# NDA/BLA Multi-Disciplinary Review and Evaluation

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| **Application Type** | Efficacy Supplement |
| **Application Number(s)** | NDA 215309/S-007 |
| **Priority or Standard** | Standard |
| **Submit Date(s)** | August 19, 2024 |
| **Received Date(s)** | August 19, 2024 |
| **PDUFA Goal Date** | June 19, 2025<br>September 19, 2025 under Major Amendment |
| **Division/Office** | Division of Dermatology and Dentistry |
| **Review Completion Date** | September 15, 2025 |
| **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)** | Topical short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised adult and pediatric patients 2 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. |
| **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)** (if applicable) | OPZELURA is indicated for the topical short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised patients 2 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. |
| **Recommended SNOMED CT Indication Disease Term for each Indication** (if applicable) | 24079001 \| Atopic dermatitis (disorder) |
| **Recommended Dosing Regimen** | Apply a thin layer of OPZELURA topically twice daily to affected areas of up to 20% body surface area. |

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## Reviewers of Multi-Disciplinary Review and Evaluation

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

## Signatures

| DISCIPLINE | REVIEWER | OFFICE/DIVISION | SECTIONS AUTHORED/ APPROVED | AUTHORED/ APPROVED |
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# Glossary

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|---|---|
| AC | advisory committee |
| AD | atopic dermatitis |
| ADME | absorption, distribution, metabolism, excretion |
| AE | adverse event |
| AR | adverse reaction |
| AUC | area under the plasma concentration-time curve |
| $AUC_{tau}$ | area under the plasma concentration-time curve from time zero to the end of the dosing interval (tau) |
| $AUC_{0\text{-}12h}$ | area under the plasma concentration-time curve from time 0-12 hours. |
| BID | twice daily |
| BPCA | Best Pharmaceuticals for Children Act |
| BRF | Benefit Risk Framework |
| BSA | body surface area |
| CDER | Center for Drug Evaluation and Research |
| CDRH | Center for Devices and Radiological Health |
| CDTL | Cross-Discipline Team Leader |
| CFR | Code of Federal Regulations |
| CM | centimeter |
| 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 |
| Css | maximum observed concentration at steady state |
| 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 |
| IGA | Investigator's Global Assessment |
| IND | Investigational New Drug |
| ISE | integrated summary of effectiveness |
| ISS | integrated summary of safety |

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|---|---|
| ITT | intent to treat |
| JAK(i) | Janus kinase (inhibitor) |
| LTS | long-term safety |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mITT | modified intent to treat |
| MUsT | maximal usage trial |
| NCI-CTCAE | National Cancer Institute-Common Terminology Criteria for Adverse Event |
| NDA | new drug application |
| nM | nano molar |
| NME | new molecular entity |
| OCP | Office of Clinical Pharmacology |
| 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 |
| STD | standard deviation |
| TEAE | treatment emergent adverse event |
| VC | vehicle-controlled |

# 1 Executive Summary

## 1.1. Product Introduction

Ruxolitinib, a Janus kinase (JAK) inhibitor, inhibits 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. The relevance of inhibition of specific JAK enzymes to therapeutic effectiveness for the treatment of atopic dermatitis is not currently known.

Ruxolitinib is currently marketed as oral tablets (proprietary name Jakafi) for the treatment of:

- intermediate or high-risk myelofibrosis (MF), including primary MF, post-polycythemia vera MF and post-essential thrombocythemia MF in adults
- polycythemia vera (PV) in adults who have had an inadequate response to or are intolerant of hydroxyurea
- steroid-refractory acute graft-versus-host disease (aGVHD) in adult and pediatric patients 12 years and older
- chronic graft-versus-host disease (cGVHD) after failure of one or two lines of systemic therapy in adult and pediatric patients 12 years and older

Ruxolitinib is also marketed as a topical cream (proprietary name Opzelura), 1.5% for the following indications:

- topical short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised adult and pediatric patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable
- topical treatment of nonsegmental vitiligo in adult and pediatric patients 12 years of age and older

