with small EASI scores at baseline. (b) (4) . Thus, EASI 75 may not be appropriate for labeling and provides limited additional information beyond the IGA success endpoint. Efficacy was also demonstrated for the secondary endpoint of ≥4-point improvement on the Itch NRS.

(b) (4)

(b) (4)

8.4. Conclusions and Recommendations

The totality of the data supports that the benefits of ruxolitinib cream 1.5% outweigh its risks for treatment of mild to moderate atopic dermatitis in patients 12 years and older.

The review team recommends approval of this application.

9 Advisory Committee Meeting and Other External Consultations

An Advisory Committee meeting was not held for this application.

10 Pediatrics

See Section 8.2.9.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Labeling negotiations were underway as this review was being finalized.

12 Risk Evaluation and Mitigation Strategies (REMS)

None

13 Postmarketing Requirements and Commitment

1. Conduct a one-year, open-label safety study in subjects with atopic dermatitis ≥ 12 years to < 18 years.

2. Conduct a randomized, double-blind, 8-week trial of ruxolitinib 1.5%, ruxolitinib 0.75%, and vehicle, followed by a 44-week long-term safety extension where vehicle subjects are randomized to either ruxolitinib 1.5% or ruxolitinib 0.75%. The study should enroll 250 subjects ≥ 2 to < 12 years with atopic dermatitis of at least 3 months duration, an Investigator's Global Assessment score of 2 to 3, and % body surface area involvement (excluding scalp) of 3% to 20% (Study INCB 18424-305).

3. Conduct an open-label safety study in 100 subjects ≥ 3 months to < 24 months with atopic dermatitis with ruxolitinib cream applied twice daily (BID) for 4 weeks with a 48-week extension treatment period and assess PK under maximal use conditions in a subset of at least 16 subjects.

4. The applicant should be required to conduct a Pregnancy Exposure Registry, a prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to ruxolitinib during pregnancy to an unexposed control population. The registry should be designed to detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life. For more information, see the May 2019 FDA draft Guidance for Industry Postapproval Pregnancy Safety Studies.

5. The applicant should be required to conduct an additional pregnancy study that uses a different design from the Pregnancy Registry (for example a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to ruxolitinib during pregnancy compared to an unexposed control population.

6. The applicant should be required to conduct a lactation study (milk only) in women prescribed ruxolitinib who are willing to discontinue breastfeeding their infants. A milk only study is recommended because of the risk of serious adverse events seen in adult patients who have taken ruxolitinib. In this type of study, the infant is not exposed to ruxolitinib. For more information, see the May 2019 FDA draft Guidance for Industry Clinical Lactation Studies: Considerations for Study Design.

14 Appendices

14.1. References

See footnotes.

14.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): INCB 18424-303; INCB 18424-304;18424-103

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 151		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

14.3. Nonclinical Pharmacology/Toxicology

14.3.1. Review of the 2-year dermal carcinogenicity study report

Study title: INCB018424: A 104-Week Dermal Carcinogenicity Study in CD-1 Mice

Study no.:	(b) (4)-519093
Study report location:	SD 2, NDA 215309
Conducting laboratory and location:	(b) (4)
Date of study initiation:	03/31/2009
GLP compliance:	Yes
Drug, lot #, and % purity:	INCB018424 vehicle cream, lot# ALX-C INCB018424 cream 0.5%, lot# ALZ-C, purity 101.9-102.6% INCB018424 cream 1.0%, lot# AFA-C, purity 101.0-102.7% INCB018424 cream 1.5%, lot# AFB-C, purity 104.4-106.4%
Prior ECAC dose concurrence:	Yes
Basis for dose selection	Maximum feasible dose (MFD)

Reviewer Carcinogenicity Conclusion: Negative
ECAC Carcinogenicity Conclusion: Negative

Tumor Findings:

No significant toxicity was noted in this study. A complete list of tissues was examined histopathologically for all main study animals. In male mice, statistical significance was achieved in the incidence of kidney adenoma (if this tumor type is considered rare) in the trend test using vehicle control, but not in the trend test using untreated control, or in any pairwise comparison. Statistical significance was also achieved in the incidence of malignant lymphoma in the trend test using untreated control and in pairwise comparison of high dose vs. untreated control, but not in the trend test using vehicle control or other pairwise comparisons. This finding did not appear to be INCB018424-related. Considering that malignant lymphoma is a systemic tumor, and systemic (oral) carcinogenicity studies have been conducted in two species with negative results, this finding is not considered biologically significant. In female mice, statistical significance was achieved in the incidence of malignant hemangiosarcoma in pairwise comparison of low dose vs. vehicle control and in the incidence of malignant lymphoma in pairwise comparison of untreated control vs. vehicle control. However, the trend tests were all negative and these findings are therefore not considered biologically significant.

Overall, no biologically significant test article-related neoplastic findings were noted in this study. INCB018424 cream up to 1.5% was not carcinogenic when administered topically to mice once daily for 2 years. The NOAEL identified in this study was the high dose tested, 1.5% cream applied at 100 µl/dose once daily for two years.

Methods

Doses:	For both males and females: 0 (untreated control), 0 (vehicle control), 0.5%, 1.0%, and 1.5% INCB018424 cream (applied at 100 µl/day; ~15, 30, and 45 mg/kg/day INCB018424 for a 35 g mouse)
Frequency of dosing:	Once daily, to ~10% BSA
Dose volume:	100 µl/dose
Route of administration:	Dermal, unoccluded.
Formulation/Vehicle:	Clinical vehicle ((b) (4)% propylene glycol, (b) (4)% methylparaben, (b) (4)% propylparaben, (b) (4)% xanthan gum, (b) (4)% light mineral oil, (b) (4)% glyceryl stearate SE, (b) (4)% polysorbate (b) (4)% white petrolatum, (b) (4)% cetyl alcohol, (b) (4)% stearyl alcohol, (b) (4)% dimethicone 350, (b) (4)% medium chain triglycerides, (b) (4)% edetate disodium, (b) (4)% polyethylene glycol 200, (b) (4)% phenoxyethanol, and (b) (4)% purified water)
Species/Strain:	CD-1 mouse
Number/Sex/Group:	Main study: 60/sex/group TK animals: 16/sex/group for vehicle control, 42/sex/group for three dose groups.
Age:	~7 weeks at the start of dosing
Comment on study design and conduct:	Animals were individually housed in stainless steel, wire-mesh cages.
Dosing comments	None
Dosing solution analysis	Not conducted by the contract lab. The test articles were directly provided by the sponsor.

Observations and Results

Mortality

Per the statistical reviewer's analysis, there were no significant treatment-related findings in mortality in either males or females (refer to the statistical review by Dr. Hepei Chen).

Animal survival at the end of the 2-year dermal mouse carcinogenicity study:

		Group 1 (untreated)	Group 2 (vehicle)	Group 3 (low dose)	Group 4 (mid dose)	Group 5 (high dose)
Male	Survival number	18	15	21	17	16
	Survival rate	30%	25%	35%	28%	27%
Female	Survival number	20	21	23	16	30
	Survival rate	33%	35%	38%	27%	50%

Clinical Signs

There were no significant treatment-related clinical signs.

Dermal Observations

There were no significant treatment-related dermal observations at the administration sites.

Body Weights

Body weight was measured weekly for the first 14 weeks and biweekly thereafter. There were no significant treatment-related effects on body weights.

Feed Consumption

Food consumption was measured weekly for the first 14 weeks and biweekly thereafter. There were no significant treatment-related effects on food consumption.

Gross Pathology

There were no significant treatment-related findings.

Histopathology

Peer Review: Yes
Historical Control Provided for Tumor Incidence: Not provided

Neoplastic:

A complete tissue list was examined for all main study animals. The tumor incidence data were analyzed by the statistical reviewer Dr. Hepei Chen. Two dose-response relation tests (trend tests) were conducted across the vehicle control group, low, mid, and high dose groups and across the untreated control group, low, mid, and high dose groups, respectively. Pairwise comparison tests were conducted for untreated control group and three dose groups against the vehicle control group. A Poly-k method was used for the data analysis (k=3).

According to the FDA guidance for statistical design and data analysis of carcinogenicity studies, Dr. Chen used significance levels of $\alpha = 0.005$ for common tumors and $\alpha = 0.025$ for rare tumors (with a background incidence rate of 1% or less) for dose response relation tests and significance levels of $\alpha = 0.01$ for common tumors and $\alpha = 0.05$ for rare tumors for multiple pairwise comparisons.

Refer to Dr Chen's review for the complete results of tumor incidence data analysis. Per Dr. Chen's analysis, the tumor types with p-values less than or equal to 0.05 for dose response relationship and/or pairwise comparisons are shown in the following table (copied from Dr. Chen's review).

Tumor types with p-values ≤ 0.05 for dose-response relation tests and/or pairwise comparisons tests in the 2-year dermal mouse carcinogenicity study:

Organ name	Tumor name	Placebo (PC) 0 % P – Trend (PC)	Low (L) 0.5 % P - PC vs. L P - UC vs. L	Mid (M) 1 % P - PC vs. M P - UC vs. M	High (H) 1.5 % P - PC vs. H P - UC vs. H	Untreated (UC) 0 % P - PC vs. UC P – Trend (UC)
Male						
Kidneys	#B Adenoma	0/60 (33)	0/60 (35)	1/60 (32)	3/60 (32)	2/60 (31)
		0.0161 $	NC	0.4923	0.1136	0.2307
Systemic Tumors	#M Lymphoma, Malignant	8/60 (37)	4/60 (37)	6/60 (36)	15/60 (38)	3/60 (31)
		0.0293 @	0.9439	0.7976	0.0765	0.9547
			0.6003	0.3197	0.0047 $	0.0007 $
Harderian Glands	#B Adenoma	1/60 (42)	0/60 (41)	0/60 (36)	5/60 (44)	3/60 (39)
		0.0218 @	1.0000	1.0000	0.1120	0.2801
	#M Carcinoma	0/60 (42)	0/60 (41)	1/60 (37)	0/60 (44)	0/60 (39)
		0.4939	NC	0.4684	NC	NC
	#B Adenoma/#M Carcinoma	1/60 (42)	0/60 (41)	1/60 (37)	5/60 (44)	3/60 (39)
		0.0206 @	0.4940	0.7205	0.1120	0.7199
Female						
Systemic Tumors	#B Hemangioma	2/60 (42)	1/60 (41)	0/60 (36)	2/60 (44)	4/60 (39)
		0.6518	0.8751	1.0000	0.7094	0.3028
	#M Hemangiosarcoma	2/60 (42)	11/60 (43)	6/60 (39)	8/60 (46)	8/60 (42)
		0.1617	0.0076 $	0.1093	0.0609	0.0441 @
	#B Hemangioma/ #M Hemangiosarcoma	4/60 (43)	12/60 (44)	6/60 (39)	10/60 (46)	12/60 (43)
		0.1890	0.0283 @	0.3075	0.0927	0.9749
	#M Lymphoma, Malignant	11/60 (47)	22/60 (49)	18/60 (47)	14/60 (50)	23/60 (45)
		0.4558	0.0222 @	0.0899	0.3885	0.0054 $

[&] X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed
NC = Not calculable.
$ = Statistically significant at 0.025 level in rare tumor for test of dose response relationship or at 0.01 level in common tumor for test of pairwise comparisons
@ = Not statistically significant at 0.005 level in common tumor for test of dose response relationship or at 0.01 level in common tumor for test of pairwise comparisons;

In male mice, statistical significance was achieved in the incidence of kidney adenoma (if this tumor type is considered rare) in the trend test using vehicle control (p = 0.0161), but not in the trend test using untreated control, or in any pairwise comparison. Usually for a neoplastic finding considered to be biologically significant, statistical significance should be achieved in both the trend test and pairwise comparison test. This finding is not considered biologically significant. Also, kidney adenoma is not considered a rare tumor. Statistical significance was also achieved in the incidence of malignant lymphoma in the trend test using untreated control (p = 0.0007) and in pairwise comparison of high dose vs. untreated control (p = 0.0047), but not in the trend test using vehicle control or other pairwise comparisons. This finding did not appear to be INCB018424-related. Considering that malignant lymphoma is a systemic tumor, and

systemic (oral) carcinogenicity studies have been conducted in two species with negative results, this finding is not considered biologically significant.

In female mice, statistical significance was achieved in the incidence of malignant hemangiosarcoma in pairwise comparison of low dose vs. vehicle control (p = 0.0076) and in the incidence of malignant lymphoma in pairwise comparison of untreated control vs. vehicle control (p = 0.0054). However, the trend tests were all negative and these findings are therefore not considered biologically significant.

Overall, there were no biologically significant test article-related neoplastic findings in either sex.

Non-neoplastic:

There were no significant test-article related findings.

Toxicokinetic Analysis

TK parameters of INCB018424 for Days 0 and 188 were measured (shown in the table below). There were no marked gender differences on Day 188. Generally systemic exposure to INCB018424 at Day 188 increased with dose in a roughly dose-proportional manner across the dose range. Drug accumulation was not noted over repeat dosing.

Summary toxicokinetic results of the 2-year dermal mouse carcinogenicity study:

Dosage	$AUC_{0\text{-}24hr}$ (µM•hr)		C_{max} (µM)		C_{ss} [a] (µM)	
	Day 0	Day 188	Day 0	Day 188	Day 0	Day 188
Males						
INCB018424 0.5%	0.581	0.722	0.287	0.214	NA	0.0624
INCB018424 1.0%	1.73	1.55	1.17	0.537	NA	0.160
INCB018424 1.5%	3.63	2.37	2.76	0.834	NA	0.222
Females						
INCB018424 0.5%	1.69	1.02	1.14	0.522	NA	0.134
INCB018424 1.0%	7.55	1.80	7.35	0.804	NA	0.213
INCB018424 1.5%	10.5	2.70	4.39	1.44	NA	0.360

[a] = Calculated as the mean concentration of all time-points for the given group on study day 188.
NA = Not applicable.

14.3.2. Multiples of human exposure calculation

The multiples of human exposure based on AUC comparison between the NOAELs identified in pivotal toxicology studies and the clinical dose tested in a maximum use clinical trial (Study INCB 18242-103, ruxolitinib cream 1.5% BID applied to baseline-

affected BSA 25-40% in adult and adolescent subjects with atopic dermatitis) are shown in the table below.

Multiples of human exposure for NOAELs identified in pivotal toxicology studies:

Study	Route	NOAEL (mg/kg/day)	AUC[b] (nM•hr)	Multiples of human exposure[e] (based on AUC comparison)
6-month rat study	Oral	30	662	0.8
52-week dog study	Oral	1.5	2360	2.8
9-month minipig study	Dermal	Dermal: 6.6	145	0.2
		Systemic: 9.9	167	0.2
2-year carcinogenicity study in rats	Oral	60[a]	2990	3.5
2-year carcinogenicity study in mice	Dermal	45[a]	2370	2.8
Fertility and early embryonic development study in rats	Oral	Fertility: 60	19000[c]	22
		Embryofetal: 10	N/A[c]	N/A
Embryofetal development study in rats	Oral	Maternal: 30	2980[c]	3.5
		Embryofetal: 30	2980[c]	3.5
Embryofetal development study in rabbits	Oral	Maternal: 30	68	0.1
		Embryofetal: 30	68	0.1
Pre- and postnatal development study in rats	Oral	Maternal: 30	2680	3.1
		Developmental: 30	2680	3.1
Juvenile toxicity study in rats	Oral	5[d]	M: Not reported	None
			F: 337	0.4

[a] Dose level of no neoplastic findings for carcinogenicity studies
[b] The lower AUC value between males and females was used for the calculation
[c] The AUC values were from a different study (Study# 1603-0794) and the 10 mg/kg/day dose was not tested (N/A: Not available).
[d] The NOAEL for dosing period of postpartum days 7-63. It should be noted that the AUC values were much higher at postpartum day 7 than day 63; while the AUC value for females at day 63 was used for calculation (136 ng•hr/ml = 337 nM•hr)

[e] Compared with the mean human AUC_{0-24h} value at Day 28 in the clinical PK study (Study INCB 18242-103, 1.5% cream BID applied to baseline-affected BSA 25-40% in adult and adolescent subjects with atopic dermatitis): 854 nM•hr (mean AUC_{0-12h} value: 427 nM•hr)

14.3.3. Recommended revisions to the nonclinical portions of labeling

Revisions to the applicant's proposed wording for the nonclinical and related sections of the labeling are provided below. It is recommended that the underlined wording be inserted into and the ~~strikethrough~~ wording be deleted from the OPZELURA label proposed by the applicant. The subheadings in Section 8.1 should be in underlined format. A clean copy of the recommended nonclinical portions of labeling is also provided.

(b) (4)

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

14.4. OCP Appendices (Technical documents supporting OCP recommendations)

Study INCB 18424-103 (Maximal use PK study in adults and pediatrics)
Title: A maximum use trial of ruxolitinib cream in adolescent and adult subjects with atopic dermatitis.
Objective: To evaluate the systemic exposure of ruxolitinib cream 1.5% in subjects with AD under maximum use conditions, with highest treated % BSA at 90%.
Study population: A total of 41 subjects were enrolled, 39 completed Day 28 (the treatment period). A total of 20 subjects (48.8%) were ≥ 18 years of age, 14 subjects (34.1%) were aged 13-15 years, and 7 subjects (17.1%) were aged 16 or 17 years.
Dosing regimen: Twice daily (BID) for 28 days (total 56 topical applications).
Study duration: 28-day treatment period followed by a 3-day follow-up period.
Methods: The study enrolled a total of 41 subjects with atopic dermatitis (≥25% BSA). Ruxolitinib 1.5% cream was applied twice daily (BID) for 4 weeks with serial blood sampling taken throughout the study. Subjects were instructed to treat the areas of the skin affected by their AD, as identified at baseline, for the duration of the treatment period (initial 28 days) even if the skin changes began to improve/ decrease in size. After completion of the Day 28 assessments, eligible subjects with no additional safety concerns were offered the option to continue treatment of affected areas only for an additional 28 days, followed by a 30-day safety follow-up period.

Blood samples for plasma concentrations of ruxolitinib after topical applications of ruxolitinib 1.5% cream BID were collected at pre-dose (0 hour) and at 1, 2, 4, and 12 hours post-dose on Day 1 and Day 28. Pre-dose and 1 hour post-dose PK samples were collected on Day 15. Pre-dose PK samples were also collected on Days 56 and 86, if applicable.

Results:

Demographics: The PK of ruxolitinib cream 1.5% was investigated in 41 subjects aged ≥ 13 years with AD with a mean ± SD BSA involvement of 37.5 ± 16.1% (range: 25% - 90%). The equivalent lesion area treated ranges from 4,100 to 17,000 cm^2 and the mean lesion area treated was 6,570 cm^2. A total of 20 subjects (48.8%) in the study were ≥18 years of age, 7 subjects (17.1%) were aged 16 or 17 years, and 14 subjects (34.1%) were aged 13 - 15 years. A total of 28 subjects (68.3%) had the total affected % BSA at baseline between 25% and 35%, while the remaining 13 subjects (31.7%) had their affected %BSA at baseline ranged between 43% and 90%. The maximum affected %BSA at baseline in adolescent subjects was < 55% whereas 5 adult subjects had >55% BSA involvement at the baseline.

The PK sample collected from early termination visits (1.10 nM on Day 36 from subject (b) (6) and 3.95 nM on Day 14 from subject (b) (6)) were excluded.

PK analysis: Subjects applied approximately 1.5 mg/cm^2 of ruxolitinib 1.5% cream (mean ± SD API dose was 152 ± 89.1 mg ranging from 18.0 mg to 564 mg per application) to constant skin areas BID for 28 days. Plasma concentrations of ruxolitinib were quantifiable in all subjects. The mean ± SD plasma C_{max} and $AUC_{0\text{-}tau}$ for ruxolitinib in all subjects on Day 1 were 271 ± 650 nM and 1948 ± 4607 h·nM, respectively (Table 1). The mean ± SD plasma C_{max} and $AUC_{0\text{-}tau}$ for ruxolitinib on Day 28 were 137 ± 377 nM and 1122 ± 2930 h·nM, respectively (Table 2). Tables 3 and 4 show individual PK parameters on Days 1 and 28, respectively. Based on comparative PK data on Day 1 and Day 28, there was no drug accumulation. Based on C_{trough} levels on Day 1 and Day 15, systemic concentrations of ruxolitinib were at steady state by Day 15, and the arithmetic and geometric mean of steady state concentration (Css) were 104 nM and 26.5 nM, respectively.

Comparison of ruxolitinib plasma concentrations over time between Day 1 and Day 28 is illustrated in overall subjects in the study and also by stratifications of subject age group (i.e., 13 - ≤15 years of age, 16-17 years of age, ≥18 years of age) or by %BSA (i.e., 25 - <40%, ≥40%) in Figure 2. Overall, plasma concentration of ruxolitinib decreased over the treatment period from Day 1 to Day 28. Among different age groups, adult subjects showed notably higher ruxolitinib exposure compared to both pediatric age groups (i.e., 13- 15 years of age and 16 – 17 years of age) throughout 28-day treatment period (Figure 2) and this is due to adults with higher %BSA involvement and using higher doses compared to adolescent subjects in this study. Between two age groups in adolescent subjects, a higher plasma ruxolitinib concentration was observed in the young adolescent group (13-15 years of age) than the adolescent group age between 16 - 17 years on Day 28 (Figure 2). Between two BSA groups, subjects

with ≥40% BSA showed higher plasma ruxolitinib concentrations compared to those with <40% BSA (Table 1 and Figure 2).

Figure 1. Total BSA (%) at baseline and individual ruxolitinib plasma concentration over time *(Source: Figure 1 of Study report dmb-20-55-3)*

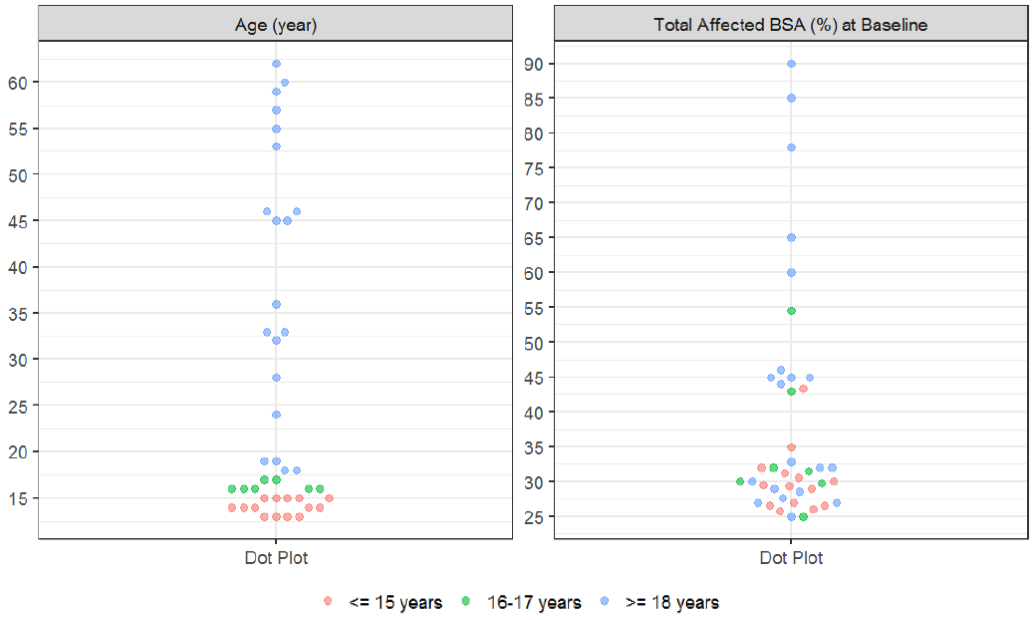


Table 1. Summary of ruxolitinib PK parameters by stratified age groups on Day 1 *(Source: Table 5 of Study report dmb-20-55-3)*

Strata	N	Total Affected BSA (%) at Baseline	Cmax (nM)	Tmax (h)	AUC(0-t) (h*nM)	C12h (nM)
Overall	40	38.4 ± 16.4 (35.9, 35.7%)	271 ± 650 (57.1, 480%)	4.00 (1.00, 12.0)	1950 ± 4610 (414, 458%)	119 ± 245 (34.7, 371%)
12-15 years	14	30.1 ± 4.64 (29.8, 14.1%)	114 ± 305 (28.5, 286%)	12.0 (1.00, 12.0)	856 ± 2450 (199, 265%)	60.7 ± 113 (25.5, 218%)
16-17 years	7	35.1 ± 10.1 (34.0, 26.8%)	102 ± 118 (48.1, 267%)	4.00 (2.00, 12.0)	690 ± 758 (371, 226%)	47.4 ± 43.4 (29.7, 190%)
≥ 18 years	19	45.6 ± 20.5 (41.9, 43.0%)	449 ± 883 (101, 681%)	4.00 (1.00, 12.0)	3220 ± 6190 (739, 666%)	188 ± 332 (46.0, 692%)
≥ 25 and < 40% BSA	27	29.3 ± 2.61 (29.2, 8.97%)	51.4 ± 69.7 (25.3, 193%)	12.0 (1.00, 12.0)	359 ± 510 (181, 179%)	39.0 ± 51.3 (20.0, 196%)
≥ 40% BSA	13	57.2 ± 17.1 (55.1, 28.0%)	727 ± 1010 (310, 312%)	4.00 (1.00, 12.0)	5250 ± 7140 (2310, 282%)	284 ± 381 (109, 495%)

Note: Summary values are mean ± SD (geometric mean, geometric CV%) except for T_{max} in median (min, max) if n > 2; otherwise, individual value is presented.