For supplemental NDA S-007, which is the subject of this review, Incyte Corporation ("Incyte" or "the Applicant") seeks approval of Opzelura (ruxolitinib) cream, 1.5%, for the topical short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised adult and pediatric patients 2 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. The proposed treatment regimen is ruxolitinib 1.5% cream applied twice daily to affected areas, up to 20% of body surface area (BSA). Although the Applicant seeks approval of only the 1.5% strength for patients 2 years and older with mild to moderate atopic dermatitis, the Applicant conducted trial INCB 18424-305 (Study 305) with ruxolitinib cream 0.75% in addition to the 1.5% strength in the 2 to <12-year age group as required under the Pediatric

Research Equity Act (PREA) postmarketing requirement (PMR) (PMR 4147-1; refer to Corrected Approval letter dated October 13, 2021). Therefore, the review team reviewed the data for both the 0.75% and 1.5% strengths.

## 1.2.Conclusions on the Substantial Evidence of Effectiveness

The Applicant submitted data from one adequate and well-controlled trial, INCB 18424-305 (Study 305) which provided evidence of the effectiveness of ruxolitinib cream, 0.75% and 1.5% for the topical treatment of non-immunocompromised subjects 2 years of age to <12 years of age with mild to moderate atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. The primary endpoint of IGA-Total Success (IGA-TS) at Week 8, defined as a score of clear or almost clear on the IGA with at least a 2-grade reduction from baseline, was statistically significant relative to vehicle for both ruxolitinib 1.5% and ruxolitinib 0.75%, with appropriate control for multiplicity. The IGA-TS response rates at Week 8 were 56.6% for ruxolitinib 1.5%, 36.6% for ruxolitinib 0.75%, and 10.8% for vehicle. IGA-TS response rates were consistent across age groups and other demographic subgroups and the findings were robust to the handling of missing data.

The Applicant has demonstrated that ruxolitinib cream, 1.5% is effective for its intended use in the target population and have met the evidentiary standard required by 21 Code of Federal Regulations (CFR) 314.126 (a)(b) to support approval.

## 1.3.Benefit-Risk Assessment

**Benefit-Risk Summary and Assessment**

Ruxolinitib cream, 1.5% and 0.75%, and is a topical JAK-1/2 inhibitor that targets the JAK-STAT signaling pathway, which is implicated in the inflammation and itch of atopic dermatitis (AD). Ruxolitinib cream, 1.5% cream is currently marketed under the proprietary name, Opzelura. Currently marketed indications of OPZELURA include:

- Topical short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised adult and pediatric patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

The Applicant proposes expansion of the AD indication for the "topical treatment of mild to moderate atopic dermatitis in non-immunocompromised adult and pediatric patients 2 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable". The Applicant is seeking approval of the currently-marketed 1.5% strength via a 505(b)(1) regulatory pathway.

To establish the effectiveness of ruxolitinib cream in the treatment of mild to moderate AD in children 2 to < 12 years of age, the Applicant submitted results from a single phase 3, randomized, multicenter, vehicle-controlled, trial, Study INCB 18424-305 (Study 305) that evaluated 2 dose concentrations: 0.75% cream and 1.5% cream. The dosing regimen was application to affected areas twice daily (BID). The double-blind treatment period was 8 weeks.

Study 305 randomized 330 subjects aged 2 to < 12 years old (yo) with mild to moderate AD, defined as having an Investigator's Global Assessment (IGA) score of 2 or 3 and AD Body Surface Area (BSA) of 3-20% (excluding the scalp) at baseline, to one of three arms (2:2:1): ruxolitinib 1.5% cream, ruxolitinib 0.75% cream, or vehicle. For children aged 6 to <12 years, the baseline itch numerical rating score (NRS) score was ≥4. The primary endpoint was the proportion of subjects who achieve IGA-Total Success (IGA-TS), defined as IGA score of 0 to 1 with ≥ 2-grade improvement from baseline, at Week 8. The key secondary endpoint was the proportion of subjects with a ≥ 4-point improvement in Itch NRS score from baseline to Week 8.