Table 2. Summary of ruxolitinib PK parameters by stratified age groups on Day 28 *(Source: Table 6 of Study report dmb-20-55-3)*

Strata	N	Total Affected BSA (%) at Baseline	C_{max} (nM)	T_{max} (h)	C_{min} (nM)	AUC(0-12h) (h*nM)	T1/2 (h)	C12h (nM)	C_{max}/C12h (unitless)	C_{max}/C_{min} (unitless)
Overall	38	37.6 ± 16.5 (35.1, 35.4%)	137 ± 377 (43.9, 219%)	4.00 (0.0, 12.0)	62.6 ± 165 (NC)	1120 ± 2930 (349, 241%)	116 ± 251 (32.5, 267%) [n = 9]	80.8 ± 166 (31.2, 224%)	1.67 ± 1.37 (1.41, 54.6%)	2.72 ± 1.91 (2.32, 56.8%) [n = 33]
12-15 years	14	30.1 ± 4.64 (29.8, 14.1%)	66.2 ± 93.3 (38.7, 141%)	12.0 (0.0, 12.0)	32.8 ± 64.5 (NC)	555 ± 863 (287, 178%)	266 ± 442 (45.2, 2090%) [n = 3]	52.1 ± 75.0 (29.7, 141%)	1.62 ± 1.71 (1.30, 58.8%)	3.20 ± 2.39 (2.64, 67.0%) [n = 11]
16-17 years	7	35.1 ± 10.1 (34.0, 26.8%)	24.5 ± 12.9 (22.5, 43.6%)	1.00 (0.0, 12.0)	11.0 ± 12.2 (NC)	196 ± 149 (160, 75.5%)	18.3 ± 7.02 (17.6, 40.9%) [n = 2]	16.9 ± 15.2 (12.4, 103%)	2.15 ± 1.52 (1.81, 66.7%)	2.90 ± 1.59 (2.58, 55.7%) [n = 6]
≥ 18 years	17	44.7 ± 21.6 (40.7, 45.1%)	242 ± 548 (64.3, 381%)	4.00 (0.0, 12.0)	108 ± 235 (NC)	1970 ± 4230 (566, 345%)	51.3 ± 49.0 (34.5, 143%) [n = 4]	131 ± 232 (47.5, 319%)	1.52 ± 0.994 (1.35, 45.6%)	2.32 ± 1.66 (2.03, 50.0%) [n = 16]
≥ 25 and < 40% BSA	27	29.2 ± 2.65 (29.1, 9.09%)	49.2 ± 51.2 (30.3, 147%)	4.00 (0.0, 12.0)	23.5 ± 29.3 (NC)	427 ± 499 (237, 173%)	159 ± 305 (40.1, 412%) [n = 6]	41.3 ± 48.8 (22.2, 182%)	1.64 ± 1.46 (1.37, 56.0%)	2.80 ± 1.89 (2.39, 57.2%) [n = 23]
≥ 40% BSA	11	58.1 ± 18.2 (55.7, 29.9%)	353 ± 669 (109, 287%)	1.00 (0.0, 12.0)	159 ± 290 (NC)	2830 ± 5170 (904, 265%)	28.0 ± 26.0 (21.4, 106%) [n = 3]	178 ± 284 (72.3, 217%)	1.74 ± 1.19 (1.51, 53.0%)	2.55 ± 2.05 (2.15, 58.3%) [n = 10]

N = number of participants; n = number of observations; NC = not calculable.
Note: Summary values are mean ± SD (geometric mean, geometric CV%) except for T_{max} in median (min, max) if n > 2; otherwise, individual values are presented.

Table 3. Individual and Summary of ruxolitinib PK parameters on Day 1 *(Source: Table 12 of Study report dmb-20-55-3)*

SUBJID	Age (year)	Total Affected BSA (%) at Baseline	C_{max} (nM)	T_{max} (h)	$AUC_{(0-t)}$ (h*nM)	$AUC_{(0-inf)}$ (h*nM)	$t_{½}$ (h)	Cl/F (L/h)	V_2/F (L)	C12h (nM)
(b) (6)	19	65.0	1260	4.00	8820					381
	45	25.0	245	12.0	2260					245
	32	45.0	742	4.00	6530					503
	60	90.0	3820	4.00	26600					1420
	18	44.0	144	12.0	1190					144
	57	45.0	630	2.00	4340					246
	46	27.0	19.7	2.00	163					11.0
	36	30.0	6.26	4.00	53.9					4.20
	18	85.0	284	4.00	2050					56.1
	59	46.0	18.1	4.00	142					11.8
	46	29.0	4.10	4.00	28.2					2.13
	16	32.0	20.5	12.0	208					20.5
	53	32.0	7.10	4.00	55.3					4.63
	13	32.0	30.3	1.00	291	777	17.9	662	17100	18.8
	13	35.0	34.0	1.00	344					32.6
	16	43.0	34.7	4.00	383					32.9
	15	30.0	4.84	4.00	43.8					4.52
	16	25.0	5.10	4.00	38.3					2.65
	24	32.8	165	2.00	1550					121
	14	29.4	50.8	12.0	321					50.8
	45	28.6	54.9	12.0	327					54.9
	16	29.8	25.9	12.0	176					25.9
	15	29.0	113	12.0	487					113
	14	25.7	30.7	12.0	212					30.7
	15	26.9	35.3	12.0	186					35.3
	28	27.6	20.4	12.0	109					20.4

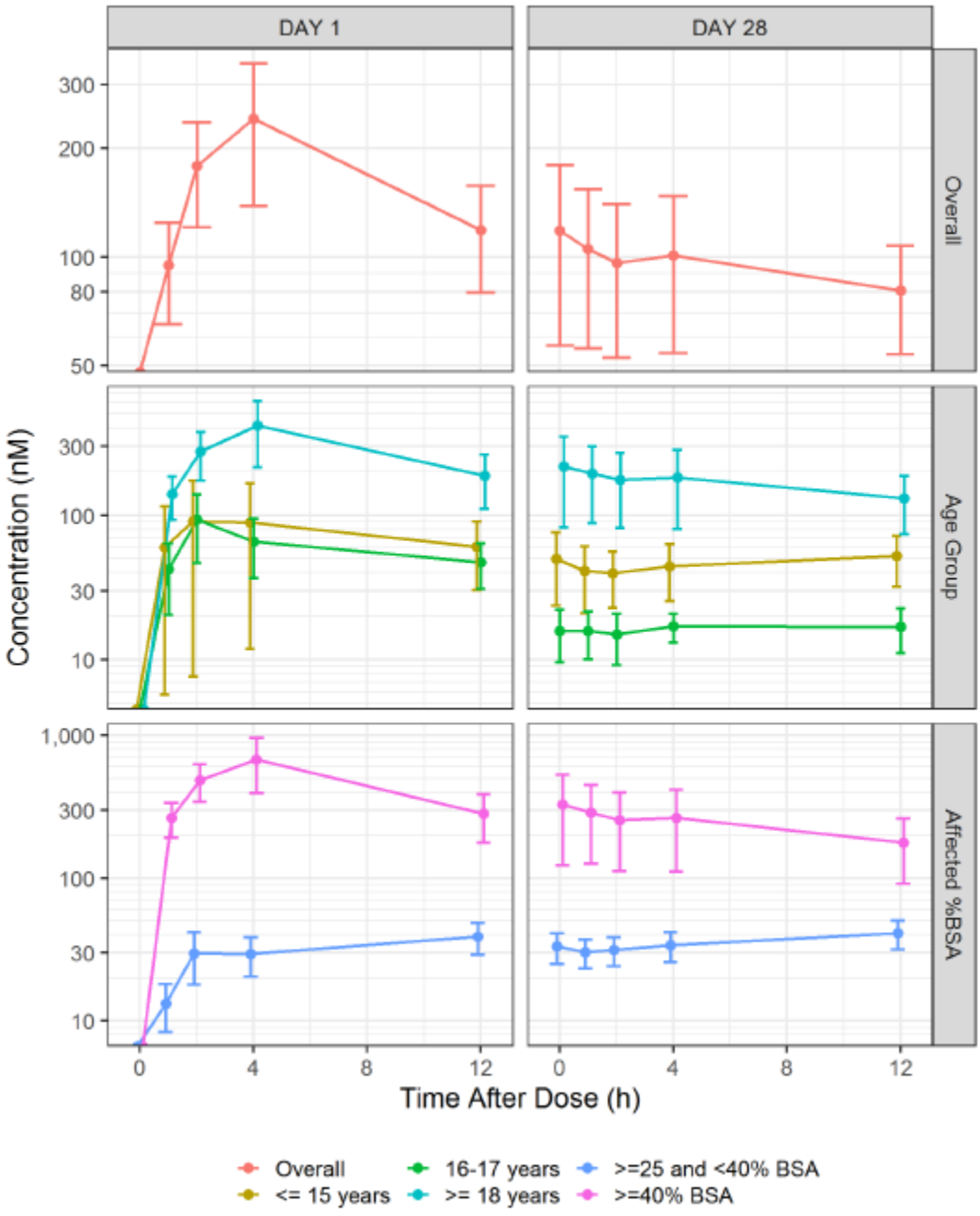
SUBJID	Age (year)	Total Affected BSA (%) at Baseline	C_{max} (nM)	T_{max} (h)	$AUC_{(0-t)}$ (h*nM)	$AUC_{(0-inf)}$ (h*nM)	$t_{½}$ (h)	Cl/F (L/h)	V_z/F (L)	C12h (nM)
(b) (6)	14	26.5	23.1	12.0	123					23.1
	13	43.4	1170	2.00	9350					441
	14	31.2	8.12	12.0	68.5					8.12
	14	30.6	21.6	12.0	148					21.6
	15	26.5	52.8	12.0	282					52.8
	33	60.0	599	4.00	4700					268
	33	32.0	35.7	4.00	281					16.9
	19	78.0	420	1.00	1470	1480	1.26	117	213	1.67
	15	26.0	1.99	12.0	15.3					1.99
	17	30.0	85.5	4.00	796					60.8
	55	45.0	52.5	12.0	411					52.5
	13	29.5	15.3	12.0	115					15.3
	16	31.5	270	2.00	1020					54.2
	17	54.5	273	2.00	2210					135
	N	**40.0**	**40.0**	**40.0**	**40.0**	**2.00**	**2.00**	**2.00**	**2.00**	**40.0**
	NObs	**40.0**	**40.0**	**40.0**	**40.0**	**40.0**	**40.0**	**40.0**	**40.0**	**40.0**
	Mean	**38.4**	**271**	**6.88**	**1950**	**1130**	**9.58**	**390**	**8660**	**119**
	SD	**16.4**	**650**	**4.55**	**4610**	**494**	**11.8**	**385**	**12000**	**245**
	SE	**2.60**	**103**	**0.720**	**729**	**349**	**8.33**	**272**	**8450**	**38.7**
	CV%	**42.8**	**240**	**66.2**	**237**	**43.9**	**123**	**98.8**	**138**	**206**
	Min	**25.0**	**1.99**	**1.00**	**15.3**	**777**	**1.26**	**117**	**213**	**1.67**
	Median	**31.4**	**35.5**	**4.00**	**306**	**1130**	**9.58**	**390**	**8660**	**32.8**
	Max	**90.0**	**3820**	**12.0**	**26600**	**1480**	**17.9**	**662**	**17100**	**1420**
	Geometric Mean	**35.9**	**57.1**	**5.18**	**414**	**1070**	**4.74**	**279**	**1910**	**34.7**
	Geometric CV%	**35.7**	**480**	**98.6**	**458**	**47.8**	**576**	**186**	**12300**	**371**

Table 4. Individual and Summary of ruxolitinib PK parameters on Day 28 *(Source: Table 15 of Study report dmb-20-55-3)*

SUBJID	Age (year)	Total Affected BSA (%) at Baseline	C_{max} (nM)	T_{max} (h)	C_{min} (nM)	$AUC_{(0-tau)}$ (h*nM)	$t_{½}$ (h)	Cl_{ss}/F (L/h)	V_z/F (L)	C12h (nM)
(b) (6)	19	65.0	31.5	12.0	10.7	319		2300		31.5
	45	25.0	158	2.00	76.2	1260		442		113
	32	45.0	743	2.00	387	7170		142		387
	60	90.0	2260	0.00	949	17000	12.6	108	1960	949
	18	44.0	77.8	1.00	0.00	518		756		72.5
	46	27.0	227	12.0	120	2340		256		227
	36	30.0	3.19	4.00	2.16	35.2		14000		3.11
	18	85.0	73.4	4.00	30.5	693		525		57.3
	59	46.0	25.3	4.00	20.4	279		1850		21.6
	16	32.0	14.5	0.00	0.00	58.0		9110		5.98
	53	32.0	14.0	1.00	5.97	125	16.4	4080	96700	8.48
	13	32.0	94.1	0.00	12.6	257	10.0	2050	29700	12.6
	13	35.0	24.9	2.00	14.4	226		2210		14.4
	16	43.0	27.6	1.00	14.4	227	13.3	2200	42400	14.4
	15	30.0	23.5	1.00	12.6	210	11.8	2280	38700	12.6
	62	27.0	3.73	2.00	1.24	30.0		8520		2.14
	16	25.0	19.4	4.00	3.65	113		600		3.65
	24	32.8	57.8	0.00	50.6	636	118	770	131000	52.9
	14	29.4	78.2	0.00	61.5	809	777	551	618000	62.3
	45	28.6	67.9	12.0	51.0	708		788		67.9
	16	29.8	18.1	4.00	9.06	188		2580		17.0
	15	29.0	41.0	12.0	14.9	402		1270		41.0
	14	25.7	53.5	12.0	28.8	558		913		53.5
	15	26.9	5.83	12.0	0.00	30.5		15400		5.83
	28	27.6	41.0	12.0	27.2	414		933		41.0

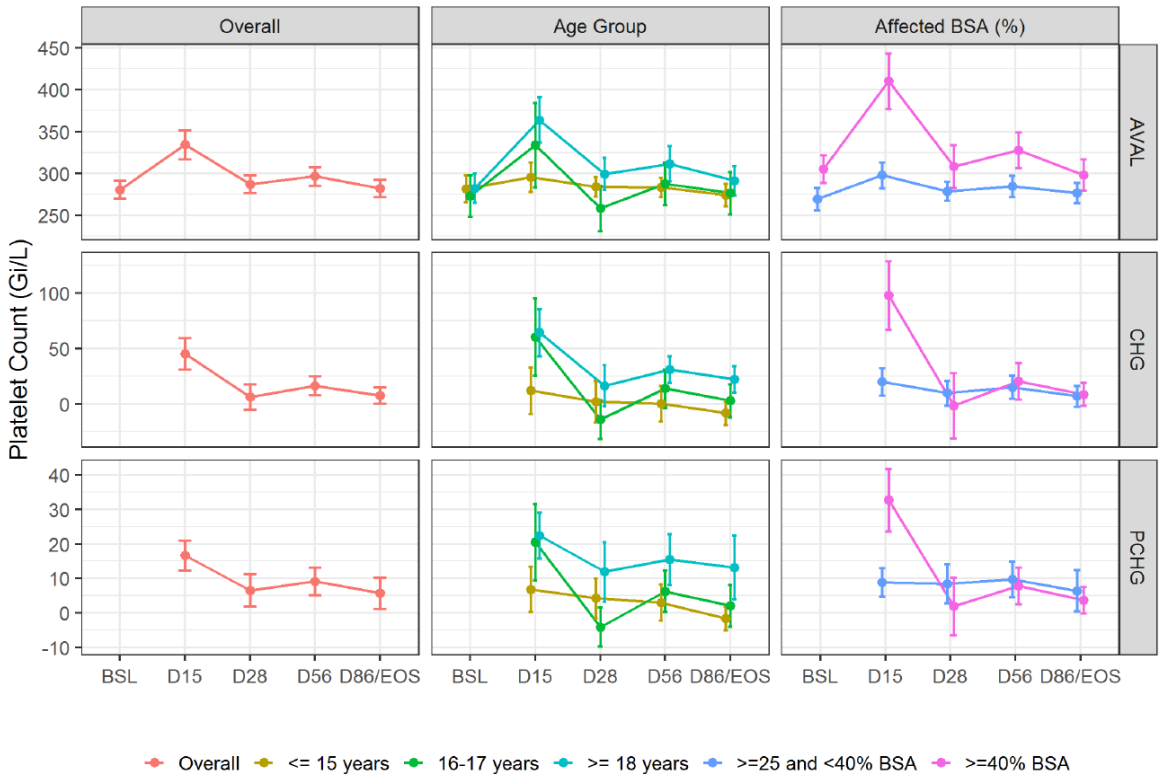
SUBJID	Age (year)	Total Affected BSA (%) at Baseline	C_{max} (nM)	T_{max} (h)	C_{min} (nM)	$AUC_{(0\text{-}tau)}$ (h*nM)	$t_{½}$ (h)	Cl_{ss}/F (L/h)	V_z/F (L)	C12h (nM)
(b) (6)	14	26.5	34.0	12.0	4.11	238		2030		34.0
	13	43.4	377	0.00	250	3450		153		301
	14	31.2	7.45	12.0	0.00	42.0		9210		7.45
	14	30.6	52.2	12.0	21.8	536		1090		52.2
	15	26.5	21.9	12.0	0.00	107		6180		21.9
	33	32.0	114	12.0	64.8	1040		449		114
	19	78.0	36.2	12.0	23.4	365		840		36.2
	15	26.0	77.4	12.0	26.6	557		405		77.4
	17	30.0	20.3	1.00	8.94	127	23.3	424	14200	8.94
	55	45.0	179	1.00	21.9	578	58.0	745	62400	35.5
	13	29.5	36.2	2.00	11.4	339		405		33.9
	16	31.5	19.6	12.0	4.36	150		913		19.6
	17	54.5	52.3	0.00	36.6	512		545		48.8
	N	**38.0**	**38.0**	**38.0**	**38.0**	**38.0**	9.00	**38.0**	9.00	**38.0**
	NObs	**38.0**	**38.0**	**38.0**	**38.0**	**38.0**	**38.0**	**38.0**	**38.0**	**38.0**
	Mean	**37.6**	**137**	**5.68**	**62.6**	**1120**	**116**	**2580**	**115000**	**80.8**
	SD	**16.5**	**377**	**5.30**	**165**	**2930**	**251**	**3770**	**193000**	**166**
	SE	**2.67**	**61.2**	**0.859**	**26.7**	**476**	**83.5**	**612**	**64300**	**26.9**
	CV%	**43.8**	**275**	**93.2**	**263**	**261**	**217**	**146**	**168**	**205**
	Min	**25.0**	**3.19**	**0.00**	**0.00**	**30.0**	**10.0**	**108**	**1960**	**2.14**
	Median	**30.9**	**38.6**	**4.00**	**14.7**	**352**	**16.4**	**913**	**42400**	**34.8**
	Max	**90.0**	**2260**	**12.0**	**949**	**17000**	**777**	**15400**	**618000**	**949**
	Geometric Mean	**35.1**	**43.9**			**349**	**32.5**	**1180**	**44400**	**31.2**
	Geometric CV%	**35.4**	**219**			**241**	**267**	**194**	**335**	**224**

Figure 2. Ruxolitinib plasma concentrations (Mean ± SE) over time on Days 1 and 28 (Semi-log plot; *Source: Figure 7 of Study report dmb-20-55-3)*



PD analysis: The mean platelet count profiles were stratified by age group or baseline %BSA were shown in Figure 3. Overall platelet count increased on Day 15 and returned to the baseline level by Day 28. In subgroup analysis, subjects with ≥40% BSA, the transient increase of platelet count on Day 15 is more prominent compared to the increase in subjects with <40% BSA (Figure 3).

Figure 3. Mean platelet count and the changes by visit (*Source: Figure 20 of Study report dmb-20-55-3)*



Reviewer's analysis: To investigate any potential correlation between plasma ruxolitinib concentration and other factors such as %BSA treated or applied API dose, additional analyses were performed. Overall systemic ruxolitinib exposure increased with an increase in %BSA treated (Figure 4): The similar trend was found in both adult and adolescent groups. As each subject was instructed to apply topical ruxolitinib cream 1.5% to BSA involvement identified at baseline through 28 days, the larger BSA involvement appears correlated to the amount of API applied (Figure 5). The correlation between %BSA treated and amount of API applied is stronger in adult group than that in adolescent group (Figure 5). As expected, strong correlation between amount of API applied and systemic exposure of ruxolitinib was present overall and this correlation was also stronger in adult group than in adolescent group (Figure 6).