Efficacy

In Study 305, 131 subjects were randomized to receive ruxolitinib 1.5% cream BID and 134 subjects were randomized to receive ruxolitinib 0.75% cream . Ruxolitinib cream, 1.5% and 0.75%, was statistically superior to the vehicle cream for the primary efficacy endpoint intended for labeling for the intent-to-treat (ITT) population at Week 8. Neither strength achieved statistical significance for the key secondary efficacy endpoint of the proportion of participants 6 to < 12 years of age with a ≥ 4-point improvement in Itch NRS score from baseline to Week 8.

- For the primary efficacy endpoint of the proportion of subjects achieving IGA-TS at Week 8, the ruxolitinib 0.75% group, compared to the vehicle group, achieved a response of 36.6% versus 10.8% (a difference from vehicle of 25.8%, (95% confidence interval (CI) 14.7%, 36.9%), p-value 0.0001). The ruxolitinib 1.5% group, compared to the vehicle group, achieved a response of 56.6% versus 10.8% (a difference from vehicle of 45.7% (95% confidence interval (CI) 34.4%, 57.1%), p-value <0.0001). These results were similar when reviewed by age group: 60.6% vs 15.2% (45.5% difference) and 52.3% vs 6.3% (46.1% difference) for 2-6 yo and 7-11 yo in the ruxolitinib 1.5% cream cohort, and 35.3% vs 15.2% (20.1% difference) and 37.9% vs 6.3% (31.6% difference) for 2-6 yo and 7-11 yo in the ruxolitinib 0.75% cream cohort.
- For the key secondary efficacy endpoint of the proportion of participants 6 to < 12 years of age with a ≥ 4-point improvement in Itch NRS score from baseline to Week 8, the ruxolitinib 0.75% group, compared to the vehicle group, achieved a response of 37.5% versus 29.7% (a difference from vehicle of 7.77%, CI -10.4%, 25.9%, p-value 0.4198). The ruxolitinib 1.5% group, compared to the vehicle group, achieved a response of 43.4% versus 29.7% (a difference from vehicle of 13.7%, CI -4.8%, 32.2%, p-value 0.1685). Neither result was statistically significant.

Safety

The Applicant evaluated the safety of ruxolitinib cream, 1.5% and 0.75% in subjects with mild to moderate AD. The primary safety analysis was conducted on the vehicle-controlled population for Study 305, which consisted of 329 subjects with mild-to-moderate AD, 130 of whom were treated with ruxolitinib 1.5% cream and 134 of whom were treated with ruxolitinib 0.75%. After the vehicle-controlled period of 8 weeks, eligible subjects continued treatment as needed for AD flares in a follow-on, 44-week, open-label long-term safety (LTS) extension period. The Applicant also submitted supportive safety and pharmacokinetic data from a 4-week, maximal usage study (INCB 18424-109, Study 109) in 22 subjects age 2 to <12 years with moderate to severe AD (IGA ≥3, %BSA ≥35%) who applied ruxolitinib cream, 1.5%. Study 109 also included an additional 4-week treatment extension period and a follow-on 44-week, open-label LTS extension period.

Adverse Events and Adverse Reactions:

The safety analysis of Study 305 was adequate to characterize the safety profile of ruxolitinib cream, 1.5% and 0.75%, for the treatment of mild to moderate AD in subjects ages 2 to <12 years of age. There were no deaths and no serious adverse events (SAE) related to ruxolitinib cream, 1.5% and 0.75%, during the vehicle-controlled phases of Studies 305 and 109. In Study 305, 45 subjects (34.6%) in the ruxolitinib 1.5% cream group, 34 subjects (25.4%) in the ruxolitinib 0.75% group, and 16 subjects (24.6%) in the vehicle group experienced at least one AE. The adverse reactions occurring in ≥1% pediatric subjects 2 to 11 years of age treated with ruxolitinib cream, 1.5%, for atopic dermatitis through Week 8 in Study 305 include upper respiratory tract infection (15% in the ruxolitinib 1.5% group and 11% in the vehicle group), COVID-19 (5%, 3%), application site reaction (5%, 2%), pyrexia (2%, 0%), and white blood cell decreased (2%, 0%).