Figure 4. Correlation between systemic ruxolitinib exposure vs. %BSA treated (*Source: Reviewer's analysis)*

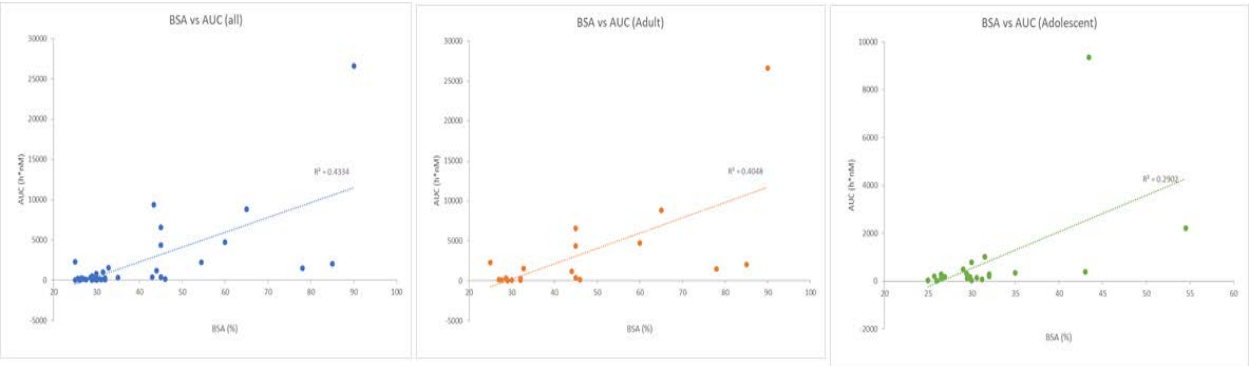


Figure 5. Correlation between API dose vs. %BSA treated (*Source: Reviewer's analysis)*

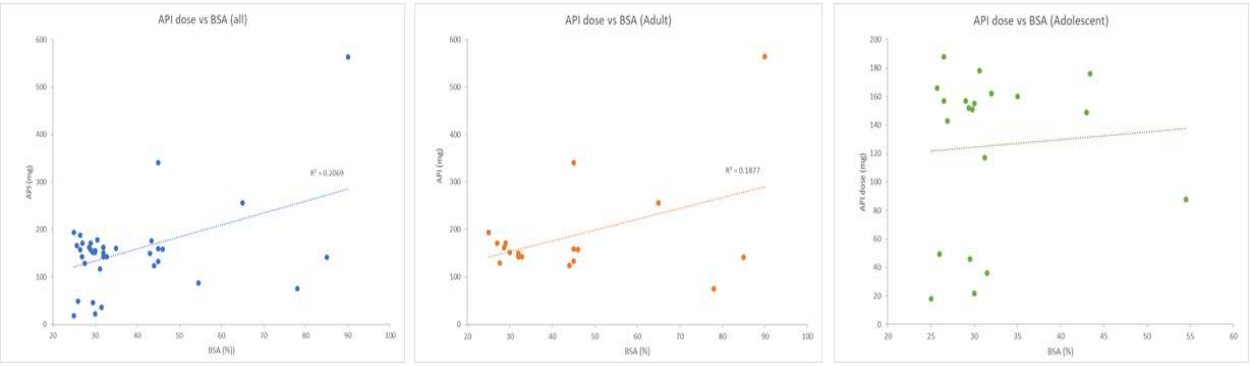
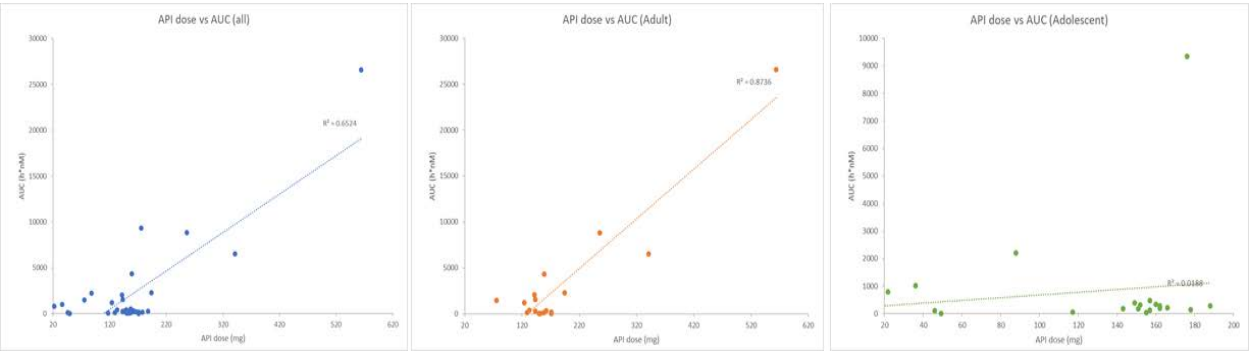


Figure 6. Correlation between API dose vs. systemic ruxolitinib exposure (*Source: Reviewer's analysis)*



Reviewer's comments: *The demographic data of the study indicated that the maximal use PK study did not have a 12 years-old subject in the study but had four subjects at 13 years of age. The PK information in the label will reflect 13 years-old as the youngest while phase 3 trials include subjects at 12 years of age. Overall, the PK data demonstrated that ruxolitinib cream 1.5% is relatively well absorbed through the skin*

*leading to measurable ruxolitinib concentration in all subjects in the study. The systemic exposure of ruxolitinib following topical application in subjects with %BSA of greater than 40% is higher than that following oral ruxolitinib (Jakafi) 5 mg dose: The mean AUC_{0-t} of plasma ruxolitinib following topical application in all subjects was 1948 h*nM compared to 862 h*nM following oral administration of 5 mg Jakafi indicating greater than 2-fold higher AUC observed with topical ruxolitinib cream application. The difference is even greater in subjects with large BSA treated (≥40% BSA): The mean C_{max} and AUC_{0-tau} of plasma ruxolitinib following topical application in subjects with ≥40% BSA treated were 727 nM and 5250 h*nM, respectively. The increases in C_{max} and AUC_{0-tau} of plasma ruxolitinib in subjects with ≥40% BSA compared to mean Cmax and AUC following oral ruxolitinib 5mg were 3.5- and 6.1-folds, respectively. The mean C_{max} and AUC_{0-tau} of plasma ruxolitinib following topical application in subjects with ≥25% and <40% BSA were 51.4 nM and 359 h*nM, respectively. Thus, limiting the BSA to 20% in the label appears reasonable. Furthermore, since the maximum %BSA treated in the phase 3 trials was 22%, limiting the treatment area to a BSA of 20% in the label appears reasonable.*

Study INCB 18424 -303 and -304 (Phase 3 trials – PK assessment)

Title: A Phase 3, Double-Blind, Randomized, 8-Week, Vehicle-Controlled Efficacy and Safety Study of Ruxolitinib Cream Followed by a Long-Term Safety Extension Period in Adolescents and Adults with Atopic Dermatitis

Objectives:

Objectives	Endpoints
Primary	
To establish the efficacy of ruxolitinib cream in participants with atopic dermatitis.	• Proportion of participants achieving Investigator's Global Assessment – Treatment Success (IGA-TS) at Week 8.[a,b]
Key Secondary	
To further assess the treatment effects of ruxolitinib cream.	• Proportion of participants who achieve ≥ 75% improvement in Eczema Area and Severity Index (EASI75) at Week 8.[a] • Proportion of participants with a ≥ 4-point improvement in Itch Numerical Rating Scale (NRS) score from baseline to Week 8. • Proportion of participants with a clinically meaningful (≥ 6-point) improvement in the Patient-Reported Outcomes Measurement Information System (PROMIS®) Short Form – Sleep Disturbance (8b – 24-hour recall) score at Week 8. • Proportion of participants with a clinically meaningful (≥ 6-point) improvement in the PROMIS Short Form – Sleep-Related Impairment (8a – 24-hour recall) score at Week 8.
	(b) (4)

[b] IGA-TS is defined as an Investigator's Global Assessment score of 0 or 1 with a ≥ 2-grade improvement from baseline.

Study population:
Study 303**:** Approximately 600 subjects were planned, and 631 subjects were randomized into the study. All randomized subjects (ie, the intent-to-treat population) applied study drug at least once (ie, the safety population), and 542 of these subjects applied ruxolitinib cream at least once during the LTS period (LTS evaluable population). Plasma samples from 477 subjects during the VC period and 514 subjects during the LTS period were analyzed for pharmacokinetics.
Study 304**:** Approximately 600 subjects were planned, and 618 subjects were randomized into the study. All randomized subjects (i.e., the intent-to-treat [ITT] population) applied study drug at least once (i.e., the safety population), and 530 of these subjects applied ruxolitinib cream at least once during the LTS period (LTS evaluable population). Plasma samples from 474 subjects during the VC period and 514 subjects during the LTS period were analyzed for pharmacokinetics.
Dosing regimen and study duration: Twice daily (BID) for 8 weeks in the VC period and 44 weeks in the LTS period followed by 30 days of safety follow-up.
Methods: Both studies are identical in terms of methodology. This is a randomized, double-blind, vehicle-controlled study in adolescent and adult subjects (≥ 12 years old) with atopic dermatitis eligible for topical therapy. Approximately 600 subjects (~20% of whom were adolescents) with atopic dermatitis involvement of 3% to 22% BSA (excluding the scalp) and an Investigator's Global Assessment (IGA) score of 2 to 3 at baseline were planned to be randomized 2:2:1 to receive ruxolitinib 0.75% cream BID, ruxolitinib 1.5% cream BID, or vehicle cream BID in a blinded manner for 8 weeks (ie, the vehicle control [VC] period). Areas identified for treatment at baseline were treated throughout the VC period even if they began to improve. Subjects who developed additional areas of atopic dermatitis could treat these additional areas with approval by the investigator as long as the total treated %BSA did not exceed 22%, and there were no safety concerns regarding the additional application of study drug. Subjects who completed Week 8 assessments with no safety concerns could continue into the 44-week, double-blind, long-term safety (LTS) period. Those on active treatment during the VC period continued with the same treatment regimen during the LTS period. Subjects who applied vehicle cream during the VC period were equally assigned in a blinded manner to 1 of the 2 active treatment groups during the LTS period. The IGA score and %BSA required for the subjects to enter the LTS period was 0 to 4 and 0% to 20%, respectively. Subjects have study visits every 4 weeks during the LTS period. At each visit, atopic dermatitis lesions are evaluated by the investigator to confirm whether the subject requires continuation of therapy (IGA score ≥ 1) or can (re)enter the observation/no treatment cycle (IGA score = 0). Between study visits, subjects self-evaluate for recurrence of atopic dermatitis and treat areas of the skin with active lesions (not to exceed 22% BSA).

Results:
Study 303
Demographics: Table 5 summarizes the PK population's characteristic by and across ruxolitinib cream treatment during the VC period. The overall range of BSA was from 1.21 m2 to 3.07 m2, with an overall mean ± SD of 1.89 ± 0.3 m2. The overall range of %BSA involvement at baseline was from 3% to 22% with an overall mean ± SD of 9.56

± 5.26% (Table 5). The mean ± SD amount of ruxolitinib cream application was 1.5 ± 1.01 mg/cm2 and 1.6 ± 1.24 mg/cm2 for treatment groups of ruxolitinib cream 0.75% BID and 1.5% BID, respectively (Table 5). The mean ± SD values of average application dose of API were 18.9 ± 15.3 mg and 36.7 ± 31.1 mg, respectively, for treatment groups of 0.75% BID and 1.5% BID, which is expected given the comparable cream product application rates and the 1:2 ratio between the formulation strengths (Table 5).

Summary of PK: Table 6 presents the summary of C_{trough} of ruxolitinib by clinic visit during the VC period, and Figure 2 presents the mean C_{trough} over the VC period. The mean ± SD C_{trough} levels at Weeks 2, 4, and 8 were 26.8 ± 51.2 nM, 25.1 ± 42.7 nM, and 24.0 ± 39.7 nM, respectively, for the 0.75% BID treatment group, and 33.4 ± 49.9 nM, 34.7 ± 43.3 nM, and 33.3 ± 49.5 nM, respectively, for the 1.5% BID treatment group (Table 6). The mean C_{trough} levels during the VC period was nearly constant indicating no systemic accumulation. C_{trough} levels in ruxolitinib cream 1.5% group were higher but less-than-proportional compared to C_{trough} levels in 0.75% treatment group (Table 6 and Figure 7). The mean values of Css were similar between age groups of 12 to < 18 years and 18 to < 65 years for each treatment group (Figure 7). The mean value of Css in the age group of ≥ 65 years seemed a little higher in subjects aged ≥ 65 years compared to those < 65 years for 0.75% BID, but was comparable to those <65 years (Figure 7).

Table 5. Summary of Baseline Population Characteristics and Pharmacokinetic Parameters During VC Period (*Source: Table 5 of Study report DMB-20.83.2)*

	0.75% BID (N = 236)	1.5% BID (N = 241)	Pooled (N = 477)
Body surface area (m^2)			
Mean (SD)	1.88 (0.287)	1.89 (0.316)	1.89 (0.302)
Median	1.84	1.87	1.85
Total BSA involvement in current AD (%)			
Mean (SD)	9.86 (5.32)	9.27 (5.19)	9.56 (5.26)
Median	8.00	8.00	8.00
Lesion area treated (cm^2)			
Mean (SD)	1840 (1030)	1750 (1020)	1790 (1020)
Median	1580	1430	1500
Cream application rate (mg/cm^2)			
Mean (SD)	1.50 (1.01)	1.60 (1.24)	1.55 (1.13)
Median	1.24	1.35	1.30
Average API dose during VC (mg)			
Mean (SD)	18.9 (15.3)	36.7 (31.1)	
GeoMean (GCV%)	14.4 (85.0)	27.3 (91.9)	
C_{ss} (nM)			
Mean (SD)	25.0 (37.1)	33.4 (40.2)	
GeoMean (GCV%)	10.7 (254)	14.5 (312)	
Skin flux ($ng/cm^2/h$)			
Mean (SD)	66.8 (88.0)	98.8 (109)	
GeoMean (GCV%)	32.6 (220)	47.1 (275)	
Bioavailability (%)			
Mean (SD)	8.16 (9.80)	6.40 (7.19)	
Median	5.42	4.11	

Table 6. Summary of Trough Plasma Concentrations (nM) of Ruxolitinib During VC Period (*Source: Table 3 of Study report DMB-20.83.2)*

	0.75% BID (N = 236)	1.5% BID (N = 241)
AVISIT 2		
n	227	230
Mean (SD)	26.8 (51.2)	33.4 (49.9)
GeoMean (GCV%)	9.34 (359)	12.8 (361)
AVISIT 4		
n	229	232
Mean (SD)	25.1 (42.7)	34.7 (43.3)
GeoMean (GCV%)	8.93 (333)	13.4 (408)
AVISIT 8		
n	218	224
Mean (SD)	24.0 (39.7)	33.3 (49.5)
GeoMean (GCV%)	7.41 (444)	10.2 (504)

Figure 7. Ruxolitinib Plasma Trough Concentration (Mean ± SE) by Visit During VC Period (*Source: Figure 2 of Study report DMB-20.83.2)*

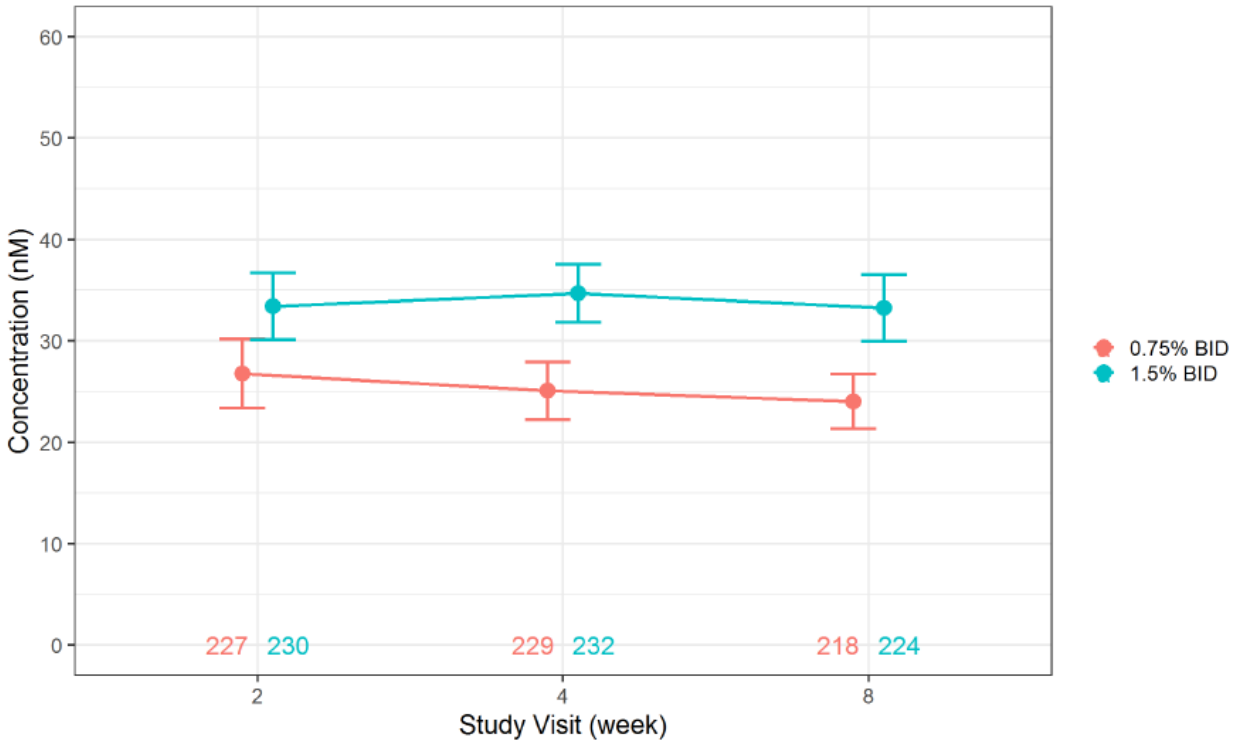
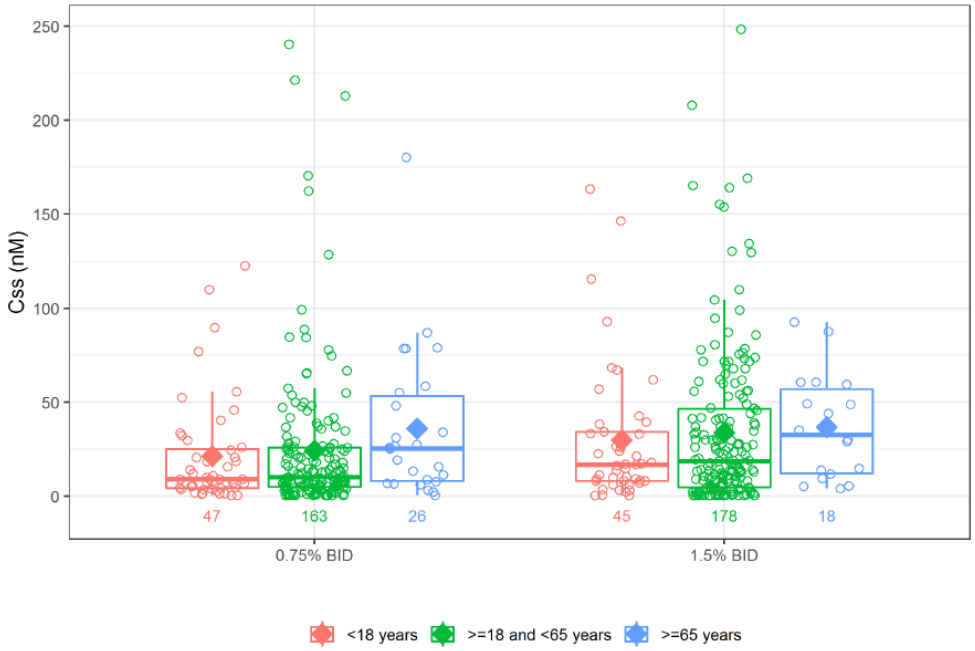


Figure 8. Boxplots of Ruxolitinib Css by Age Group During VC Period (*Source: Figure 7 of Study report DMB-20.83.2)*



Note: Arithmetic mean values are shown in diamonds.

Summary of Efficacy: Both ruxolitinib cream strengths (i.e., 0.75% and 1.5%) were statistically superior to vehicle cream on the primary endpoint; 50.0% and 53.8% of subjects in the ruxolitinib 0.75% and 1.5% cream treatment groups, respectively, achieved IGA-TS at Week 8 compared with 15.1% of subjects in the vehicle cream treatment group ($p < 0.0001$ for both comparisons). A separation for both active treatment groups from the vehicle cream treatment group was observed at Week 2, and the proportion of responders was highest at each visit during the VC period for subjects who applied ruxolitinib crem 1.5% strength.

Study 304

Demographics: Table 7 summarizes the PK population's characteristic by and across ruxolitinib cream treatment during the VC period. The overall range of BSA was from 1.28 m2 to 3.04 m2, with an overall mean ± SD of 1.91 ± 0.29 m2. The overall range of %BSA involvement at baseline was from 3% to 22% with an overall mean ± SD of 9.96 ± 5.36% (Table 7). The mean ± SD amount of ruxolitinib cream application was 1.38 ± 1.08 mg/cm2 and 1.38 ± 0.91 mg/cm2 for treatment groups of ruxolitinib cream 0.75% BID and 1.5% BID, respectively (Table 7). The mean ± SD values of average application dose of API were 18.8 ± 16.6 mg and 36.7 ± 28.8 mg, respectively, for treatment groups of 0.75% BID and 1.5% BID, which is expected given the comparable cream product application rates and the 1:2 ratio between the formulation strengths (Table 7).

Summary of PK: Table 8 presents the summary of C_{trough} of ruxolitinib by clinic visit during the VC period, and Figure 9 presents the mean C_{trough} over the VC period. The mean ± SD C_{trough} levels at Weeks 2, 4, and 8 were 25.2 ± 37.4 nM, 22.6 ± 35.2 nM, and 22.4 ± 36.1 nM, respectively, for the 0.75% BID treatment group, and 38.5 ± 64.5 nM, 41.8 ± 83.6 nM, and 36.1 ± 66.6 nM, respectively, for the 1.5% BID treatment group

(Table 8). The mean C_{trough} levels during the VC period was nearly constant indicating no systemic accumulation. C_{trough} levels in ruxolitinib cream 1.5% group were higher but less-than-proportional compared to C_{trough} levels in 0.75% treatment group (Table 8 and Figure 9). The mean values of Css were similar between age groups of 12 to < 18 years and 18 to < 65 years for each treatment group (Figure 10). Between age groups of 18 to < 65 years and ≥ 65 years, the median values were comparable for each treatment group, but the mean value of Css of ≥ 65 years was higher than younger age groups within the treatment group of 1.5% BID (Figure 10).

Table 7. Summary of Baseline Population Characteristics and Pharmacokinetic Parameters During VC Period (*Source: Table 5 of Study report DMB-20.84.1)*

	0.75% BID (N = 236)	**1.5% BID (N = 238)**	**Pooled (N = 474)**
Body Surface Area (m^2)			
Mean (SD)	1.90 (0.302)	1.91 (0.282)	1.91 (0.292)
Median	1.85	1.90	1.88
Total BSA Involvement in current AD (%)			
Mean (SD)	9.98 (5.33)	9.93 (5.40)	9.96 (5.36)
Median	9.00	9.00	9.00
Lesion Area Treated (cm^2)			
Mean (SD)	1880 (1020)	1890 (1070)	1890 (1040)
Median	1670	1610	1640
Cream Application Rate (mg/cm^2)			
n	235	237	472
Mean (SD)	1.38 (1.08)	1.38 (0.910)	1.38 (0.996)
Median	1.14	1.13	1.14
Average API Dose during VC (mg)			
n	235	237	
Mean (SD)	18.8 (16.6)	36.7 (28.8)	
GeoMean (GCV%)	NC	27.3 (94.6)	
C_{ss} (nM)			
n	236	238	
Mean (SD)	22.7 (32.9)	38.0 (66.8)	
GeoMean (GCV%)	9.08 (300)	12.3 (395)	
Skin Flux ($ng/cm^2/h$)			
n	236	238	
Mean (SD)	53.0 (58.5)	91.6 (171)	
GeoMean (GCV%)	27.0 (216)	36.7 (265)	
Bioavailability (%)			
n	234	237	
Mean (SD)	7.20 (7.84)	6.03 (8.11)	
Median	4.52	3.19	

Table 8. Summary of Trough Plasma Concentrations (nM) of Ruxolitinib During VC Period (*Source: Table 3 of Study report DMB-20.84.1)*

	0.75% BID (N = 236)	1.5% BID (N = 238)
AVISIT 2		
n	227	226
Mean (SD)	25.2 (37.4)	38.5 (64.5)
GeoMean (GCV%)	8.75 (379)	11.3 (512)
AVISIT 4		
n	222	226
Mean (SD)	22.6 (35.2)	41.8 (83.6)
GeoMean (GCV%)	7.98 (376)	10.9 (523)
AVISIT 8		
n	212	223
Mean (SD)	22.4 (36.1)	36.1 (66.6)
GeoMean (GCV%)	6.61 (463)	8.05 (708)

Figure 9. Ruxolitinib Plasma Trough Concentration (Mean ± SE) by Visit During VC Period (*Source: Figure 2 of Study report DMB-20.84.1)*