PK results:
In Study 109, the maximal usage study in subjects with AD ages 2-11 years with BSA ≥35% treated with ruxolitinib 1.5% cream, the mean % BSA treated was 63%. In Study 109, the mean plasma concentration at steady state ($C_{ss}$)was 98.2 nM (SD 148 nM). In Study 305 (subjects with ≤20% BSA, mean %BSA of 11.3%), the $C_{ss}$ was 15.7 nM (SD 31 nM) for subjects receiving ruxolitinib 0.75% cream and 29.7 nM (SD 60.7 nM) for those receiving ruxolitinib 1.5% cream. For both strengths, the $C_{ss}$ was higher in the 2-6 yo age groups compared to the 7-11 yo age groups: 19.4 nM vs 11.8 nM for ruxolitinib 0.75% cream and 36 nM vs 22.7 nM for ruxolitinib 1.5% cream. The mean weekly dose applied in the phase 3 study 305 was approximately 30g per week.

The review team concludes that the Applicant has provided data to demonstrate substantial evidence of efficacy and an acceptable risk-benefit profile for both strengths of ruxolitinib cream, 1.5% and 0.75%, for the treatment of mild to moderate atopic dermatitis (up to 20% BSA) in subjects 2 to <12 years of age. Although subjects applying ruxolitinib cream, 0.75% had a lower incidence of TEAEs (25.4%) compared to those applying 1.5% (34.6%), there was a difference in efficacy based on the primary efficacy endpoint of the IGA-TS response rates at Week 8 (56.6% for ruxolitinib 1.5% cream vs 36.6% for ruxolitinib 0.75% cream) in Study 305, such that the benefit-risk assessment supports the 1.5% strength as proposed by the Applicant based on currently available data. None of the currently FDA-approved treatments provide a permanent cure or universal response for mild to moderate AD, and all are associated with one or more risks. Because treatment may be complicated by inadequate response, loss of response, adverse reactions, and the presence of comorbidities or concomitant illnesses, there is still a need for additional therapeutic options, particularly topical, for younger pediatric patients with AD.

| 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. In 60% of patients, the onset of disease is in the first year of life, with onset by the age of 5 years in approximately 85% of affected individuals. The prevalence of AD in the United States in individuals 4-8 years of age has been reported as 10.63% and as 9.96% in those 9-12 years. For 10-30% of individuals, AD persists into the adult years.<br><br>AD is clinically diagnosed and relies principally on disease pattern (morphology and | While AD is not a life-threatening condition, it may be serious. It may significantly impact the quality of life of the patient, as well as family members. 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.<br><br>Patients with AD often experience sleep |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | distribution), disease history, and medical history (e.g., personal and/or family history of atopy). In patients older than 2 years of age, the presentation is similar to that in adults. It is particularly characterized by lichenified plaques in flexural regions of the extremities (antecubital and popliteal) and that may also involve the neck, wrists, and volar aspects of the wrists. AD may be generalized.<br><br>Common comorbidities of AD include asthma, allergic rhinitis/rhinoconjunctivitis, and food allergies. | disturbance, largely attributable to the associated extreme pruritus. During disease flares, approximately 80% of patients may experience disturbed sleep. The disruption in sleep could have carryover effects to impact behavior and neurocognitive functioning. Sleep disturbance may also disrupt the sleep of family members. Affected children may also experience depression, anxiety, social isolation, and impaired psychosocial functioning. |
| 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.<br>• Tacrolimus ointment, 0.03% and pimecrolimus cream, 1% are topical calcineurin inhibitors that are approved for treatment of AD in patients 2 years and older. 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 rare cases of malignancy (e.g., skin and lymphoma) that have been reported in patients treated with topical calcineurin inhibitors.<br>• Crisaborole ointment, 2% is a topical phosphodiesterase 4 (PDE-4) inhibitor and is a non-steroidal option for treatment of mild to moderate AD in patients 3 months and older. 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.<br>• Roflumilast cream, 0.15%, a PDE-4 inhibitor, is approved for patients 6 years of age and older with mild to moderate AD that is not manageable by available topical therapies. Adverse reactions for roflumilast described in labeling include headache, nausea, application site pain, diarrhea, and vomiting.<br>• Ruxolitinib cream, 1.5% (this product), is a JAK-1/2 inhibitor indicated for the | There are several FDA-approved products with an acceptable benefit-risk profile for topical treatment of mild-to-moderate AD in pediatric patients ages 2 to <12 years. However, there is still an unmet need for alternative topical treatments because although efficacy varies, no product produces a response in all patients or provides a permanent cure. In addition, parents of children in this age range may be reluctant to use systemic treatment.<br><br>The currently available topical treatments have drawbacks. Chronic use of topical corticosteroids is associated with multiple potential adverse effects; and the topical calcineurin inhibitors (pimecrolimus cream and tacrolimus ointment) have a boxed warning for malignancy. These classes of medications are not indicated for long-term/chronic use. Management of AD in this younger pediatric population may also be complicated by inadequate response, loss of response, adverse reactions, and the presence of |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | topical short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised adult and pediatric patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.<br>• Tapinarof cream, 1%, is an aryl hydrocarbon receptor (AhR) modulating agonist recently approved for the indication of atopic dermatitis (AD) in adult and pediatric patients ages 2 years and older. | comorbidities or concomitant illnesses. Approval of ruxolitinib 1.5% cream would represent important steroid-sparing treatment options for children ages 2 to <12 years with mild to moderate AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable |
| Benefit | In Study 305, ruxolitinib cream, 1.5% and 0.75% were both statistically superior to the vehicle cream for the primary efficacy endpoint intended for labeling for the intent-to-treat (ITT) population at Week 8. For the primary efficacy endpoint of the proportion of subjects achieving IGA-TS at Week 8, the ruxolitinib 1.5% group, compared to the vehicle group, achieved a response of 56.5% versus 10.8% (a difference from vehicle of 45.7%, (95% confidence interval (CI) 34.7%, 57.1%), p-value <0.0001). The ruxolitinib 0.75% group, compared to the vehicle group, achieved a response of 36.6% versus 10.8% (a difference from vehicle of 25.8%, (95% confidence interval (CI) 14.7%, 36.9%), p-value 0.0001).<br><br>For the key secondary efficacy endpoint of the proportion of participants 6 to < 12 years of age with a ≥ 4-point improvement in Itch NRS score from baseline to Week 8, the ruxolitinib 1.5% group, compared to the vehicle group, achieved a response of 43.4% versus 29.7% (a difference from vehicle of 13.7%, CI -4.8%, 32.2%, p-value 0.1685). This result was not statistically significant. The ruxolitinib 0.75% group, compared to the vehicle group, achieved a response of 37.5% versus 29.7% (a difference from vehicle of 7.77%, CI -10.4%, 25.9%, p-value 0.4198). This was also not statistically significant. | The data submitted by the Applicant met the evidentiary standard for provision of substantial evidence of effectiveness under the proposed conditions of use. Study INCB 18424-305 was adequate, well-controlled, and achieved its primary efficacy endpoint for both the 1.5% and 0.75% strengths. Due to the higher efficacy rates in the 1.5% strength, the Applicant only proposed marketing the currently available strength, 1.5%, for the 2 to less than 12 year age group. |
| Risk and Risk Management | The primary safety database consisted of 329 subjects in Study 305: 130 subjects received ruxolitinib 1.5% cream, 134 subjects received ruxolitinib 0.75%, and 65 subjects received vehicle cream. Study 109 consisted of 29 subjects who received ruxolitinib 1.5% cream. | The safety profiles of ruxolitinib 0.75% and 1.5% cream have been adequately characterized by the premarket safety data for mild to moderate AD in patients ages 2 to <12 years. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | The safety analysis of Study 305 was adequate to characterize the safety profile of ruxolitinib cream, 1.5% and 0.75%, for the treatment of mild to moderate AD in subjects ages 2 to <12 years of age. There were no deaths and no serious adverse events (SAE) related to ruxolitinib cream, 1.5% and 0.75%, during the vehicle-controlled phases of Studies 305 and 109. In Study 305, 45 subjects (34.6%) in the ruxolitinib 1.5% cream group, 34 subjects (25.4%) in the ruxolitinib 0.75% group, and 16 subjects (24.6%) in the vehicle group experienced at least one AE. The adverse reactions occurring in ≥1% pediatric subjects 2 to 11 years of age treated with ruxolitinib cream, 1.5%, for atopic dermatitis through Week 8 in Study 305 include upper respiratory tract infection (15% in the ruxolitinib 1.5% group and 11% in the vehicle group), COVID-19 (5%, 3%), application site reaction (5%, 2%), pyrexia (2%, 0%), and white blood cell decreased (2%, 0%).<br><br>Overall, while ruxolitinib cream, 0.75% resulted in fewer AEs in both age groups (2-6 and 7-11 years) than ruxolitinib 1.5% with the exception of pyrexia (higher in the 2-6 year age group, 3.7% vs 2.3%), there was no notable difference in safety between the two strengths in Study 305.<br><br>PK results:<br>In Study 109, the maximal usage study in AD subjects ages 2-11 years with BSA ≥35% treated with ruxolitinib 1.5% cream, the mean % BSA treated was 63%. In Study 109, the mean plasma concentration at steady state ($C_{ss}$)was 98.2 nM (SD 148 nM). In Study 305 (subjects with ≤20% BSA, mean %BSA of 11.3%), the $C_{ss}$ was 15.7 nM (SD 31 nM) for subjects using ruxolitinib 0.75% cream and 29.7 nM (SD 60.7 nM) for those using ruxolitinib 1.5% cream. For both strengths, the $C_{ss}$ was higher in the 2-6 yo age groups compared to the 7-11 yo age groups: 19.4 nM vs 11.8 nM for ruxolitinib 0.75% cream and 36 nM vs 22.7 nM for ruxolitinib 1.5% cream. The mean weekly dose applied in the phase 3 study 305 was approximately 30g per week. | In addition to those currently listed in the PI for patients with AD, the following recommendations on dosage and administration are recommended:<br>• Application to up to 20% BSA.<br>• Do not use OPZELURA with occlusive dressings.<br>For ages 2-11 years:<br>• Do not use more than one 60 gram tube of ruxolitinib cream, 1.5%, per 2 weeks.<br><br>Prescription labeling, patient labeling, and routine pharmacovigilance are adequate to manage the potential risks of this product. |