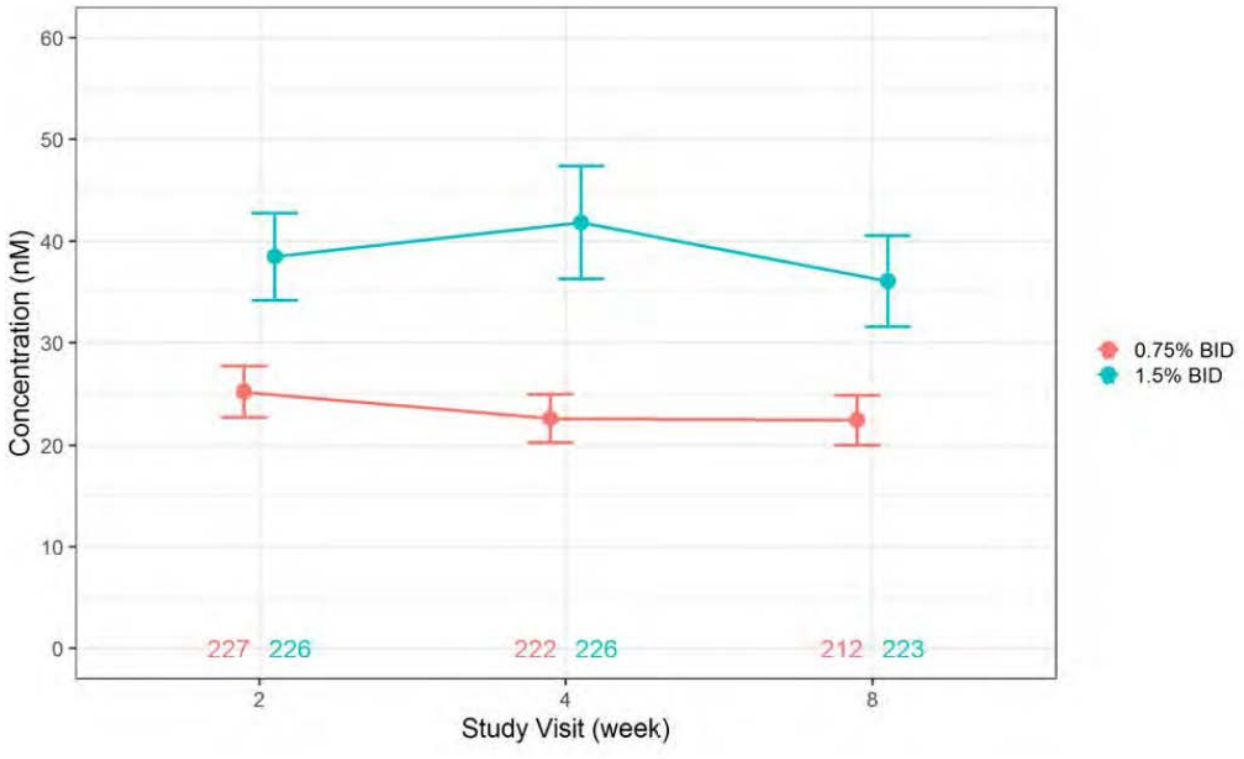
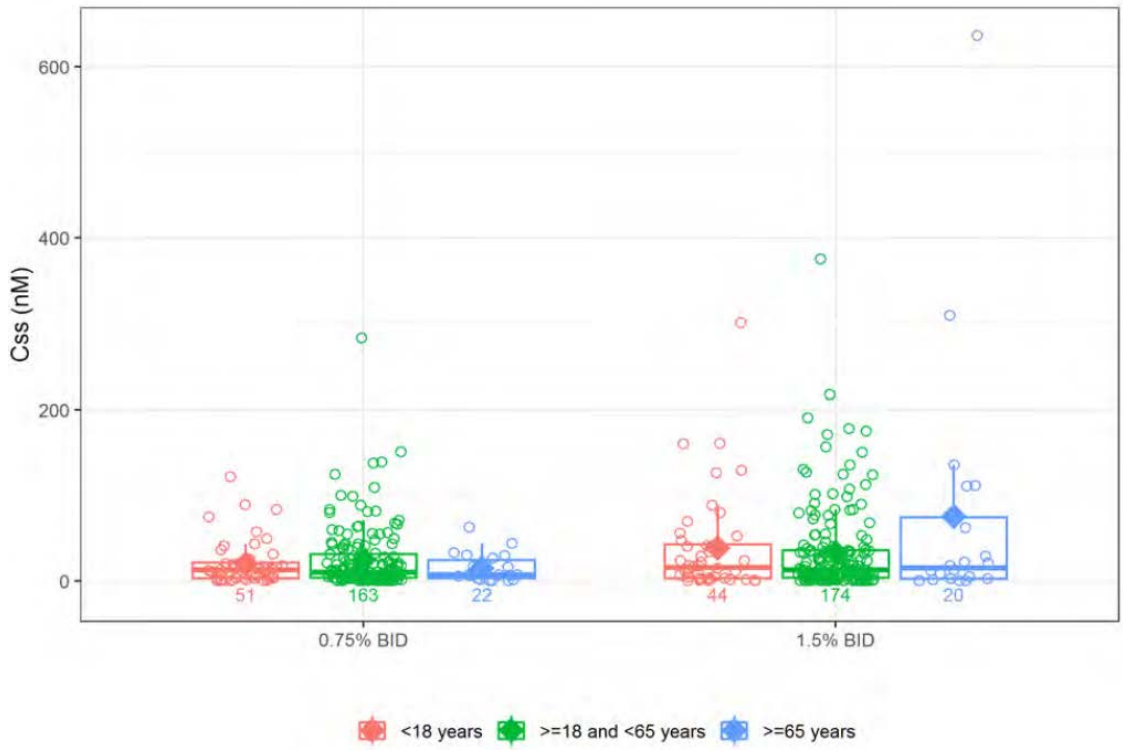


Figure 10. Boxplots of Ruxolitinib Css by Age Group During VC Period (*Source: Figure 7 of Study report DMB-20.84.1)*



Note: Arithmetic mean values are shown in diamonds.

Summary of Efficacy: The proportions of subjects achieving IGA-TS at Week 8 were statistically significantly superior for both ruxolitinib treatment groups (39.0% and 51.3% for the ruxolitinib 0.75% and 1.5% cream treatment groups, respectively) compared with the vehicle cream treatment group (7.6%)($p < 0.0001$ for both comparisons). A separation for both active treatment groups from the vehicle cream treatment group was observed at Week 2, and the proportion of responders was highest at each visit during the VC period for subjects who applied ruxolitinib crem 1.5% strength.

Summary of Safety: There was no deaths and both ruxolitinib cream 0.75% and 1.5% were well-tolerated. The most frequently reported TEAEs in the active treatment groups during the VC period were nasopharyngitis (3.2% and 1.6% of subjects in the ruxolitinib 0.75% and 1.5% cream treatment groups, respectively) and headache (0.8% and 2.0%, respectively). During the VC period, local application site reaction events occurred in 2.4%, 1.6%, and 8.9% of subjects in the ruxolitinib 0.75% cream, ruxolitinib 1.5% cream, and vehicle cream treatment groups, respectively. The majority of local application site reaction events were Grade 1 (mild) in severity.

Concentration-Response relationship (Exploratory analysis)
The Applicant conducted relationships between C_{trough} of ruxolitinib and clinical efficacy responses such as IGA-TS (treatment success), EASI75 (≥75% improvement from baseline in Eczema Area and Severity Index score), and ITCH4 [≥4-point improvement from baseline in Itch NRS score (1) or not (0)] during the VC period of the phase 3 trials. This analysis is considered as exploratory as this is a topical product and drug is administered at the target site (skin). Hence the efficacy is expected to be as a result of local exposure. The degree of contribution of systemic levels towards efficacy is unclear and will be considered exploratory.

The response rate of these endpoints at Week 8 were the primary and 2 of the secondary efficacy points. The concentration-response relationship was characterized using a generalized nonlinear model.

For semi-log graphical representation, the vehicle group was assigned a concentration value of 0.1 nM (denoted as Veh) and subjects who had below quantifiable level (BQL) were assigned a concentration value of 0.5 nM (Figures 11, 13, and 14).

The primary efficacy endpoint was IGA-TS, and a total of 1080 subjects with IGA-TS responses versus (vs.) and C_{trough} of ruxolitinib were included in the concentration-response analysis (Figure 11). The efficacy responses in IGA-TS in the ruxolitinib treatment groups were observed as early as Week 2, and the responses continued to Week 8. The analysis shows that an increase in C_{trough} level is correlated to an increase in response rate during the VC period (Figure 11). By Week 8, the correlation became relatively weak at C_{trough} level higher than 10 nM compared to Weeks 2 and 4 (Figure 11). The applicant conducted Emax model of IGA-TS including an intercept, a treatment (ruxolitinib vs. vehicle) intercept effect, an Emax term of the effect of Css, and 2 covariate predictors: geographic region (Europe vs North America) and baseline IGA score (3 vs 2). The odd ratio for the treatment effect was 2.15 (Figure 12); the odds of subjects treated with ruxolitinib cream achieving IGA-TS are 2.15 fold of those treated with vehicle cream. The odds ratios for baseline IGA score (3 vs. 2) or geographic region (Europe vs North America) were 4.61 and 1.45, respectively (Figure 12). The odds of subjects with IGA score 3 achieving IGA-TS are 4.61-fold of those with IGA score 2. Similarly, the odds of concentration effects are 4.52 (Figure 12). Analyses of both secondary endpoints (EASI75 and ITCH4) vs. C_{trough} level of ruxolitinib demonstrated comparable trends to the IGA-TS vs. C_{trough} relationship (Figures 13 and 14).

Figure 11. IGA-TS: Exploratory graphical analysis of responses vs. Ctrough during the VC period in pooled phase 3 trials *(Source: Figure 21 of Study report DMB-20.96.1)*

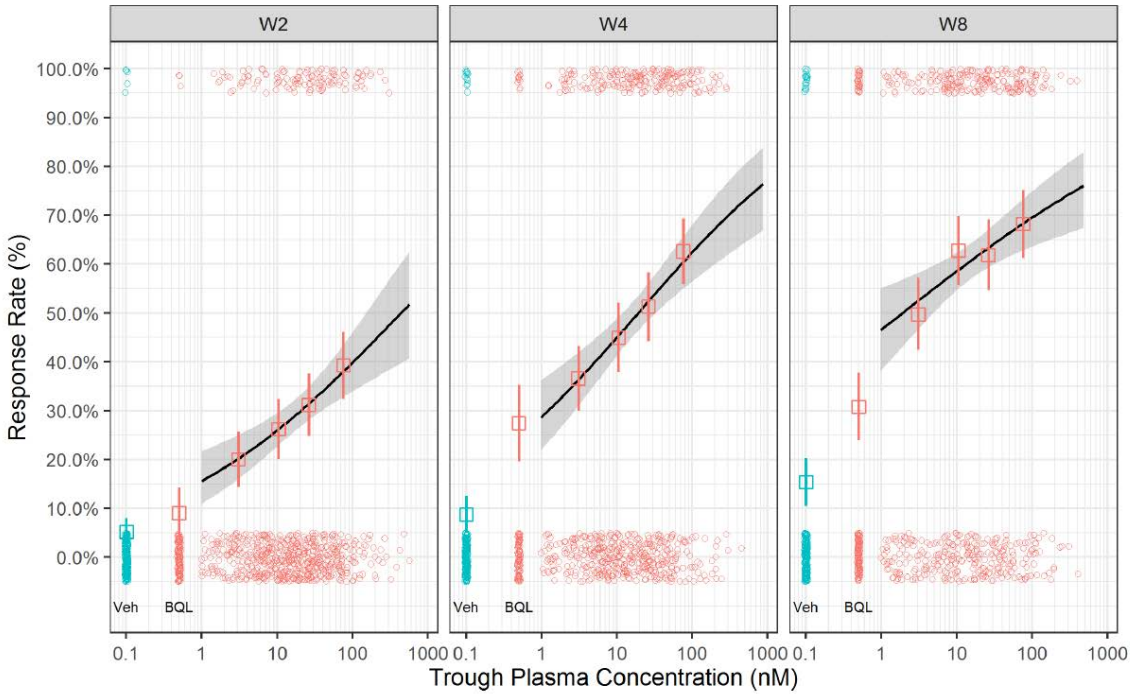


Figure 12. Forest plot of impacts of covariates on IGA-TS responses *(Source: Figure 23 of Study report DMB-20.96.1)*

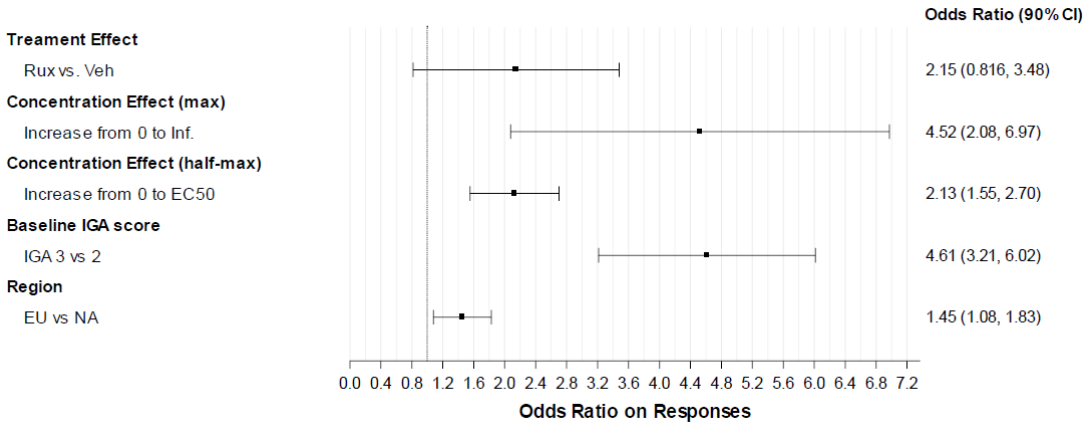


Figure 13. EASI75: Exploratory graphical analysis of responses vs. Ctrough during the VC period in pooled phase 3 trials *(Source: Figure 26 of Study report DMB-20.96.1)*

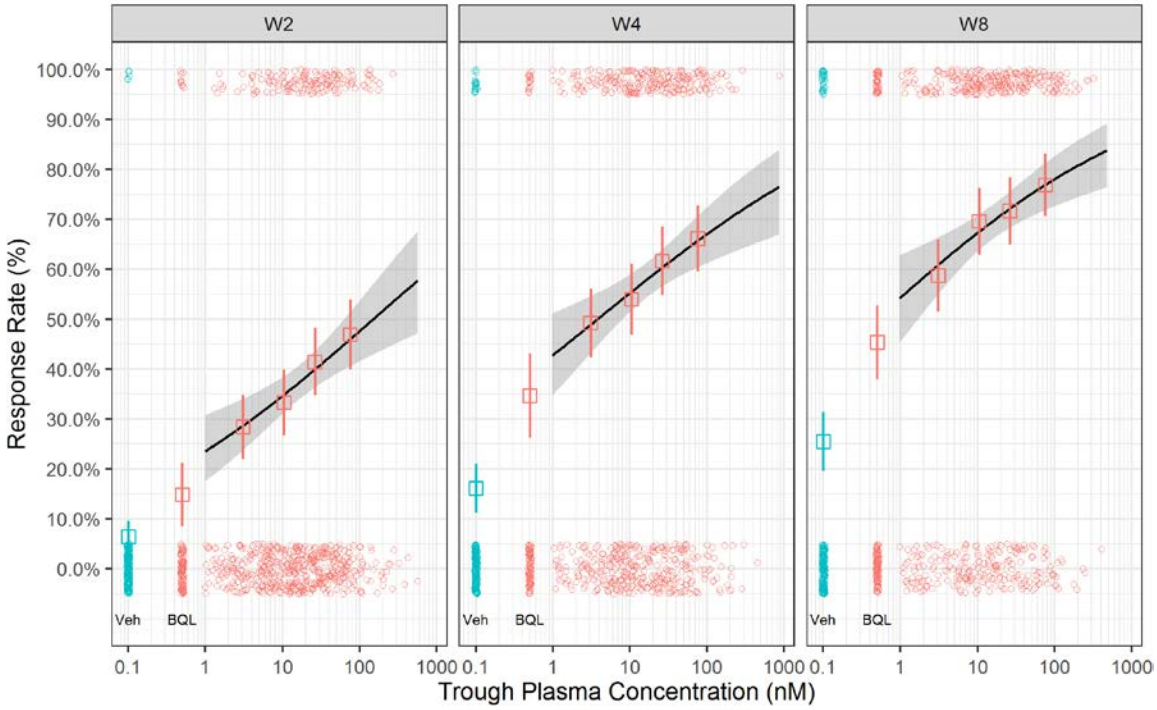
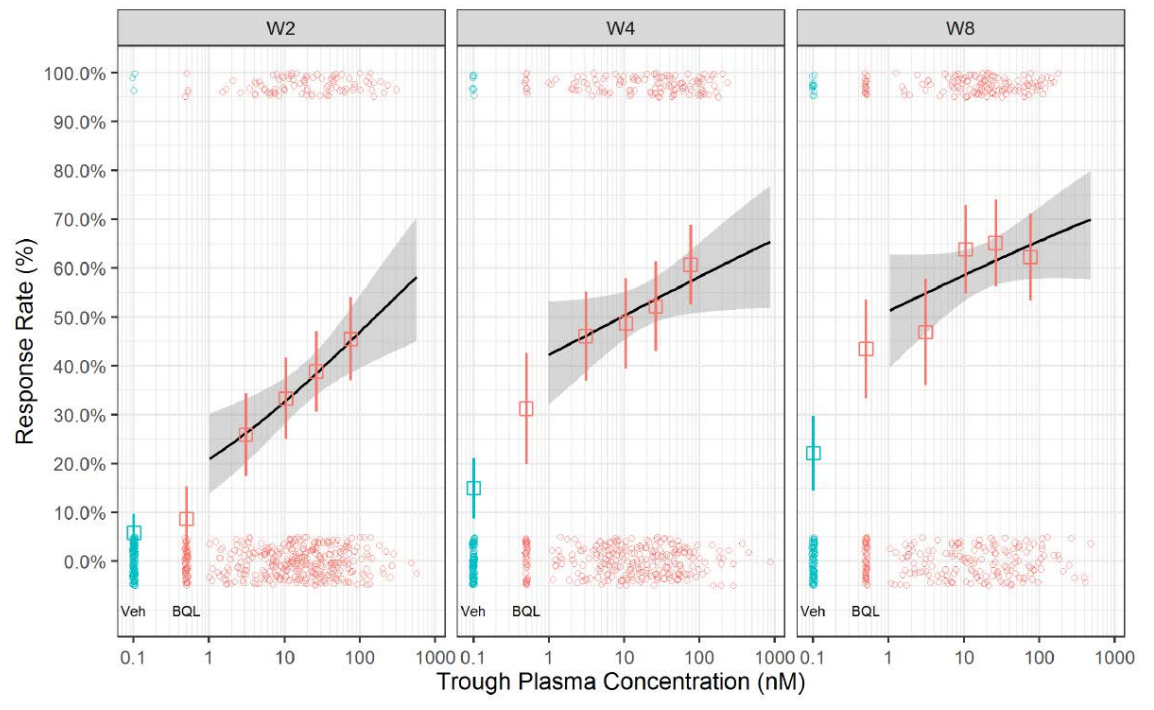


Figure 14. ITCH4: Exploratory graphical analysis of responses vs. Ctrough during the VC period in pooled phase 3 trials *(Source: Figure 31 of Study report DMB-20.96.1)*



Bioanalytical method validation

The Applicant, Incyte Corporation, and (b) (4) developed and validated the bioanalytical methods for determination of ruxolitinib concentration in human plasma. The plasma levels of ruxolitinib were determined using a validated liquid chromatographic-mass spectrometry (LC-MS/MS) method. The linear range of 1 nM to 1000 nM and a lower limit of quantitation (LLOQ) of 1 nM. An assay range of 1.32 nM to 1320 nM and the LLOQ of 1.32 nM was subsequently validated using the same methodology. The Applicant found retrospectively the difference occurred due to a stock solution error. Ruxolitinib at low quality control (QC) level (3 nM) and at high QC level (800 nM) in human plasma was stored at ambient temperature for various time periods prior to analysis. The results showed that ruxolitinib in human plasma is stable for up to 24 hours at ambient temperature. The samples of ruxolitinib in human plasma were tested for freeze-thaw cycles prior to analysis, and the results showed that ruxolitinib in human plasma is stable for at least 3 freeze-thaw cycles. Ruxolitinib in human whole blood in an ice-water bath and at ambient temperature was verified to be stable for at least 120 minutes. In long-term storage, ruxolitinib in human plasma is stable for 672 days at -70^{o}C and this was deemed adequate. The performance characteristics of the bioanalytical assay is shown in Table 9.

Table 9. Precision and accuracy of the bioanalytical method *(Source: Summary of acceptance criteria and validation parameters in Study report DMB-07.111.3)*

Variable	Range (%)
Inter-Assay Precision	4.7 – 7.1
Inter-Assay Accuracy	96.3 - 100
Intra-Assay Precision	1.8 – 6.0
Intra-Assay Accuracy	90.9 -108

Incurred sample reanalysis: Thirty incurred samples were reanalyzed, and 26/30 (87%) sample values were within 20% of the original concentration. This meets the criteria of at least two-thirds (67%) of the sample values need to be within 20% of the original concentration.

Pharmacometrics (PM) Review

The relationships between dose, plasma concentration, and clinical responses to ruxolitinib cream in participants with atopic dermatitis (AD) were investigated as following:

1) Dose-concentration analysis
2) Systemic ruxolitinib concentration-efficacy response analyses
3) Systemic ruxolitinib concentration-hematology analyses

1.1. Data Description:

Data from 3 studies of ruxolitinib cream in participants with AD (≥ 12 years) were included in the PM analyses. The primary analyses were performed on the pooled data of the 2 identically designed Phase 3 studies INCB 18424-303 and INCB 18424-304. Sensitivity analyses were performed with the Phase 2 data from Study INCB 18424-206 added to the pool.

The overall population consisted of 1441 participants with AD from the 3 studies in the vehicle and ruxolitinib cream treatment groups. The population was mostly female (60.9%), mostly white (68.1%), and mostly non-Hispanic (87.4%). The age range was 18 to 70 years for the Phase 2 study and 12 to 85 years for both Phase 3 studies. The overall mean (median) age was 36.4 (33.0) years. The Phase 3 studies were global studies in both North America and Europe with an approximate ratio of 3:1. The distribution of %BSA affected by AD at baseline was similar between the vehicle and ruxolitinib treatment groups and between Phase 2 and Phase 3, with an overall mean (median) of 9.70% (8.00%).

A total of 2696 trough PK samples collected at Week 2, 4, and 8 visits during the vehicle control (VC) period from 951 ruxolitinib-treated participants with AD enrolled in the 2 Phase 3 studies were included in the PK analysis. The steady state concentration (Css) of ruxolitinib was derived as the average of the C_{trough} during the VC period per participant. A total of 47 trough PK samples collected at Week 4 from 47 participants in the ruxolitinib 1.5% cream twice daily (BID) treatment group in the Phase 2 study were added to the pooled Phase 3 PK data for a sensitivity analysis.

In the Phase 3 PK population, there was an approximately 13:1 ratio of participants with a baseline IGA score of 3 versus 2 in Europe and an approximately 2:1 ratio in North America. Further, of the 282 participants with a baseline IGA score of 3 in Europe, 131 participants (46.5%) had ≥ 15% BSA affected by AD at baseline. In contrast, of 438 participants with a baseline IGA score of 3 in North America, 77 participants (17.6%) had ≥ 15% BSA affected by AD at baseline. The overall range of %BSA affected by AD at baseline was from 3% to 22%, with an overall mean ± SD (median) value of 9.76% ± 5.31% (8.10%).

1.2. Applications of Ruxolitinib Cream:

In the Phase 3 studies, ruxolitinib 0.75% and 1.5% cream was applied BID to the areas affected by AD at baseline during the VC period; during the long-term safety (LTS) period of the Phase 3 studies, participants were instructed to apply the ruxolitinib cream to active lesion area(s) only to treat persistent AD or new episodes of AD (intermittent therapy), which is a close reflection of the clinical practice of managing AD in the outpatient setting. In the Phase 2 Study INCB 18424-206, 4 treatment groups applied

ruxolitinib cream (0.15% QD, 0.5% QD, 1.5% QD, and 1.5% BID) topically onto skin area(s) affected by AD at baseline during the double-blind, VC period.

1.3. PK Sample Collection:

In the Phase 3 studies, trough PK samples were collected preapplication at the Week 2, 4, and 8 visits during the vehicle control (VC) period and preapplication every 4 weeks from Week 12 to Week 52 during the LTS period. Trough PK samples were collected preapplication at the Week 4 visit in Study INCB 18424-206.

1.4. Clinical Efficacy Assessment:

The IGA-TS is defined as an IGA score of 0 or 1 with ≥ 2-grade improvement from baseline. EASI75 is defined as ≥ 75% improvement from baseline in EASI score. EASI50 and EASI90 are defined similarly. ITCH4 is defined as ≥ 4-point improvement from baseline in Itch NRS score. Participants with a baseline Itch NRS score of unknown or < 4 were excluded from the analysis.

1.5. Clinical Hematology Laboratory Tests:

In this analysis, clinical hematology laboratory tests of selected blood cell count and hemoglobin levels were evaluated because they are commonly affected during systemic therapy (oral) with ruxolitinib. Clinical hematology laboratory tests on hemoglobin, absolute neutrophil count (ANC), platelet count, mean platelet volume (MPV), and plateletcrit were performed at central laboratories. The baseline value was determined using the last non-missing value collected before the first application, prioritizing scheduled assessments for baseline identification over unscheduled visits.

2. Dose-Concentration Analysis

2.1. Objectives:

• To characterize the relationship between ruxolitinib Css and the topical application dose of ruxolitinib free base equivalent (i.e., the API dose).
• To identify and evaluate the impacts of covariates, intrinsic factors, and/or extrinsic factors, such as age, sex, race, study design stratification factors, and baseline disease severity such as %BSA involvement with AD at baseline, EASI score at baseline, and IGA score at baseline on ruxolitinib Css .