## 1.4.Patient Experience Data

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

| | | | | |
|---|---|---|---|---|
| X | **The patient experience data that were submitted as part of the application include:** | | | Section of review where discussed, if applicable |
| | x | Clinical outcome assessment (COA) data, such as | | |
| | | x | Patient reported outcome (PRO) | Section 8.1 |
| | | x | Observer reported outcome (ObsRO) | Section 8.1 |
| | | x | Clinician reported outcome (ClinRO) | Section 8.1 |
| | | □ | 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 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. In 60% of patients, the onset of disease is in the first year of life, with onset by the age of 5 years in approximately 85% of affected individuals (Weston and Howe 2020). Shaw et al. reported the prevalence of AD in the United States in individuals 4-8 years of age to be 10.63% and in those 9-12 years of age to be 9.96% (Shaw et al. 2011). For 10-30% of individuals, AD persists into the adult years (Eichenfield et al. 2014a).

AD is clinically diagnosed and relies principally on disease pattern (morphology and distribution), disease history, and medical history (e.g., personal and/or family history of atopy). In patients older than 2 years of age, the presentation is similar to that in adults. It is particularly characterized by lichenified plaques in flexural regions of the extremities (antecubital and popliteal) and that may also involve the neck, wrists, and volar aspects of the wrists (Weston and Howe 2020). AD may be generalized.