2.2. Methods:

The primary PK modeling was performed using the pooled Phase 3 data, with Study INCB 18424-206 data included in a sensitivity analysis. A linear regression framework was adopted on account that the ruxolitinib Css was 1 value per participant that was derived as the average of C_{trough} during the VC period. The concentration and API dose were log-transformed. Participants' demographic assessments (sex, age, race, BSA), baseline disease severity such as %BSA involvement with AD and EASI score, and clinical study design factors such as stratifications by IGA score (2 vs 3) and region (North America vs Europe) were explored as potential covariate predictors of the ruxolitinib Css. The covariate search was performed in a stepwise univariate fashion during the forward selection process followed by a backward elimination process. The

likelihood ratio test was used to evaluate the significance of the inclusion/dropping of covariates into/from the working model.

2.3. Results:

A dose-PK linear model (**Figure 1**) was developed to characterize the relationship between the ruxolitinib Css during the VC period and the average application dose of API, both transformed into the logarithmic domain, as well as the impacts of significant covariate predictors. A sub-proportional relationship between the API dose and the ruxolitinib Css was quantified with an exponent of 0.462 (95% CI: 0.356, 0.567) on API dose; that is doubling of the API dose would result in a 37% (95% CI: 28%, 48%) increase in Css. The final dose-PK model includes the study design factors of geographic region (Europe vs North America), baseline IGA score (3 vs 2), and the continuous covariate of %BSA treated as significant covariates, and the parameter estimates for these covariates are 0.782 (95% CI: 0.594, 0.970), 0.322 (95% CI: 0.123, 0.522), and 0.602 (95% CI: 0.436, 0.767), respectively. The precision of parameter estimation was < 32% RSE (**Table 1**). The model diagnostic plots (**Figure 2**) of the standardized residuals versus fitted values, API dose, %BSA treated, geographic region, and baseline IGA score show that the standardized residuals are in general distributed around 0 with an approximately constant variance. There were only very few possible outlying observations outside ± 3 standard deviations (SDs).

Geographic region, baseline IGA score, and %BSA treated were identified as statistically significant predictors of the Css of ruxolitinib. The magnitude of impact of these covariates on the Css of ruxolitinib is illustrated in a Forest plot (**Figure 3**).

Figure 1. Final PK Model Equations (Upper equation: in log form; Lower equation: in multiplicative form)

$$\text{Log(Css [nM])} = 0.561 + 0.462 \times \text{Log(API Dose [mg])} + 0.782 \times \boldsymbol{I}(\text{Region = North America}) + 0.602 \times \log(\%\text{BSA} / 8.10) + 0.322 \times \boldsymbol{I}(\text{IGA = 3})$$

$$\text{Css (nM)} = 1.75\ (\text{nM}) \times [\text{API Dose (mg)}]\text{^}0.462 \times 2.19\text{^}\ \boldsymbol{I}(\text{Region = North America}) \times (\%\text{BSA} / 8.10)\text{^}0.602 \times 1.38\text{^}\ \boldsymbol{I}(\text{IGA = 3})$$

Note: 1. ***I***() is an indicator function that equals 1 if the condition is true and equals 0 if false; 2. The median %BSA was 8.10%

Table 1. Final PK Model Parameter Estimations

Effect	Estimate	RSE (%)[a]	p-value	95% CI	
				Lower	Upper
Linear model parameterization in the log-domain					
Intercept	0.561	30.9	<0.0001	0.221	0.901
Exponent on LnDose	0.462	11.6	<0.0001	0.356	0.567
Effect of region Europe (vs North America)	0.782	12.3	<0.0001	0.594	0.970
Exponent on transformed %BSA	0.602	14.0	<0.0001	0.436	0.767
Effect of baseline IGA 3 (vs IGA 2)	0.322	31.5	0.0016	0.123	0.522
In the multiplicative form of the model equation[b]					
Intercept (nM) in the multiplicative model equation	1.75	—	—	1.25	2.46
Fractional change in trough concentration for Europe (vs North America)	1.19	—	—	0.811	1.64
Fractional change in trough concentration for baseline IGA 3 (vs IGA 2)	0.380	—	—	0.131	0.685

[a] Relative SE (RSE) = standard error / estimate * 100 (%).
[b] The transformation into the multiplicative form was exp(x) for both the estimates and the lower/upper limits, except that the fractional change was derived as exp(x) − 1.

Source: Table 9. Pharmaceutical Development Report DMB-20.96.1

Figure 2. Diagnostic Plots the Final PK Model

Figure 12: PK Model Diagnostic Plot: Standardized Residuals Versus Fitted Values

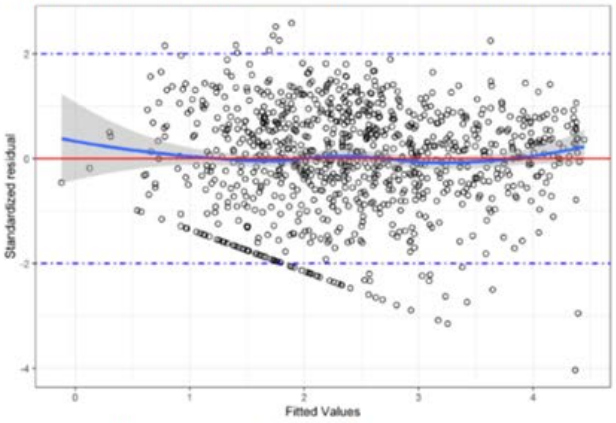


Figure 13: PK Model Diagnostic Plot: Standardized Residuals Versus API Dose

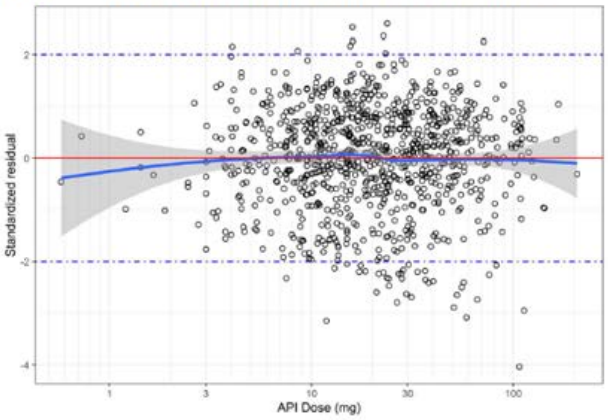


Figure 15: PK Model Diagnostic Plot: Standardized Residuals Versus Geographic Region

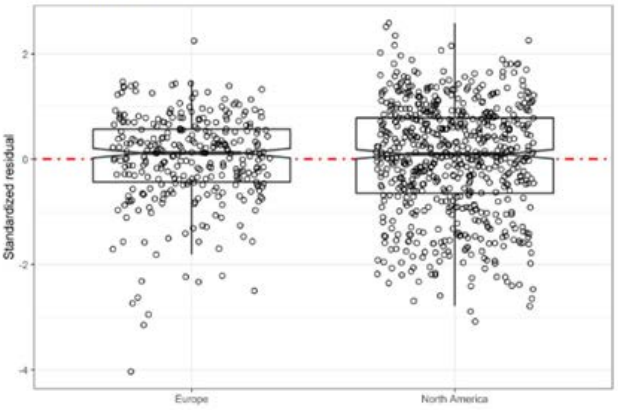


Figure 16: PK Model Diagnostic Plot: Standardized Residuals Versus Baseline IGA Score

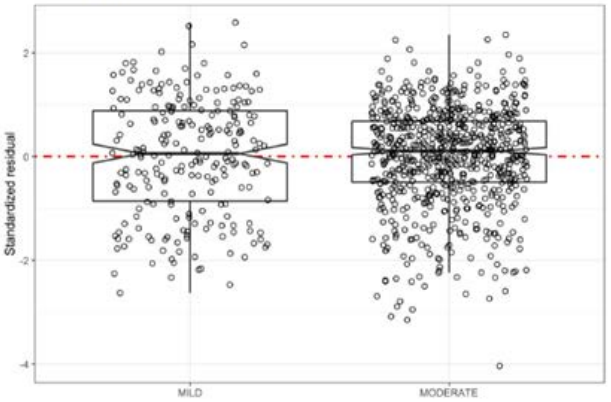


Figure 14: PK Model Diagnostic Plot: Standardized Residuals Versus %BSA Treated

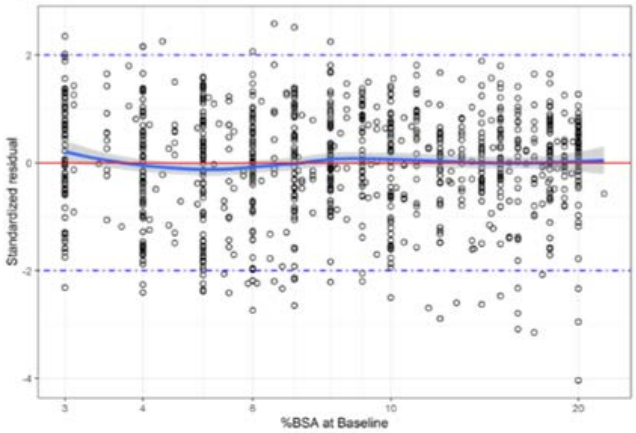
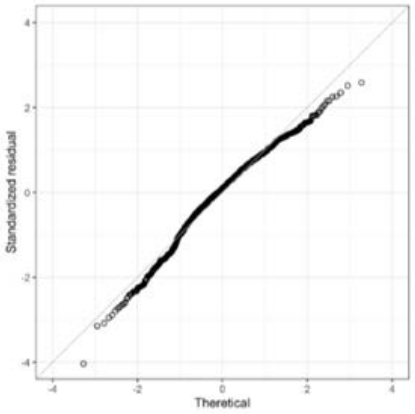
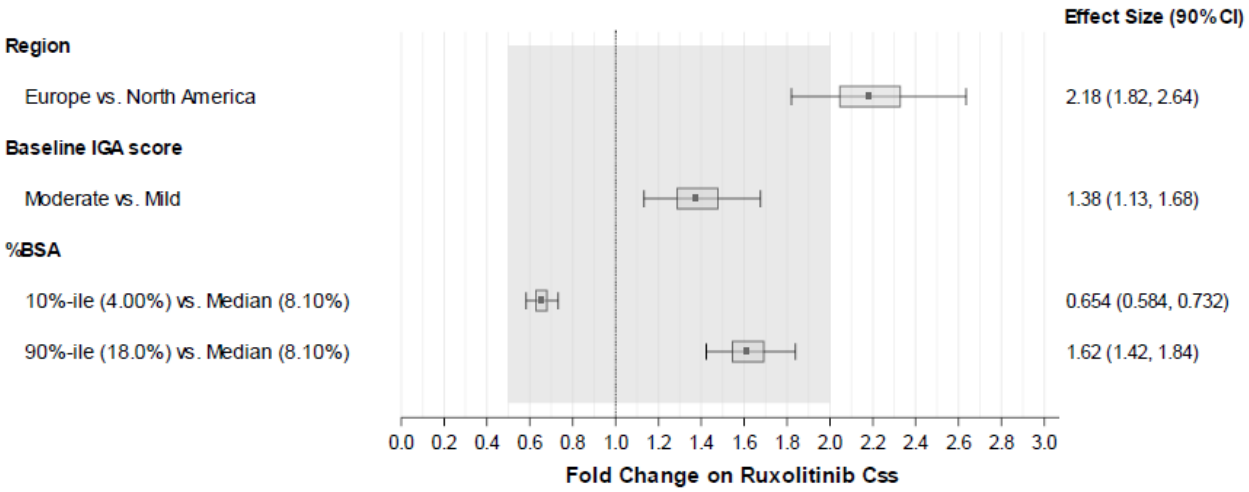


Figure 19: PK Model Diagnostic Plot: Q-Q Plot of Standardized Residuals



Source: Figures 12, 13, 14, 15, 16 and 19. Pharmaceutical Development Report DMB-20.96.1

Figure 3. Forest Plot of Impacts of Covariates on Ruxolitinib Steady-State Concentration



Source: Figures 20. Pharmaceutical Development Report DMB-20.96.1

2.4. Discussion

In the Phase 3 studies, the API dose and application rate were calculated as follows:

- Average API dose:

  Average API dose (mg) = Average application weight of drug product [g] * Strength of Cream Formulation (%) / 100 * 1000 (mg/g);

  - Strength of Cream Formulation = 0.75 or 1.5 (%).

- Application Rate:

  Application Rate (mg/cm^2) = (Average application weight of drug product [g] in clinic on Day 1, Week 2 and Week 4) * 1000 (mg/g) / Total Area of Treated Area (cm^2)

Because that the API dose and %BSA are positively correlated, it is hard to straightly interpret the established final PK-model. Hence, the PK-model was rearranged by introducing the API dose defining elements to tease out the direct %BSA impact on Css as follows:

- $Css\ (nM) = 1.75\ (nM) \times [\%BSA/100 \times BSA \times Application\ Rate\ (mg/cm^2) \times Strength]^{0.462} \times 2.19^{I(Region = North\ America)} \times (\%BSA / 8.1)^{0.602} \times 1.38^{I(IGA = 3)}$

- $Css\ (nM) = 1.75\ (nM) \times (\%BSA)^{0.406 + 0.602} \times [BSA \times Application\ Rate\ (mg/cm^2) \times Strength]^{0.462} \times 2.19^{I(Region = North\ America)} \times (1 / 8.1)^{0.602} \times (1/100)^{0.462} \times 1.38^{I(IGA = 3)}$

By assuming Region = North America and IGA = 3, the above equation can be simplified as follows:

$$Css\ (nM) = 1.75\ (nM) \times 2.19 \times 1.38 \times [BSA \times Application\ Rate\ (mg/cm^2) \times Strength]^{0.462} \times (1/ 8.1)^{0.602} \times (1/100)^{0.462} \times (\%BSA)^{\approx 1}$$

Which indicates in the Phase 3 studies, the ruxolitinib Css is linearly correlated to %BSA. Of note, the %BSA investiaged in the Phase 3 studies ranged from 3 % to 22%.

As indicated by the estabolished final PK-model, the Css of ruxolitinib is significantly influenced by the %BSA baseline, IGA score, strength of formulation, and geographic region (relevant to both IGA and %BSA). Based on the final PK-model, when all other parameters kept constant, the fractional changes on Css are calculated as shown in **Table 2**.

Table 2. Franctional Change in Trough Ruxolitinib Conctration

	Css (nM) Fractional Change
Strength of formulation change 0.75% → 1.5%	↑ 37.8%
%BSA treated from 10% → 20%	↑ 100%
Baseline IGA 2 → 3	↑ 38%

Source: Reviewer's independent analysis

Reviewer's Comments:

1. *In general, in the Phase 3 studies, patients with baseline IGA score at 3, ruxolitinib strength 1.5% and larger %BSA treated tend to have highest Css among all strata, with isolated incidence of trough Css exceeding the whole blood ruxolitinib IC50 for JAK2 inhibition at 281 nM.*

2. *Based on the established PK-model, a particular participant with BSA of 2.08 m^2 (3^{rd} quartile of BSA in the Phase 3 studies) and baseline IGA score at 3 in North America is expected to have an estimated ruxolitinib Css at 60.7 nM if treating 20% BSA with AD lesion using ruxolitinib 1.5% cream BID at the application rate of 1.47 mg/cm^2 (the mean application rate in the Phase 3 studies). Of note, this estimated ruxolitinib Css is well below the whole blood ruxolitinib IC50 for JAK2 inhibition at 281 nM. This estimation provides further evidence that specific dosing recommendation for subjects with renal or hepatic impairment is not considered necessary.*

3. *The linear scatter line spotted in the "Standardized Residual vs. Fitted Values" plot (Figure 12 PK Model Diagnostic Plot) in **Figure 2** of this document likely forms from BLOQ samples.*

3. Systemic Ruxolitinib Concentration-Efficacy Response Analyses

In current submission, ruxolitinib cream is being developed for local action on AD through a topical drug delivery approach. Systemic absorption of ruxolitinib is not intended. Hence, the systemic ruxolitinib concentration-efficacy response analyses are considered exploratory.

3.1. Objectives

• To characterize the relationship between ruxolitinib Css and the primary efficacy response rates for IGA-TS at Week 8.
• To characterize the relationship between ruxolitinib Css and the key efficacy response rates for EASI75 at Week 8.

• To characterize the relationship between ruxolitinib Css and the key efficacy response rates for ITCH4 at Week 8.
• To explore and summarize the relationships between ruxolitinib C_{trough} and binary efficacy response endpoints such as Investigator's Global Assessment – Treatment Success (IGA-TS), ≥50% improvement from baseline in EASI score (EASI50), ≥75% improvement from baseline in EASI score (EASI75), ≥90% improvement from baseline in EASI score (EASI90), and ≥ 4-point improvement from baseline in Itch NRS score (ITCH4) by visit during the VC period.

3.2. Methods

The ruxolitinib Css during the VC period paired with the efficacy responses at Week 8 for each participant was analyzed. A nonlinear generalized model with a logit link function was evaluated to characterize the primary efficacy endpoint, IGA-TS binary responses (responder or not) at Week 8, as a function of ruxolitinib Css. The structural model was parameterized in terms of the treatment effect of ruxolitinib cream (vs vehicle cream), the maximum effect attributed to the ruxolitinib Css (Emax), and the ruxolitinib Css producing 50% of the maximum effect (EC50), all in the logit domain of the probability of the IGA-TS response. Participants' demographic assessments (sex, age, race, BSA), baseline disease severity such as %BSA involvement with AD and EASI score, and clinical study design factors such as stratifications by IGA score (2 vs 3) and region (North America vs Europe) were explored as potential covariate predictors on the logit. The same modeling framework and the development process was applied for 2 of the key secondary efficacy endpoints: EASI75 and ITCH4 response endpoints.

3.3. Results

Dose-dependent efficacy was observed in the Phase 2 and Phase 3 studies, and correlation analyses of treatment with ruxolitinib cream and the plasma concentration of ruxolitinib were performed with the efficacy parameters: IGA-TS (primary) (**Figure 4**), EASI75 (key secondary) (**Figure 5**), and ITCH4 (key secondary) (**Figure 6**) using a nonlinear generalized logit-Emax model.

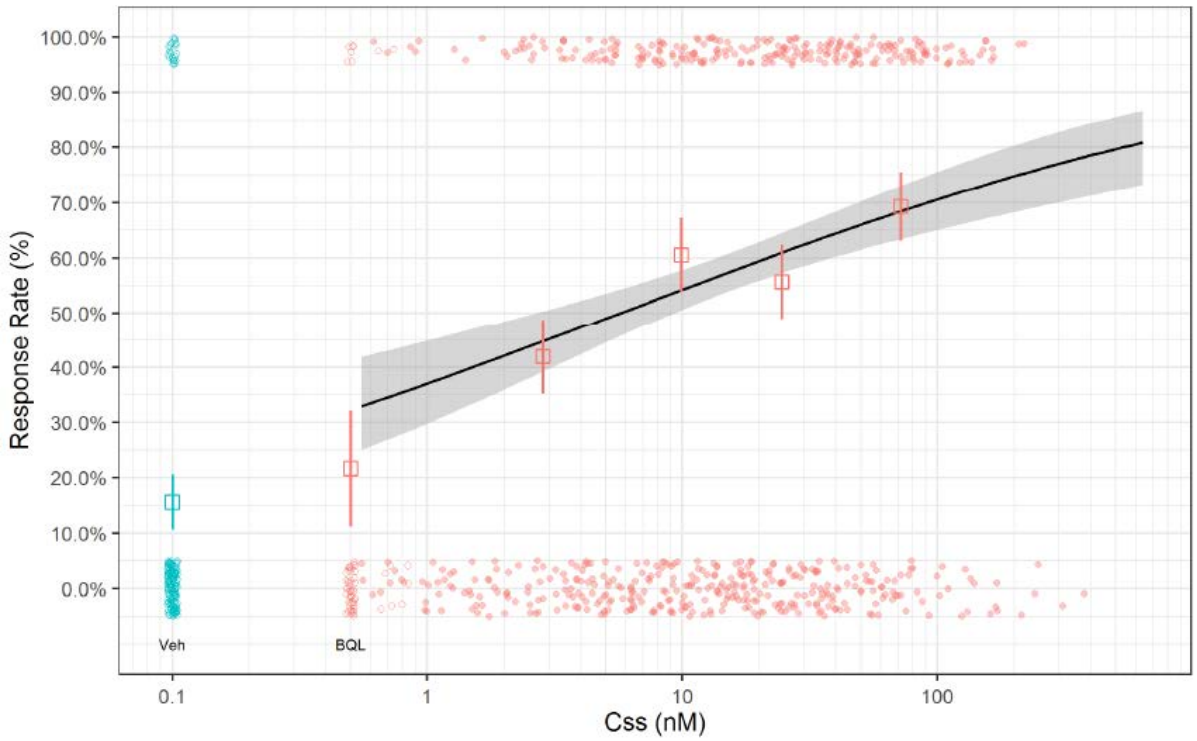
One common theme of these logit-Emax models is that there are clear and significant treatment effects of ruxolitinib. The estimated odds ratios were 2.15 for IGA-TS, 2.19 for EASI75, and 1.49 for ITCH4; that is, the odds of treatment success in the IGA measures or achieving ≥ 75% reduction in EASI score from baseline for participants treated with ruxolitinib cream are > 100% higher than for participants treated with vehicle cream. Similarly, the odds of achieving ≥ 4-point reduction in Itch NRS score from baseline are ~50% higher in participants treated with ruxolitinib cream than participants treated with vehicle cream.

Another common feature of these logit-Emax models is that the estimated EC50 values were all very low, in the range of 1 to 4 nM (1.43 nM for IGA-TS, 3.69 nM for EASI75, and 1.13 nM for ITCH4), which are approximately between the 10th and the 20th percentiles of the distribution of the observed Css among all ruxolitinib cream–treated participants. Further, the imputed EC90 values (ie, 9-fold of EC50) were 12.9 nM for IGA-TS, 33.2 nM for EASI75, and 10.2 nM for ITCH4, which are lower than the observed 50th, 75th, and 50th percentiles of Css, respectively; that is, > 50% of

ruxolitinib cream–treated participants had achieved the EC90 for IGA-TS and ITCH4 and > 25% for EASI75.

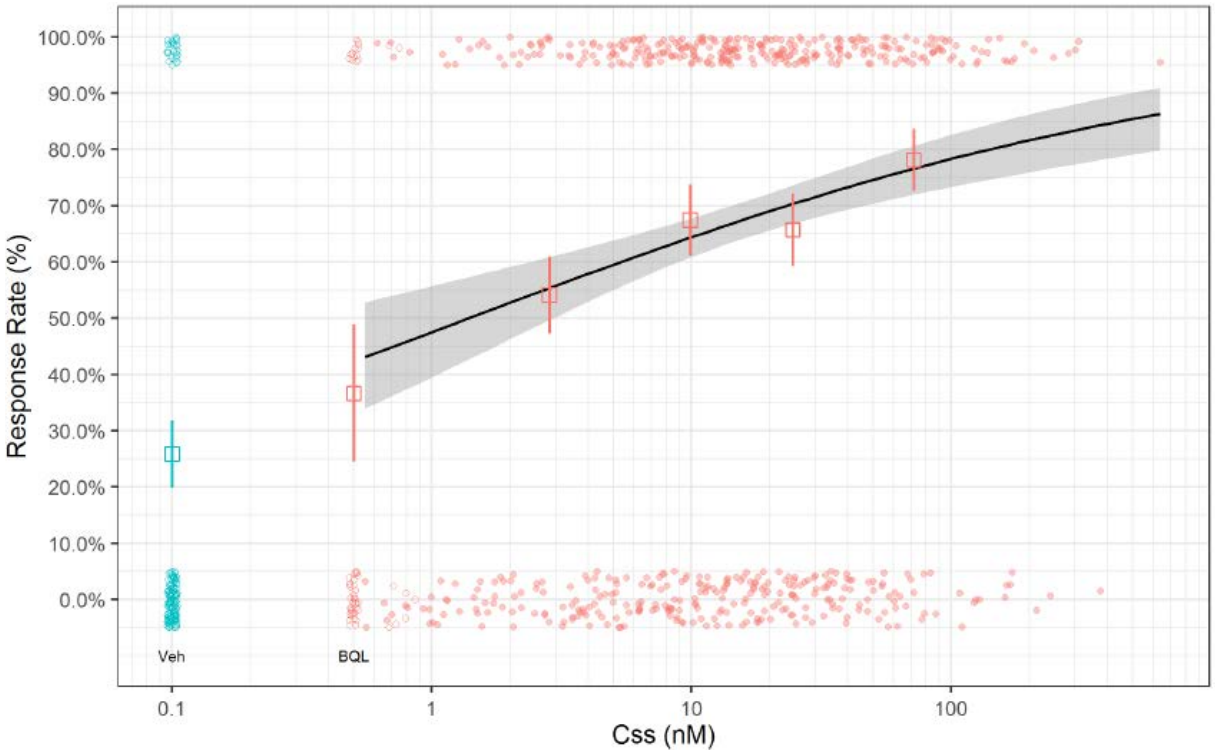
Baseline IGA score and geographic region were identified as significant predictors of IGA-TS response, in addition to the ruxolitinib cream treatment indicator variable (vs vehicle cream treatment) and the ruxolitinib Css. Geographic region was identified as the only significant covariate predictor of EASI75 response, in addition to the ruxolitinib cream treatment indicator variable (vs vehicle cream treatment) and the ruxolitinib Css. Baseline Itch NRS score was identified as the only significant covariate predictor of ITCH4 response, in addition to the ruxolitinib cream treatment indicator variable (vs vehicle cream treatment) and ruxolitinib Css. Of note, geographic region was a confounded variable representing imbalanced distributions of not only the baseline disease severity indices such as %BSA, EASI score, and IGA score but also race in each of the Phase 3 studies as well as the pooled data.

Figure 4. Exploratory Graphical Analysis of Responses at Week 8 Versus Css During the VC Period in Pooled Phase 3 Css — PK/PD Population of IGA-TS



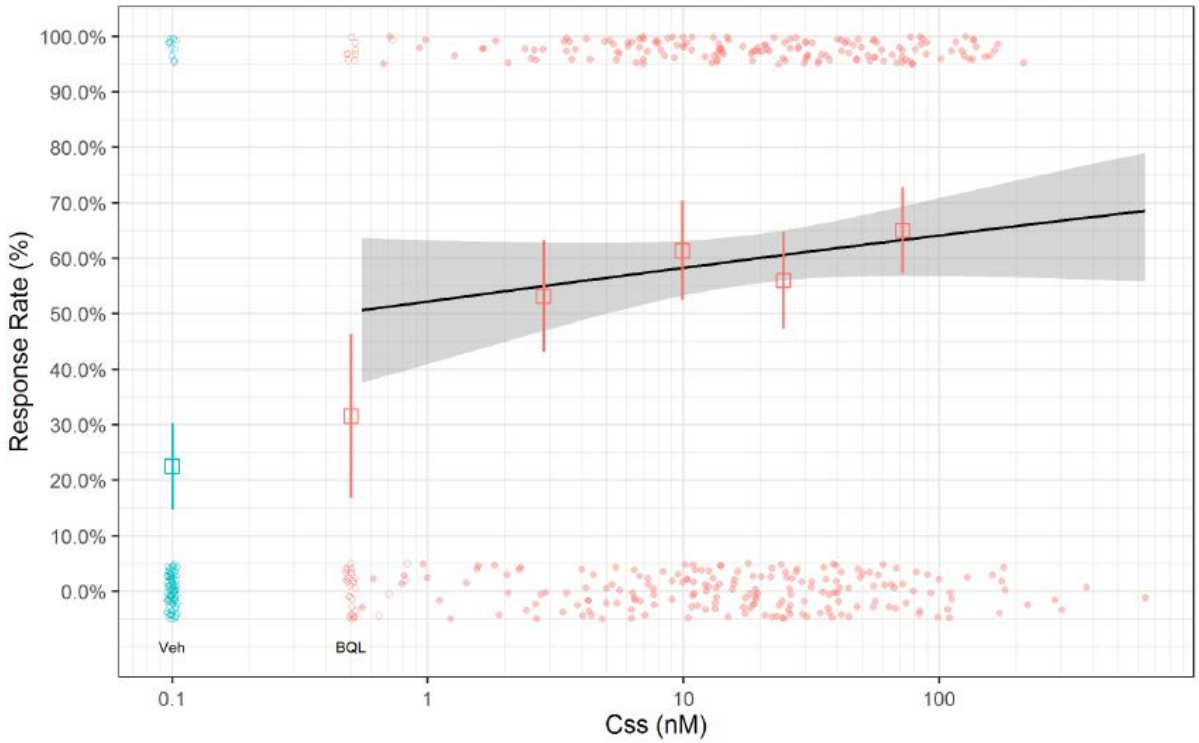
Source: Figures 22. Pharmaceutical Development Report DMB-20.96.1

Figure 5. Exploratory Graphical Analysis of Responses at Week 8 Versus Css During the VC Period in Pooled Phase 3 Css — PK/PD Population of EASI75



Source: Figures 28. Pharmaceutical Development Report DMB-20.96.1

Figure 6. Exploratory Graphical Analysis of Responses at Week 8 Versus Css During the VC Period in Pooled Phase 3 Css — PK/PD Population of ITCH4



Source: Figures 32. Pharmaceutical Development Report DMB-20.96.1

Reviewer's Comments:

Due to the local action nature of topically delivered ruxolitinib cream, the observed efficacy with ruxolitinib cream in AD treatment can be inferred to be driven by local actions of ruxolitinib in the skin. As such, the systemic ruxolitinib concentration-efficacy response analyses are considered exploratory.

4. Systemic ruxolitinib concentration-hematology analyses

4.1. Objectives

• To explore and summarize the relationships between the systemic trough plasma concentrations of ruxolitinib after topical ruxolitinib application and the clinical laboratory test results of platelet indices such as platelet count, MPV, and plateletcrit by visit during the VC period,
• To explore and summarize the relationships between the systemic trough plasma concentrations of ruxolitinib after topical ruxolitinib application and the clinical laboratory test results of hemoglobin by visit during the VC period.
• To explore and summarize the relationships between the systemic trough plasma concentrations of ruxolitinib after topical ruxolitinib application and the clinical laboratory test results of ANC by visit during the VC period.

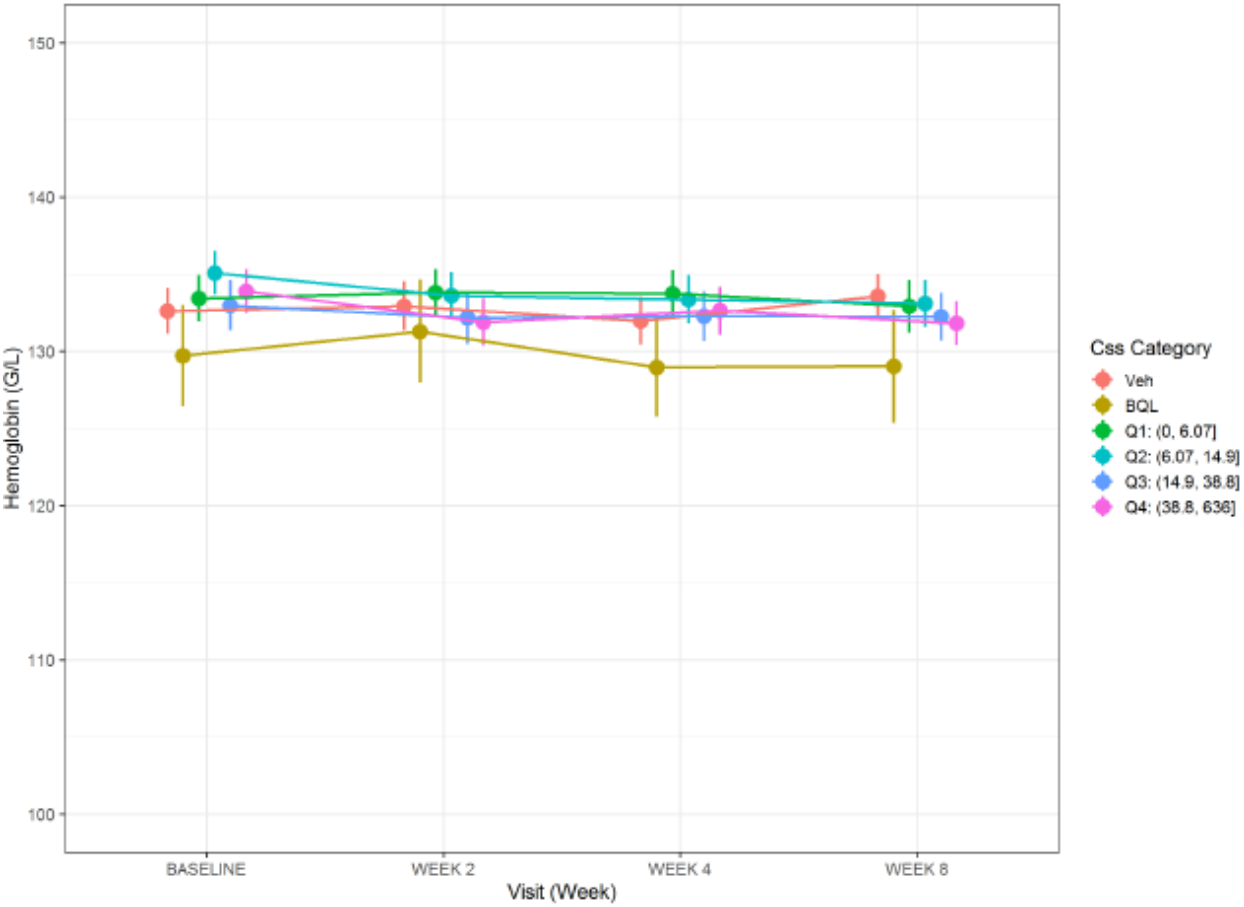
4.2. Methods

Descriptive graphical analyses of clinical laboratory tests of hemoglobin, ANC, and platelet indices (platelet count, MPV, and plateletcrit) by visit through the VC period were performed with respect to treatment groups or ordered categorical ruxolitinib concentrations. Incidences (frequencies) of increased platelet counts > 450 Gi/L or 600 Gi/L based on the clinical laboratory test data were tabulated with respect to treatment groups or ordered categories of ruxolitinib concentrations. Box plots of ruxolitinib Css in participants with any CTC grade changes in these hematology parameters were generated.

4.3. Results

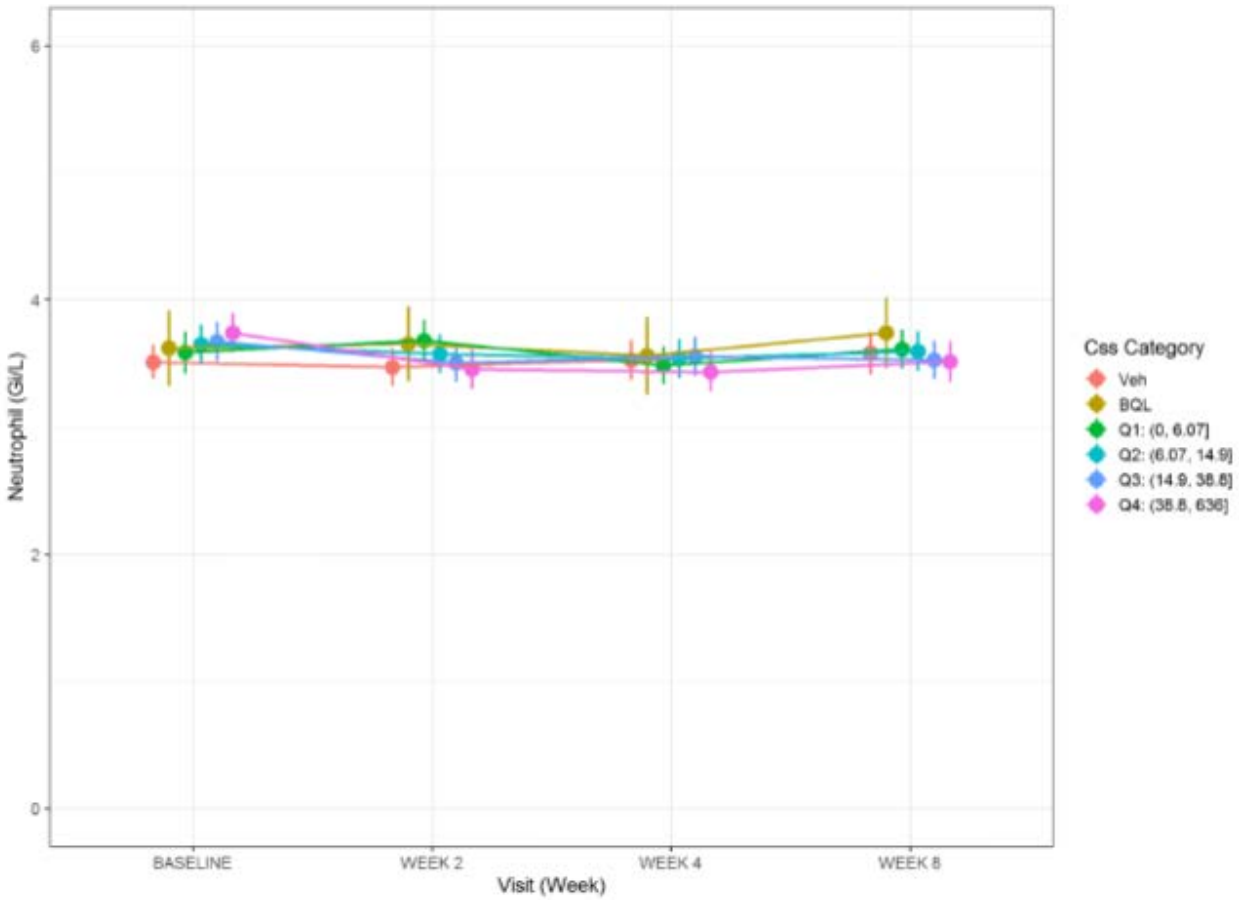
No clinically meaningful trends in hematologic parameters were observed in any of the 3 studies in AD (INCB 18424-206, INCB 18424-303, INCB 18424-304). Among the parameters examined in this report (hemoglobin level, ANC, platelet count, and MPV) (**Figures 7, 8, 9, 10**), the only discernible phenomenon in the hematologic parameters in the pooled Phase 3 data was a transient and minor (< 20%) increase from baseline in platelet counts at Week 2, with spontaneous (while on treatment) return toward baseline by the next visit at Week 4; this change was more perceptible for the fourth quartile of the Css. The incidences of postbaseline platelet count exceeding 450 Gi/L based on the clinical laboratory test data alone were few and mostly detected in the third and fourth quartiles of ruxolitinib Css, and the incidence rates decreased after Week 2. The mean platelet counts (250-325 Gi/L) remained well within the lower and upper limits of the normal range for platelet counts (163-375 Gi/L) in Phase 3 studies at all visits including Week 2, and the mechanism behind this transient and modest increase in platelet counts at Week 2 remains unknown. However, given that there was no change in MPV (indicating a lack of increase in young platelets), the pattern of a transient increase in platelet counts at Week 2 may relate to an activity that is not associated with an effect on bone marrow.

Figure 7. Exploratory Graphical Analysis of Mean (95% CI) Hemoglobin by Css Category and Visit During the VC Period (Phase 3)



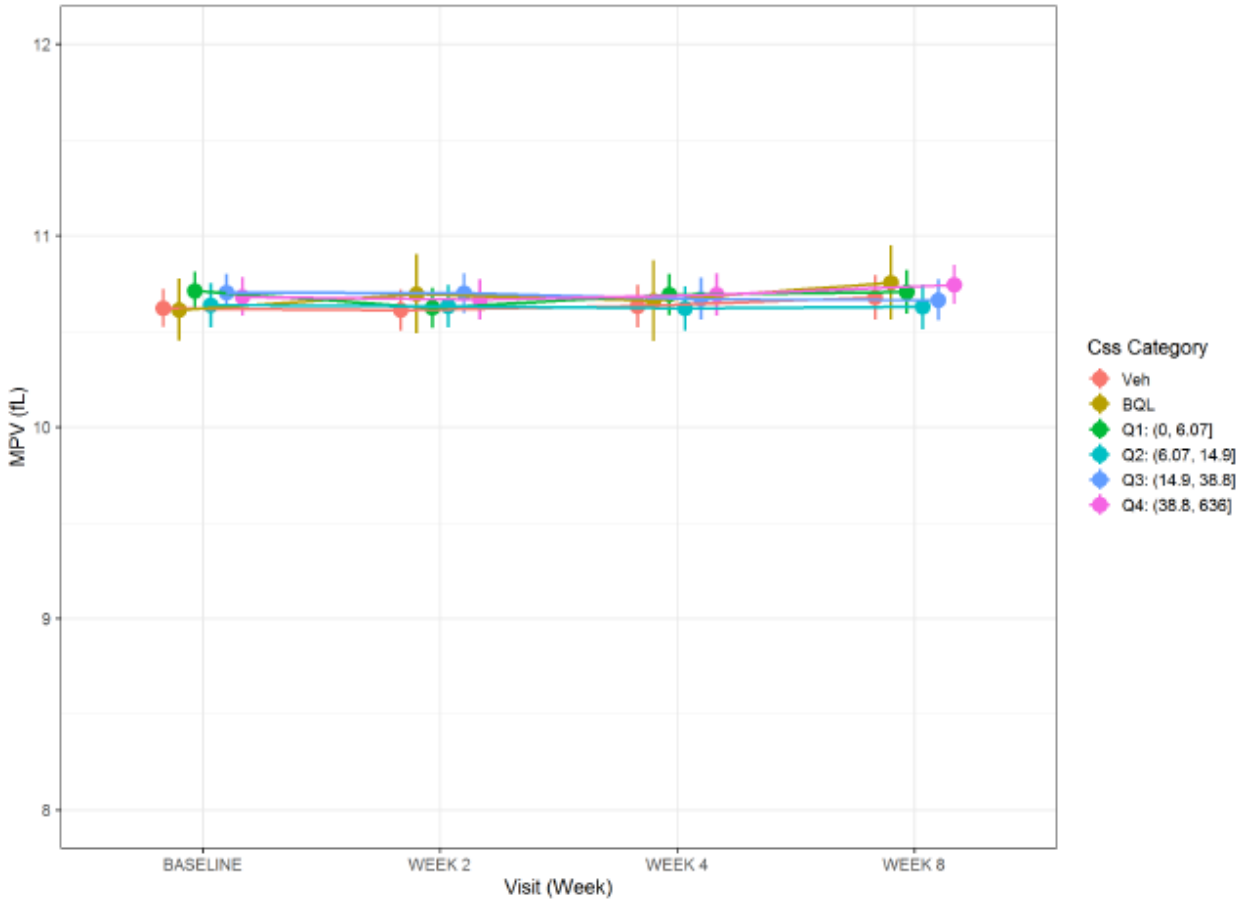
Source: Figures 36. Pharmaceutical Development Report DMB-20.96.1

Figure 8. Exploratory Graphical Analysis of Mean (95% CI) Absolute Neutrophil Count by Css Category and Visit During the VC Period (Phase 3)



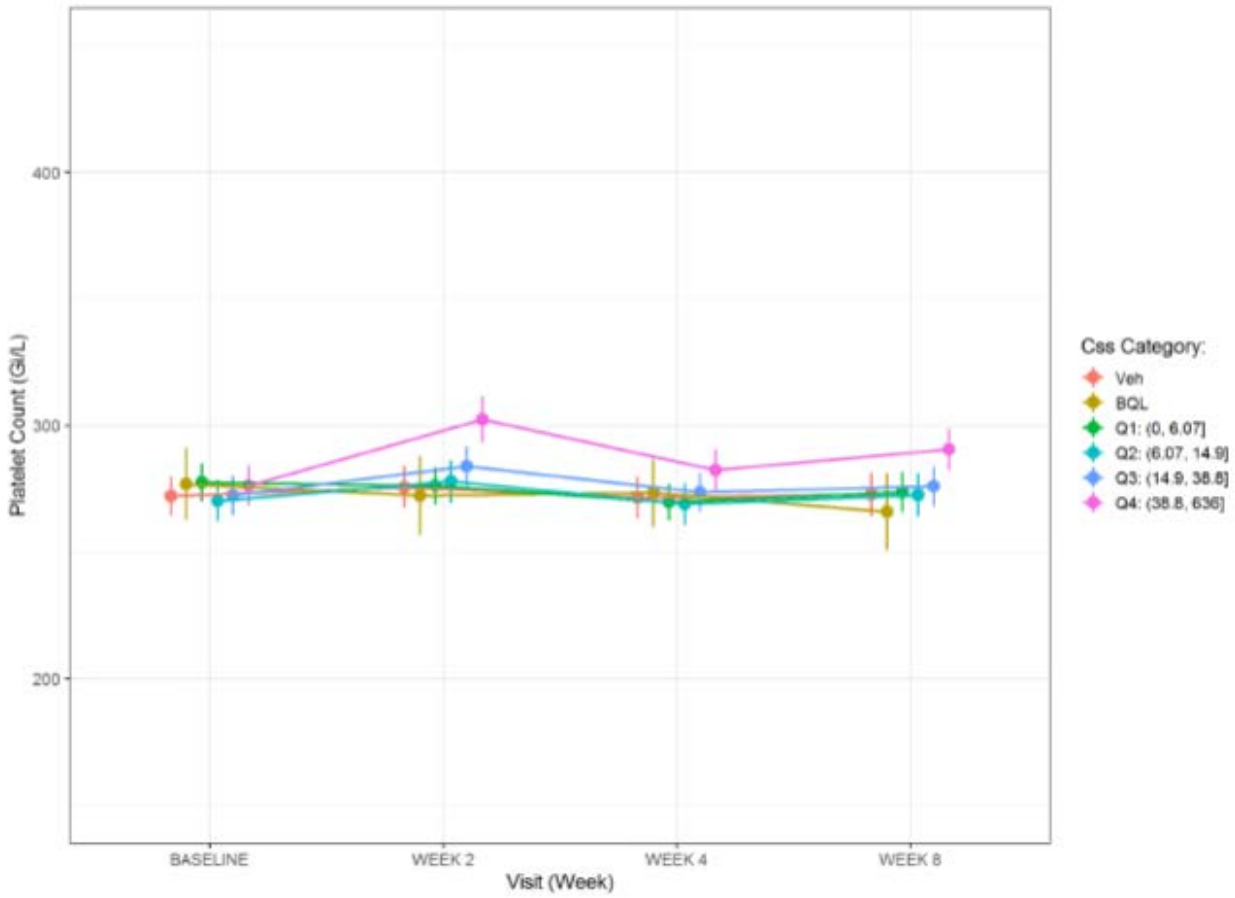
Source: Figures 38. Pharmaceutical Development Report DMB-20.96.1

Figure 9. Exploratory Graphical Analysis of Mean (95% CI) Mean Platelet Volume by Css Category and Visit During the VC Period (Phase 3)



Source: Figures 40. Pharmaceutical Development Report DMB-20.96.1

Figure 10. Exploratory Graphical Analysis of Mean (95% CI) Platelet Count by Css Category and Visit During the VC Period (Phase 3)



Note: The normal range of platelet counts was 163 to 375 Gi/L in Phase 3 studies.

Source: Figures 44. Pharmaceutical Development Report DMB-20.96.1

Reviewer's Comments:

1. *No clinically meaningful trends in hematology parameters, including hemoglobin level, ANC, and MPV, were observed in any of the 3 studies in AD.*
2. *A transient and minor increase (< 20%) in platelet counts at Week 2 with spontaneous (while on treatment) normalization by the next visit at Week 4 observed in the ruxolitinib cream treatment groups was more perceptible for the third and fourth quartiles of the ruxolitinib Css. Mean platelet counts (250-325 Gi/L) remained well within the normal range at all visits, including Week 2.*

14.5. Additional Clinical Outcome Assessment Analyses

14.5.1. Endpoint Position, Definition, and Assessment Schedule

Table 1 describes the intended placement of the COAs in the endpoint hierarchy, including the endpoint definition and assessment schedule for Studies 303 and -304.

Table 1. Endpoint Position, Definition, and Assessment Schedule for Studies 303 and 304:

Endpoint Position	Assessment (If COA, specify Name and Type)	Endpoint Definition	Assessment Frequency
• Primary • • •	• Investigator's Global Assessment (IGA) • (ClinRO)	• Proportion of participants achieving treatment success (defined as a score of 0 or 1 with a ≥ 2-grade improvement) at Week 8	• Baseline, Weeks 2, 4, and 8
• Secondary • • ☒ Multiplicity adjusted	• Itch Numeric Rating Scale (NRS) (PRO)	• Proportion of participants with a ≥ 4-point improvement in Itch NRS score from baseline to Week 8	• Daily (every evening) from Screening to Week 8
(b) (4)			

ClinRO= Clinical-reported outcome; PRO= Patient-reported outcome; (b) (4)

14.5.2. Targeted Clinical Outcome Assessment-Related Labeling Claim(s)

The sponsor has proposed the following specific targeted COA-related labeling claims (in blue italicized text):

Efficacy results for (b) (4) *from the two trials are summarized in Table 2.*

Table 2: (b) (4)

(b) (4)

	Study 1		Study 2	
	(b) (4)	Vehicle	(b) (4)	Vehicle
	(N=253)	(N=126)	(N=228)	(N=118)
IGA-TS[1]	53.8%	15.1%	51.3%	7.6%
(b) (4)				
Itch NRS (≥ 4 point reduction) (n/N)[2]	52.2% (84/161)	15.4% (12/78)	50.7% (74/146)	16.3% (13/80)

Error! Reference source not found. *Defined as an IGA score of 0 or 1 with a ≥ 2-grade improvement from baseline*

ii) *N=patients in the ITT population with a baseline Itch NRS score ≥4.*

(b) (4)

Reviewer's comment(s):
Itch NRS

This reviewer concludes that the Itch NRS is adequate to support labeling claims of itch improvement.

(b) (4)

14.5.3. Clinical Outcome Assessment Description(s)

Itch Numeric Rating Scale (Itch NRS)
The Itch NRS is single-item PRO instrument designed to assess itch intensity at its worst on an 11-point NRS, ranging from 0 ("No itch") to 10 ("Worst imaginable itch"). The recall period is the previous 24 hours. See Appendix A for a copy of the instrument.

(b) (4)

14.5.4. Conceptual Framework(s)

This submission did not include a conceptual framework for the Itch NRS; however, the Itch NRS is a single-item instrument which assesses the concept of itch intensity at its worst.

(b) (4)

(b) (4)

14.5.5. **Scoring Algorithm**

Itch NRS
The Itch NRS generates a single that ranges from 0 to 10, where higher scores indicate greater itch intensity.

Reviewer's comment(s):
The baseline Itch NRS score was determined by averaging the 7 daily NRS scores before Day 1 (Day -7 to Day -1). Similarly, the post-baseline Itch NRS scores were determined by averaging the 7 daily NRS scores before the visit day. At least 4 out of 7 daily scores were needed to be non-missing for a valid by-visit score to be calculated.

(b) (4)

14.5.6. **Content Validity**

The Applicant completed the following instrument development activities to evaluate the content validity of the Itch NRS (b) (4)

- Literature review
- Patient input (concept elicitation and cognitive interviews).

Ninety minute each telephone interviews were conducted in 25 participants (15 adults; 10 adolescents). Participant recruitment was conducted through the National Eczema Association. Patients were asked to obtain confirmation of diagnosis from their physicians via the provided Confirmation of Diagnosis form.

A total of 250 patients were screened. Of the 52 patients were eligible to participate in the study, and a total of 25 patients were consented and provided confirmation of diagnosis form. The mean age of the participants (6 males; 19 females) was 30 years (range 12-69 years; median 33 years); the level of education and work history was not included in the evidence dossier.

The key study inclusion criteria were:

- Adults (≥ 18 years) and adolescents (12-17 years; with any education level) with mild to moderate AD (IGA of 2 to 3) who,

(b) (4)

(b) (4)

Literature review:
The Applicant identified sixteen articles from their literature search. The context of the articles varied and included: qualitative interviews / focus groups, questionnaires / surveys, and development of clinical diagnosis criteria. The literature review concluded that:

- Itchy, painful, and dry skin were the most frequently mentioned signs/symptoms in the literature.

- (b) (4)

Concept elicitation interviews:
The Applicant's summary of the results of the patient interviews (Itch and Insomnia/Sleep Difficulty) is as follows:

"Itch:
All interviewed patients indicated they experienced and were disturbed by itch related to their AD. Patients indicated that some low level of itch is constant with AD, but that the most disturbing itch, and that which disturbs their sleep tends to occur during flares, colloquially defined by patients as episodes of heightened atopic dermatitis symptoms and impacts. Patients indicated that flares occur one to three weeks per month in active months and there may be 3-6 active months per year."

(b) (4)

Reviewer's comment(s):

(b) (4)

(b) (4)

Also see Reviewer's comments following cognitive interviews below.

Cognitive interviews:
In the cognitive interviews, the Itch NRS (b) (4) were tested with the 25 patients (15 adults; 10 adolescents). The participants were asked on the relevancy and clarity of the instructions, each item, and the response scales.

Reviewer's comment: *It appears that both concept elicitation and cognitive interviews were conducted with the same set of patients.*

The Applicant's summary of the results of the cognitive testing is as follows:

- All participants indicated that all items across the instruments were easy to understand and that they were able to find answer choices that reflected their current experience.
- (b) (4)
- The majority (n or % not specified in the evidence dossier) of patients did not suggest changes to the language or wording of the questionnaire items.

(b) (4)

Reviewer's comment(s):
Itch NRS
This reviewer agrees that itch is a relevant concept in patients with AD. The content validity of the Itch NRS has been well-documented in literature in adolescents and adults therefore, sponsors are not required to conduct additional qualitative work in adolescents and adults with AD who can validly and reliably self-report.

(b) (4)

(b) (4)

14.5.7. **Other Measurement Properties**

Itch-NRS
This submission did not include documentation of the other measurement properties of the Itch NRS.

Reviewer's comment(s): The other measurement properties for Itch-NRS are well-documented. No additional quantitative analyses were needed for this review.

(b) (4)

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(b) (4)

14.5.8. **Interpretation of Meaningful Within-Patient Score Changes**

Itch NRS
The Applicant proposed that a ≥ 4-point reduction in the Itch NRS (on a 0-10 scale) to be a meaningful within-patient score change. Based on previous data from other application programs, the Division agreed to this threshold.

(b) (4)

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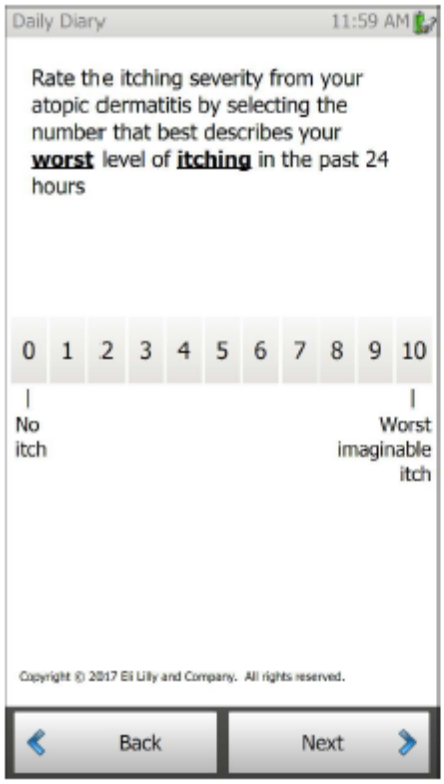
14.5.9. **ATTACHMENTS**

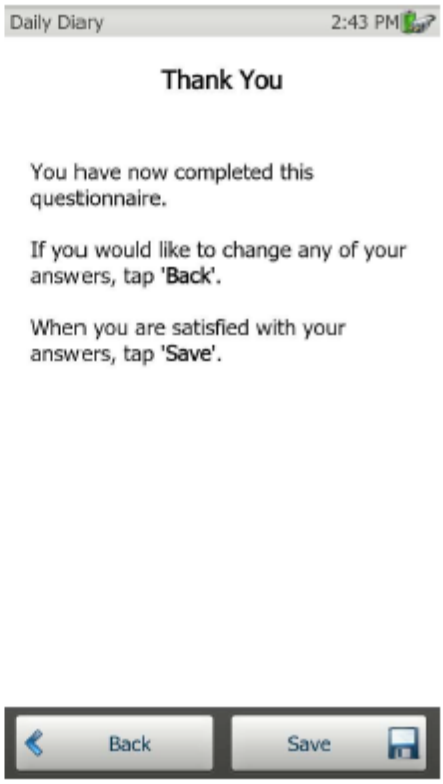
(b) (6)

Appendix A. Itch NRS

2 Form: Itch NRS



Screen 001



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/s/

MATTHEW E WHITE
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HAMID R SHAFIEI
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JIANYONG WANG
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BARBARA A HILL
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LUKE Y OH
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CHINMAY SHUKLA
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DA ZHANG
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KATHLEEN S FRITSCH
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MOHAMED A ALOSH
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YASMIN A CHOUDHRY
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SELENA R DANIELS
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ELEKTRA J PAPADOPOULOS
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BRENDA CARR
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SNEZANA TRAJKOVIC
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SHARI L TARGUM
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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

Statistical Review and Evaluation

CARCINOGENICITY STUDY

IND/NDA Number:	NDA 215309
Drug Name:	INCB018424
Indication:	The treatment of atopic dermatitis
Studies:	26-week repeated dose oral carcinogenicity study in tg.rash2 mice
Applicant:	Sponsor: Incyte Corporation Experimental Station - E400 Route 141 & Henry Clay Road Wilmington, DE 19880-0400 Testing Facility: (b) (4)
Documents Reviewed:	Electronic submission: Submitted on January 4 2021 Electronic data: Submitted on January 4 2021
Review Priority:	Standard
Biometrics Division:	Division of Biometrics - VI
Statistical Reviewer:	Dr. Hepei Chen
Concurring Reviewer:	Dr. Karl Lin
Medical Division:	Division of Pharmacology Toxicology for Immunology & Inflammation
Reviewing Pharmacologist:	Dr. Jianyong Wang
Keywords:	Carcinogenicity, Dose response

Table of Contents

1. Background

In this submission the sponsor included a report of carcinogenicity study in mice. This study was to assess the carcinogenic potential of INCB018424 in hemizygous Tg.rasH2 mice after daily oral (gavage) dosing for 26 weeks.

In this review the phrase "dose response relationship" refers to the linear component (trend) of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as dose increases.

2. Study Design and Analysis

Two separate experiments, one in male mice and one in female mice were conducted. As indicated in Table 1, in each of these two experiments there were three treated groups, one vehicle control group, and one positive control group. One hundred and twenty-five transgenic mice (Tg.rasH2) of each sex were assigned randomly in size of 25 mice per group. The dose of INCB018424 for the three treated groups were 15, 45 and 125 mg/kg/day for both male and female mice. In this review these dose groups were referred to as the low (Group 3), mid (Group 4), and high (Group 5) dose groups, respectively. The mice were dosed at a volume of 10 ml/kg in a 0.5% methylcellulose vehicle. The mice in the vehicle control group (Group 1) received 0.5% methylcellulose, and was handled for the same duration and in the same manner as the treated groups. The positive control group (Group 2) received 1000 mg/kg urethane in 0.9% Sodium administered via intraperitoneal (i.p.) injection as 3 doses of 1000 mg/kg/day on Days 1, 3, and 5.

Table 1: Experimental Design in Mouse Study

Group No.	No. of Toxicity Animals[a]		Test Material	Dosage Level (mg/kg/day)	
	Male	Female		Male	Female
1	25	25	Vehicle Control	0	0
2	25	25	Positive Control	0	0
3	25	25	INCB018424 Low	15	15
4	25	25	INCB018424 Mid	45	45
5	25	25	INCB018424 High	125	125

All animals were observed twice daily for moribundity and mortality. Main Study animals were observed for clinical signs of toxicity post-dosing (cageside) daily within 2 hours after the last dose administration (Group 2 animals were done only on Days 1, 3 and 5). All Main Study animals that died on test were necropsied as soon as possible after being found. Moribund animals were sacrificed immediately by CO_2 overdose and then necropsied. All surviving Main Study animals were sacrificed by CO_2 asphyxiation after the last treatment on study day 183 for Groups 1 and 5 and Day 184 for Groups 3 and 4 and necropsied. Positive Control animals were sacrificed as a group once those signs were evident in the majority of animals so as to avoid the loss of valuable tissues for histopathologic evaluation due to death and tissue autolysis. An extensive necropsy was performed on Main Study animals. Protocol-specified tissues from the vehicle control and all dose groups as well as target organs from the positive control animals were grossly observed, weighed, processed histopathologically and examined microscopically.

2.1. Sponsor's analyses

2.1.1. Survival analysis

In the sponsor's report, Kaplan-Meier estimates of group survival rates were calculated, by sex, and shown graphically. The generalized Wilcoxon test was conducted, by sex, to evaluate the survival rates of the vehicle control and three treated groups. If statistically significant, the generalized Wilcoxon test was conducted to make pairwise comparisons of each treated group with the control. The survival rates of the positive control group were compared to the vehicle control with the generalized Wilcoxon test.

Survival times in which the status of the animal's death was classified as an accidental death, planned interim sacrifice or terminal sacrifice, were considered censored values for the purpose of the Kaplan-Meier estimates and survival rate analyses. All tests were conducted at the 0.05 significance level without correction for multiple tests.

Sponsor's findings:

The sponsor's analysis showed that the numbers of mice surviving to their terminal necropsy were 25 (100%), 24 (96%), 22 (88%), and 25 (100%) in the vehicle control, low, mid, and high dose groups for male mice, respectively, 25 (100%), 24 (96%), 21 (84%), and 25 (100%) for female mice, respectively. Among male mice there was no statistically significant findings in the comparison of vehicle and the treated groups. Among female mice, the survival rate of the mid dose group was significantly less than that of the vehicle control. No other comparisons of vehicle and the treated dose groups were statistically significant among the females. For both males and females, there was a significant decrease in the survival rate of the positive control group when compared with the vehicle control.

2.1.2. Tumor data analysis

In the sponsor's report, the incidence of tumors was analyzed by Peto's mortality-prevalence method, without continuity correction, incorporating the-context (incidental or fatal) in which tumors were observed. The following fixed intervals were used for incidental tumor analyses: days 0 – end of study (up to, but not including, scheduled terminal sacrifices), and scheduled terminal sacrifice. All animals that died or were sacrificed after the first animal of that sex was terminally sacrificed were included in the scheduled terminal sacrifice interval for the incidental finding analyses. All tumors in the scheduled terminal sacrifice interval were considered incidental for the purpose of statistical analysis.

Tumors classified as mortality-independent were analyzed with Peto's mortality-independent method incorporating the day of detection.

Each diagnosed tumor type was analyzed separately. In addition, tumors were combined for analysis purposes at the discretion of the Study Director.

The incidence of each tumor type that occurs in a target organ was analyzed with a 1- sided trend test using ordinal coefficients as well as with pairwise comparisons of each active treatment group with the vehicle control.

An exact permutation test was conducted for analyses with low tumor incidence. Findings were evaluated for statistical significances at both the 0.01 and 0.05 levels. The positive control group was brought down early in a planned intermittent sacrifice. Therefore, the positive control was compared to the vehicle control group with a 1-sided Fisher's exact test at both the 0.01 and 0.05 significance levels.

Adjustment for multiple testing:

In the sponsor's report, no adjustment for multiple testing was provided.

Sponsor's findings:

The sponsor's report did not show any statistically significant tumor finding in comparisons among the vehicle control and the treated groups for both males and females. Among both males and females there was a statistically significant increase in the following tumors when comparing the positive control with the vehicle control: alveolar-bronchiolar carcinoma, alveolar-bronchiolar adenoma, and combined alveolar-bronchiolar carcinoma/adenoma in lungs with bronchi; hemangiosarcoma in the spleen; combined hemangioma/hemangiosarcoma and mesenchymal tumors across multiple organs.

2.2. Reviewer's analyses

To perform statistical analyses suggested by the reviewing toxicologist, this reviewer independently performed the survival and tumor data analyses using the data provided by the sponsor electronically.

2.2.1. Survival analysis

The survival distributions of mice in all five groups (positive control, vehicle control, low, mid, and high dose groups) were estimated using the Kaplan-Meier product limit method. The dose response relationship was tested across the vehicle control group, and low, mid, and high dose groups using the likelihood ratio test, and the homogeneity of survival distributions was tested using the log-rank test. The Kaplan-Meier curves for survival rates are given in Figures 1A and 1B in the appendix for all five groups in male and female mice, respectively. The intercurrent mortality data of all five groups, and the results of the tests for dose response relationship and homogeneity of survivals for the vehicle control group, and low, mid, and high dose groups are given in Tables 1A and 1B in the appendix for male and female mice, respectively.

Reviewer's findings:

The reviewer's analysis showed that the numbers of mice surviving to their terminal necropsy were 25 (100%), 24 (96%), 22 (88%), and 25 (100%) in the vehicle control, low, mid, and high

dose groups for male mice, respectively, 25 (100%), 24 (96%), 21 (84%), and 25 (100%) for female mice, respectively. For the mortality rate, statistically significant increases were noted for both male and female mice (p value = 0.0384 and 0.0164, respectively) when comparing the mid dose group to the vehicle control group, without any statistically significant dose response relationship across the three treated groups and the vehicle control group. No other statistically significant comparisons of vehicle control group and the treated dose groups were noted among both male and female mice.

2.2.2. Tumor data analysis

The tumor data were analyzed for dose response relationships across the vehicle control group, and low, mid, and high dose groups, as well as the pairwise comparisons of each of the three treated groups and the positive control group against the vehicle control group, using the Poly-k method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993).

In the ploy-k method, the adjustment for differences in mortality among treatment groups is made by modifying the number of animals at risk in the denominators in the calculations of overall tumor rates in the Cochran-Armitage test to reflect less-than-whole-animal contributions for animals that die without tumor before the end of the study (Bailer and Portier 1988). The modification is made by defining a new number of animals at risk for each treatment group. The number of animals at risk for the *i*-th treatment group R^* i is defined as $R^* i = \sum W ij$ where w *ij* is the weight for the *j*-th animal in the *i*-th treatment group, and the sum is over all animals in the group.

Bailer and Portier (1988) proposed the weight w *ij* as follows:

w*ij* = 1 to animals dying with the tumor, and

w*ij* = (t*ij* / tsacr)^3 to animals dying without the tumor,

where t*ij* is the time of death of the *j*-th animal in the *i*-th treatment group, and tsacr is the planned (or intended) time of terminal sacrifice. The above formulas imply that animals living up to the end of the planned terminal sacrifice date without developing any tumor will also be assigned w*ij* =1 since t*ij* = tsacr. Also animals developed the tumor type being tested before the end of the study will be assigned as w*ij* = 1.

Certain treatment groups of a study or the entire study may be terminated earlier than the planned (or intended) time of terminal sacrifice due to excessive mortalities. However, based on the principle of the Intention-to-treat (ITT) analysis in randomized trials, the tsacr should not be affected by the unplanned early terminations. The tsacr should always be equal to the planned (or intended) time of terminal sacrifice. For those animals that were sacrificed later than tsacr, regardless their actual terminal sacrifice time, tsacr was used as their time of terminal sacrifice in the analysis.

One critical point for Poly-k test is the choice of the appropriate value of k, which depends on the tumor incidence pattern with the increased dose. For long term 104 week standard mouse and mouse studies, a value of k=3 is suggested in the literature. The present study is a 26 week study. For this kind of medium or short term study no such suggested value of k in the literature is known to this reviewer. Following the suggested value for long term studies, this reviewer analyzed the

tumor data using k=3. Therefore, any significant finding from this analysis should be interpreted more carefully, including pathological consideration.

Multiple testing adjustment:

For the adjustment of multiple testing, this reviewer used the methodologies suggested in the FDA guidance for statistical design and analysis of carcinogenicity studies (2001). In order to keep the overall false-positive rate at the nominal level of approximately 10%, for both of the dose response relationship tests and the multiple pairwise comparisons of the treated group with the control group, the guidance suggests that for the 26 weeks mouse study, the significance level is 0.05 for both common and rare tumors. A tumor is defined as a rare tumor if the published spontaneous rate or the spontaneous rate of the placebo control of the tumor is less than 1%, and a common tumor is defined as one with tumor rate greater than or equal to 1%.

Reviewer's findings:

The tumor rates and the p-values of the tested tumor types are listed in Tables 2A and 2B in the appendix for male and female mice, respectively.

The reviewer's analysis did not report any statistically significant tumor findings in comparisons among the vehicle control and the treated groups for both males and females. When comparing the positive control with the vehicle control, statistically significant increases were noted in the following tumors for both male and female mice: alveolar-bronchiolar carcinoma, alveolar-bronchiolar adenoma, and combined alveolar-bronchiolar carcinoma/adenoma in lungs with bronchi; hemangiosarcoma in the spleen; combined hemangioma/hemangiosarcoma tumors across multiple organs. No other statistically significant tumor findings were noted in both male and female mice.

3. Summary

In this submission the sponsor included a report of carcinogenicity study in mice. This study was to assess the carcinogenic potential of INCB018424 in hemizygous Tg.rasH2 mice after daily oral (gavage) dosing for 26 weeks.

Two separate experiments, one in male mice and one in female mice were conducted. In each of these two experiments there were three treated groups, one positive control group, and one vehicle control group. One hundred and twenty-five transgenic mice (Tg.rasH2) of each sex were assigned randomly in size of 25 mice per group. The dose of INCB018424 for the three treated groups were 15, 45 and 125 mg/kg/day for both male and female mice.

The reviewer's analysis showed that the numbers of mice surviving to their terminal necropsy were 25 (100%), 24 (96%), 22 (88%), and 25 (100%) in the vehicle control, low, mid, and high dose groups for male mice, respectively, 25 (100%), 24 (96%), 21 (84%), and 25 (100%) for female mice, respectively. Statistically significant increases in mortality were noted for both male and female mice when comparing the mid dose group to the vehicle control, while no statistically significant dose response relationship was noted across the treated groups and the

vehicle control group. No other statistically significant comparisons of vehicle and the treated dose groups were noted among both male and female mice. For both males and female mice, there were significant decreases in the survival rate of the positive control group when compared with the vehicle control group.

The reviewer's analysis did not report any statistically significant tumor findings in comparisons among the vehicle control and the treated groups for both males and females. When comparing the positive control with the vehicle control, statistically significant increases were noted in the following tumors for both male and female mice: alveolar-bronchiolar carcinoma, alveolar-bronchiolar adenoma, and combined alveolar-bronchiolar carcinoma/adenoma in lungs with bronchi; hemangiosarcoma in the spleen; combined hemangioma/hemangiosarcoma tumors across multiple organs. No other statistically significant tumor findings were noted in both male and female mice.

Dr. Hepei Chen.
Mathematical Statistician

Concur: Dr. Karl Lin
Team Leader, DBVI

Cc: Archival NDA 215309

Dr. Jianyong Wang

4. Appendix

Table 1A: Intercurrent Mortality Rate in Male Mice

	Vehicle control		Low		Mid		High		Positive Control	
Week / Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 13									3	12.00
14 - 27			1	4.00	3	12.00			9	48.00
Planned intermittent sacrifice									13	100.00
Terminal sacrifice	25	100.00	24	96.00	22	88.00	25	100.00		
Total	25		25		25		25		25	

Test	All Dose Groups	Vehicle control vs. Low	Vehicle control vs. Mid	Vehicle control vs. High
Dose-Response (Likelihood Ratio)	0.7056	0.2390	0.0384*	NC
Homogeneity (Log-Rank)	0.1004	0.3173	0.0770	NC

All Cum. % Cumulative Percentage except for Terminal sacrifice;

* = Significant at 5% level; NC = Not calculable.

Table 1B: Intercurrent Mortality Rate in Female Mice

	Vehicle control		Low		Mid		High		Positive Control	
Week / Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 13									5[a]	12.00
14 - 27			1	4.00	4	16.00			7	40.00
Planned intermittent sacrifice									15	100.00
Terminal sacrifice	25	100.00	24	96.00	21	84.00	25	100.00		
Total	25		25		25		25		27	

Test	All Dose Groups	Vehicle control vs. Low	Vehicle control vs. Mid	Vehicle control vs. High
Dose-Response (Likelihood Ratio)	0.7305	0.2390	0.0164*	NC
Homogeneity (Log-Rank)	0.0259*	0.3173	0.0390*	NC

All Cum. % Cumulative Percentage except for Terminal sacrifice;

[a] Two mice died during week 0-13 in the positive control group were replaced.

* = Significant at 5% level; NC = Not calculable.

Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Mice

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 15 mg P - VC vs. L	Mid (M) 45 mg P - VC vs. M	High (H) 125 mg P - VC vs. H	Positive (PC) 0 mg P - VC vs. PC
Cavity, Nasal	Adenocarcinoma	0/25 (25)	1/25 (24)	0/25 (24)	0/25 (25)	
		0.7449	0.4898	NC	NC	
Harderian Glands	Adenoma	2/25 (25)	0/25 (24)	0/25 (24)	1/25 (25)	
		0.6044	1.0000	1.0000	0.8827	
Liver	Hepatocellular Adenoma	0/25 (25)	0/25 (24)	1/25 (24)	0/25 (25)	
		0.5000	NC	0.4898	NC	
Lungs With Bronchi	Alveolar-Bronchiolar Adenoma	2/25 (25)	2/25 (24)	3/25 (24)	2/25 (25)	25/25 (25)
		0.5138	0.6798	0.4800	0.6954	0.0000 $
	Alveolar-Bronchiolar Carcinoma	0/25 (25)	0/25 (24)	0/25 (24)	0/25 (25)	8/25 (12)
		NC	NC	NC	NC	0.0000 $
	Alveolar-Bronchiolar Adenoma/Alveolar-Bronchiolar	2/25 (25)	2/25 (24)	3/25 (24)	2/25 (25)	25/25 (25)
		0.4796	0.6798	0.4800	0.3046	0.0000 $
	Hemangiosarcoma	0/25 (25)	0/25 (24)	0/25 (24)	0/25 (25)	4/25 (9)
		NC	NC	NC	NC	0.0027 $
Skeletal Muscle (Thigh)	Hemangioma	0/25 (25)	0/25 (24)	0/25 (24)	1/25 (25)	
		0.2551	NC	NC	0.5000	
	Sarcoma	0/25 (25)	1/25 (25)	0/25 (24)	0/25 (25)	
		0.7475	0.5000	NC	NC	
Skin	Hemangiosarcoma	0/25 (25)	0/25 (24)	1/25 (24)	0/25 (25)	
		0.5000	NC	0.4898	NC	
	Sarcoma	0/25 (25)	0/25 (24)	1/25 (24)	0/25 (25)	
		0.5000	NC	0.4898	NC	
Spleen	Hemangiosarcoma	0/25 (25)	0/25 (24)	1/25 (24)	1/25 (25)	24/25 (24)
		0.1894	NC	0.4898	0.5000	0.0000 $
Testes	Hemangiosarcoma	1/25 (25)	0/25 (24)	0/25 (24)	0/25 (25)	
		1.0000	1.0000	1.0000	1.0000	
Thyroid Glands	Adenoma	0/25 (25)	1/25 (24)	0/25 (24)	0/25 (25)	
		0.7449	0.4898	NC	NC	
Whole body	Hemangioma	0/25 (25)	0/25 (24)	0/25 (24)	1/25 (24)	
		0.2551	NC	NC	0.5000	
	Hemangiosarcoma	1/25 (24)	0/25 (24)	2/25 (22)	1/25 (24)	24/25 (0)
		0.3758	1.0000	0.4844	NC	0.0000 $
	Hemangioma/Hemangiosarcoma	1/25 (24)	0/25 (24)	2/25 (22)	2/25 (23)	24/25 (0)
		0.1721	1.0000	0.4844	0.5000	0.0000 $

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Mice

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 15 mg P - VC vs. L	Mid (M) 45 mg P - VC vs. M	High (H) 125 mg P - VC vs. H	Positive (PC) 0 mg P - VC vs. PC
Cavity, Nasal	Adenocarcinoma	1/25 (25) 0.9356	2/25 (25) 0.5000	0/25 (23) 1.0000	0/25 (25) 1.0000	
Harderian Glands	Adenoma	2/25 (25) 0.2805	0/25 (25) 1.0000	0/25 (23) 1.0000	2/25 (25) 0.6954	
Lungs With Bronchi	Alveolar-Bronchiolar Adenoma	3/25 (25) 0.8891	3/25 (25) 0.6664	1/25 (23) 0.9350	1/25 (25) 0.9451	25/25 (25) 0.0000 $
	Alveolar-Bronchiolar Carcinoma	0/25 (25) 0.7449	1/25 (25) 0.5000	0/25 (23) NC	0/25 (25) NC	18/25 (19) 0.0000 $
	Alveolar-Bronchiolar Adenoma/Alveolar-Bronchiolar	3/25 (25) 0.9031	4/25 (25) 0.5000	1/25 (23) 0.6631	1/25 (25) 0.6954	25/25 (25) 0.0000 $
	Hemangiosarcoma	0/25 (25) NC	0/25 (25) NC	0/25 (23) NC	0/25 (25) NC	1/25 (6) 0.1935
Multicentric	Sarcoma	0/25 (25) 0.4949	0/25 (25) NC	1/25 (24) 0.4898	0/25 (25) NC	
Skin	Hemangiosarcoma	0/25 (25) 0.7449	1/25 (25) 0.5000	0/25 (23) NC	0/25 (25) NC	
Spleen	Hemangiosarcoma	0/25 (25) 0.7460	2/25 (25) 0.2449	2/25 (24) 0.2347	0/25 (25) NC	24/25 (24) 0.0000 $
Stomach	Papilloma	1/25 (25) 1.0000	0/25 (25) 1.0000	0/25 (23) 1.0000	0/25 (25) 1.0000	
Thymus	Thymoma	0/25 (25) 0.5534	0/25 (25) NC	3/25 (23) 0.1024	0/25 (25) NC	
Whole body	Hemangiosarcoma	0/25 (25) 0.8219	3/25 (22) 0.1173	2/25 (22) 0.2347	0/25 (25) NC	24/25 (0) 0.0000 $

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Figure 1A: Kaplan-Meier Survival Functions for Male Mice

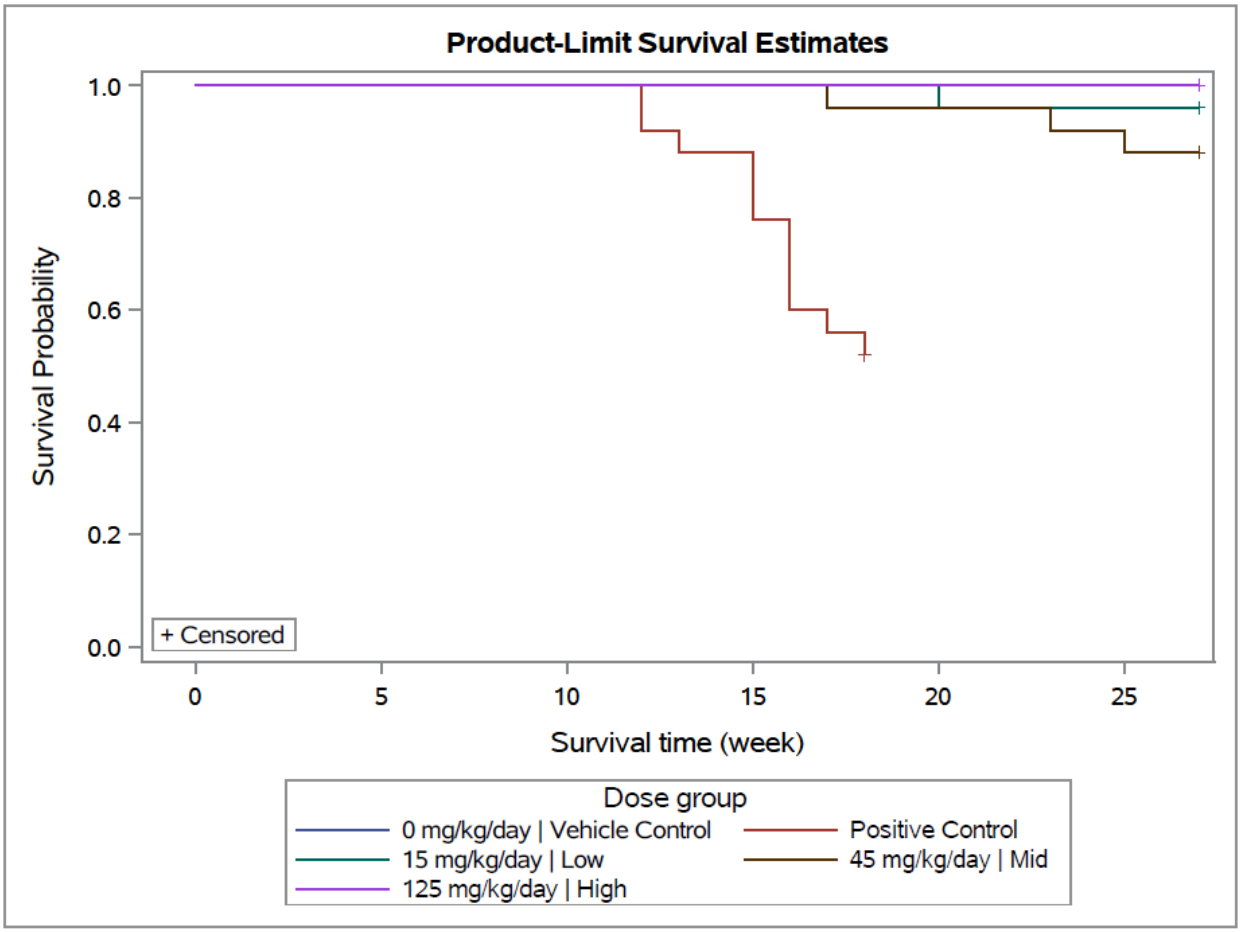
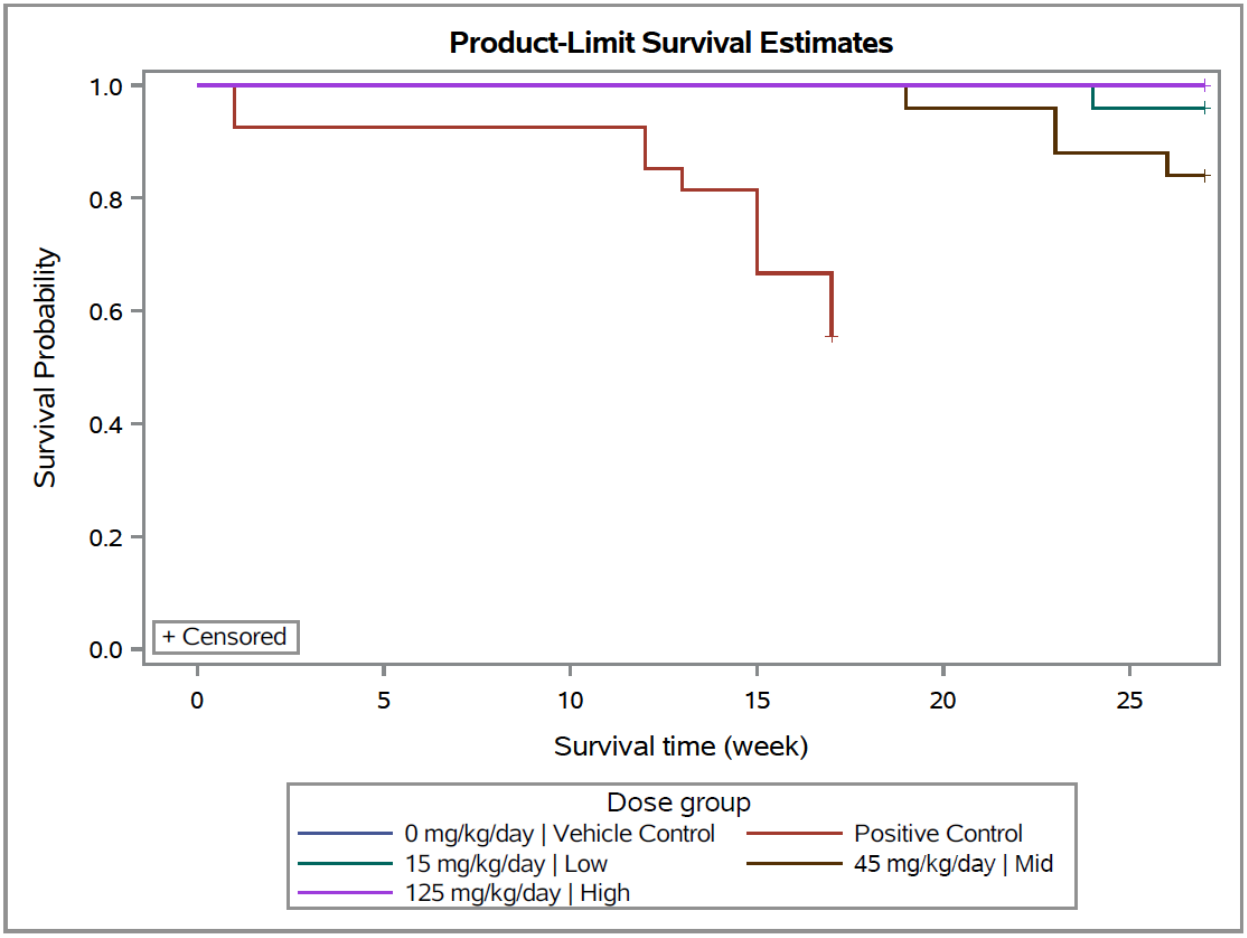


Figure 1B: Kaplan-Meier Survival Functions for Female Mice



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Concur with review.

COA Tracking ID: C2021046
NDA Number: 215309 /Referenced IND for NDA: 77101

CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

COA tracking number	C2021046
NDA#/Referenced IND for NDA	NDA 215309/IND 77101
Applicant:	Incyte Corporation
Established Name/Trade Name:	Ruxolitinib cream
Indication:	Topical treatment of atopic dermatitis in patients 12 years of age and older ☐Rare Disease/Orphan Designation ☒Pediatrics
PDUFA Goal Date:	June 21, 2021 (Priority review)
Review Division:	Division of Dermatology and Dentistry
Clinical Reviewer	Brenda Carr, M.D.
Clinical Team Leader (TL)	Snezana Trajkovic, M.D.
Regulatory Project Manager:	Matthew White, Senior Regulatory Health Project Manager
COA Reviewer:	Yasmin Choudhry, M.D.
COA TL:	Selena Daniels, PharmD, M.S.
COA Deputy Director:	Elektra Papadopoulos, M.D., M.P.H
Instruments reviewed:	1. Worst Itch Numeric Rating Scale ☒ Patient-reported outcome (PRO) 2. Patient Reported Measurement Outcome Information System® Sleep Disturbance Short Form 8b ☒ PRO

Table of Contents

1. EXECUTIVE SUMMARY

In this submission, the applicant is seeking approval of ruxolitinib for the treatment of atopic dermatitis (AD). The Applicant proposes specific targeted clinical outcome assessment (COA)-related labeling claims from two double-blind, randomized, vehicle-controlled pivotal trials of identical design (Studies INCB 18424-303 and 18424-304; from here on referred to as Studies 303 and -304) in adolescent and adult patients with AD. To support these claims, the applicant submitted a COA evidence dossier. The primary objective of this review is to evaluate from a COA perspective if the submitted information supports the COA-related labeling claims.

The ranked secondary efficacy patient-reported outcome (PRO) endpoints proposed for labeling are:

- Proportion of participants with a ≥ 4-point improvement in the Itch-Numeric Rating Scale (NRS) score from baseline to Week 8 (A copy of the instrument is in Appendix A)
- (b) (4)

The data from Studies 303 and -304 demonstrated that ruxolitinib had statistically significant improvements in itch as measured by the Itch-NRS compared with vehicle. (b) (4)

From a COA perspective, the Itch NRS is adequate to support labeling claims.

(b) (4)

(b) (4)

2 REVIEW CONCLUSIONS

Itch NRS

The Itch NRS was reviewed for content validity and the other measurement properties. The Itch NRS is adequate to support labeling claims in this context of use as the instrument is:

- appropriate for measurement of itch (at its worst);
- validly and reliably measures itch (a clinically relevant and important concept to patients);

- and data can be communicated in labeling in a way that is accurate, interpretable and not misleading.

Further, the magnitude of the statistically significant treatment effect appears clinically meaningful to patients. A 4-point improvement in the 11-point Itch NRS has been documented to be a meaningful improvement to patients.

(b) (4)

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(b) (4)

4 BACKGROUND AND CORRESPONDENCE ON CLINICAL OUTCOME ASSESSMENT(S)

Regulatory Background:

(b) (4)

Disease Background:
Atopic dermatitis (AD) is a chronic, recurring, inflammatory, and pruritic skin condition that affects worldwide up to 25% of children and up to 12% of adults. Per the Applicant, although there are many treatment options, there is a significant medical need for novel, safe, topical therapies that provide rapid and effective control of the signs and symptoms of the disease.

Investigational Product:

Ruxolitinib is a Janus Kinase (JAK) inhibitor with selectivity for the JAK1 and JAK2 isoforms. Intracellular JAK signaling involves recruitment of STATs (signal transducers and activators of transcription) to cytokine receptors, and subsequent modulation of gene expression.

5 CLINICAL OUTCOME ASSESSMENT REVIEW

5.1 Clinical Trial Population

The target population for Studies 303 and -304 was adolescent and adult patients (≥12 years) diagnosed with AD (as defined by the Hanifin and Rajka criteria) with a duration of disease of at least 2 years. Eligible participants were required to have an IGA score of 2 (mild) to 3 (moderate), and AD involvement of 3% to 20% body surface area (excluding the scalp) at screening and baseline.

A complete list of the inclusion and exclusion criteria is summarized in section 5 of the clinical study protocols for Studies 303 and 304.

5.2 Clinical Trial Design

Studies 303 and 304:
Studies 303 and -304 were identical in design. Both studies were double-blind, randomized, vehicle-controlled phase 3 studies. Approximately 600 participants (~20% of whom were adolescents) were planned to be randomized 2:2:1 to receive ruxolitinib 0.75% cream BID, ruxolitinib 1.5% cream BID, or vehicle cream BID in a blinded manner for 8 weeks (i.e., the vehicle-controlled period).

Participants who completed Week 8 assessments with no safety concerns could continue into the 44-week, double-blind, long-term safety period. The duration of treatment for an individual participant is approximately 60 weeks (28 days for screening, 8 weeks in the vehicle-controlled period, 44 weeks in the long-term safety period.

Refer to the clinical study protocol for Studies 303 and -304 for more details on the clinical trial design.

5.3 Endpoint Position, Definition, and Assessment Schedule

Table 1 describes the intended placement of the COAs in the endpoint hierarchy, including the endpoint definition and assessment schedule for Studies 303 and -304.

Table 1. Endpoint Position, Definition, and Assessment Schedule for Studies 303 and 304:

Endpoint Position	Assessment (If COA, specify Name and Type)	Endpoint Definition	Assessment Frequency
Primary	Investigator's Global Assessment (IGA) (ClinRO)	Proportion of participants achieving treatment success (defined as a score of 0 or 1 with a ≥ 2-grade improvement) at Week 8	Baseline, Weeks 2, 4, and 8
Secondary ☒ Multiplicity adjusted	Itch Numeric Rating Scale (NRS) (PRO)	Proportion of participants with a ≥ 4-point improvement in Itch NRS score from baseline to Week 8	Daily (every evening) from Screening to Week 8
(b) (4)			

ClinRO= Clinical-reported outcome; PRO= Patient-reported outcome; (b) (4)

5.4 Targeted Clinical Outcome Assessment-Related Labeling Claim(s)

The sponsor has proposed the following specific targeted COA-related labeling claims (in *blue italicized* text):

Efficacy results for (b) (4) *from the two trials are summarized in Table 2.*

(b) (4)

(b) (4)

	Study 1		***Study 2***	
	(b) (4)	***Vehicle***	(b) (4)	***Vehicle***
	(N=253)	*(N=126)*	*(N=228)*	*(N=118)*
IGA-TS[i)]	*53.8%*	*15.1%*	*51.3%*	*7.6%*
(b) (4)	(b) (4)			
Itch NRS (≥ 4 point reduction) (n/N)[ii)]	*52.2% (84/161)*	*15.4% (12/78)*	*50.7% (74/146)*	*16.3% (13/80)*

(b) (4) *Defined as an IGA score of 0 or 1 with a ≥ 2-grade improvement from baseline*

(b) (4) *N=* (b) (4) *with a baseline Itch NRS score ≥4.*

(b) (4)

(b) (4)

(b) (4)

Reviewer's comment(s):
Itch NRS
This reviewer concludes that the Itch NRS is adequate to support labeling claims of itch improvement.

(b) (4)

5.5 Clinical Outcome Assessment(s)

5.5.1 Clinical Outcome Assessment Description(s)

Itch Numeric Rating Scale (Itch NRS)
The Itch NRS is single-item PRO instrument designed to assess itch intensity at its worst on an 11-point NRS, ranging from 0 ("No itch") to 10 ("Worst imaginable itch"). The recall period is the previous 24 hours. See Appendix A for a copy of the instrument.

5.5.2 Conceptual Framework(s)

This submission did not include a conceptual framework for the Itch NRS; however, the Itch NRS is a single-item instrument which assesses the concept of itch intensity at its worst.

5.5.3 Scoring Algorithm

Itch NRS
The Itch NRS generates a single that ranges from 0 to 10, where higher scores indicate greater itch intensity.

Reviewer's comment(s):
The baseline Itch NRS score was determined by averaging the 7 daily NRS scores before Day 1 (Day -7 to Day -1). Similarly, the post-baseline Itch NRS scores were determined by averaging the 7 daily NRS scores before the visit day. At least 4 out of 7 daily scores were needed to be non-missing for a valid by-visit score to be calculated.

(b) (4)

5.5.4 Content Validity

The Applicant completed the following instrument development activities to evaluate the content validity of the Itch NRS (b) (4)

- Literature review
- Patient input (concept elicitation and cognitive interviews).

Ninety minute each telephone interviews were conducted in 25 participants (15 adults; 10 adolescents). Participant recruitment was conducted through the National Eczema Association. Patients were asked to obtain confirmation of diagnosis from their physicians via the provided Confirmation of Diagnosis form.

A total of 250 patients were screened. Of the 52 patients were eligible to participate in the study, and a total of 25 patients were consented and provided confirmation of diagnosis form. The mean age of the participants (6 males; 19 females) was 30 years (range 12-69 years; median 33 years); the level of education and work history was not included in the evidence dossier.

The key study inclusion criteria were:

- Adults (≥ 18 years) and adolescents (12-17 years; with any education level) with mild to moderate AD (IGA of 2 to 3) who,

(b) (4)

(b) (4)

(b) (4)

Literature review:
The Applicant identified sixteen articles from their literature search. The context of the articles varied and included: qualitative interviews / focus groups, questionnaires / surveys, and development of clinical diagnosis criteria. The literature review concluded that:

- Itchy, painful, and dry skin were the most frequently mentioned signs/symptoms in the literature.
- (b) (4)

Concept elicitation interviews:
The Applicant's summary of the results[2] of the patient interviews (Itch and Insomnia (b) (4) (b) (4) is as follows:

"Itch:
All interviewed patients indicated they experienced and were disturbed by itch related to their AD. Patients indicated that some low level of itch is constant with AD, but that the most disturbing itch, and that which disturbs their sleep tends to occur during flares, colloquially defined by patients as episodes of heightened atopic dermatitis symptoms and impacts. Patients indicated that flares occur one to three weeks per month in active months and there may be 3-6 active months per year."

(b) (4)

[2] Section 7 Results: *Atopic Dermatitis Disease Burden* of the Appendix 1 of the sleep evidence dossier.

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In the cognitive interviews, the Itch NRS (b) (4) (b) (4) were tested with the 25 patients (15 adults; 10 adolescents). The participants were asked on the relevancy and clarity of the instructions, each item, and the response scales.

Reviewer's comment*: It appears that both concept elicitation and cognitive interviews were conducted with the same set of patients.*

The Applicant's summary of the results of the cognitive testing is as follows:

- All participants indicated that all items across the instruments were easy to understand and that they were able to find answer choices that reflected their current experience.

(b) (4)

- The majority (n or % not specified in the evidence dossier) of patients did not suggest changes to the language or wording of the questionnaire items.

(b) (4)

Reviewer's comment(s):
Itch NRS
This reviewer agrees that itch is a relevant concept in patients with AD. The content validity of the Itch NRS has been well-documented in literature in adolescents and adults therefore, sponsors are not required to conduct additional qualitative work in adolescents and adults with AD who can validly and reliably self-report.

(b) (4)

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5.5.5 Other Measurement Properties

Itch-NRS
This submission did not include documentation of the other measurement properties of the Itch NRS.

Reviewer's comment(s): *The other measurement properties for Itch-NRS are well-documented. No additional quantitative analyses were needed for this review.*

(b) (4)

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5.5.6 Interpretation of Meaningful Within-Patient Score Changes

Itch NRS

The Applicant proposed that a ≥ 4-point reduction in the Itch NRS (on a 0-10 scale) to be a meaningful within-patient score change. Based on previous data from other application programs, the Division agreed to this threshold.

(b) (4)

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6. APPENDICES

Appendix A: Itch NRS

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