The pathogenesis involves a complex interplay of genetic, immunological, and environmental factors that result in abnormal skin barrier function and immune system dysfunction (Eichenfield et al. 2014a). Irregularities in the terminal differentiation of the epidermal epithelium lead to a faulty stratum corneum which permits the penetration of environmental allergens (Leung and Guttman-Yassky 2014). The exposure to allergens may ultimately result in systemic sensitization and may predispose AD patients to other conditions, such as asthma and food allergies (Leung and Guttman-Yassky 2014).

Acute AD is associated with cytokines produced by T helper type 2 (Th2) cells (as well as other [T-cell subsets and immune elements) (Leung and Guttman-Yassky 2014). These cytokines are thought to play an important role in the inflammatory response of the skin, and IL-4 and IL-13 may have distinct functional roles in Th2 inflammation (Bao and Reinhardt 2015). IL-4 has been shown to stimulate immunoglobulin E (IgE) production from B cells (May and Fung 2015). IL-13 expression correlates with disease severity and flares (Leung and Guttman-Yassky 2014). IL-4 mediates its biological activity via binding to IL-4Rα. IL-13 receptor alpha 1 (IL-13Rα1) may then be recruited to form a signaling complex. IL-13 mediates its biological activity via binding to IL- 13Rα1 and subsequent recruitment of IL-4Rα, forming a signaling complex (May and Fung 2015). IL-4 and IL-13 reside on chromosome 5q23-31, among a grouping of genes related to development of allergic diseases.

Common comorbidities include asthma, allergic rhinitis/rhino-conjunctivitis, and food allergies (Bao and Reinhardt 2015; Eichenfield et al. 2014a). Comorbidities involving the eyes

include atopic keratoconjunctivitis, a chronic, intensely pruritic, allergic disease that is most often seen in adults with AD (Hamrah and Dana 2020). Patients with AD often experience sleep disturbance, largely attributable to the associated extreme pruritus. The disruption in sleep could have carryover effects to impact behavior and neurocognitive functioning (Camfferman et al. 2010). Sleep disturbance in the affected individual may also disrupt the sleep of family members, impacting the quality of life for all (Camfferman et al. 2010). Affected children may experience depression and anxiety (Yaghmaie et al. 2013), social isolation, and impaired psychosocial functioning (Drucker et al. 2017).

Patients with AD are predisposed to colonization or infection by microbes, particularly *Staphylococcus aureus* and herpes simplex virus. The susceptibility to *S. aureus* is related to multiple factors, including the abnormal skin barrier function and the production of serine proteases that degrade the skin barrier (Leung and Guttman-Yassky 2014).

The most common laboratory finding is an elevated IgE (Shaw et al. 2011). Up to 80% of the AD population has elevated IgE, often with accompanying eosinophilia1. IgE levels may fluctuate with disease severity; however, some patients with severe AD present with normal IgE levels (Weston and Howe 2020).

## 2.2.Analysis of Current Treatment Options

Because ruxolitinib cream, 1.5% and 0.75% are for the topical treatment of mild to moderate AD, the following discussion will focus primarily on the topical treatment of this disease. See Table 1.

The FDA-approved or FDA-licensed topical treatments for mild to moderate AD fall in the categories of topical corticosteroids; topical calcineurin inhibitors (TCIs) pimecrolimus and tacrolimus; topical phosphodiesterase-4 (PDE-4) inhibitors crisaborole and roflumilast; and topical Janus Kinase inhibitors (JAKis, ruxolitinib cream, 1.5%). In addition, phototherapy (ultraviolet A and ultraviolet B) is considered a safe and effective treatment for AD patients who are candidates for systemic therapy.

Corticosteroids are available for treatment of AD by various routes of administration, including topical, oral, and parenteral. Although the use of systemic corticosteroids may result in rapid improvement, the AD commonly recurs with higher severity on discontinuation of the systemic corticosteroids (rebound). For these reasons and the potential for adverse effects, the American Academy of Dermatology recommends that systemic corticosteroids generally be avoided in the treatment of AD because potential risks of treatment generally outweigh the benefits (Sidbury et al. 2014). Potential adverse effects include reversible hypothalamic-pituitary-adrenal axis suppression with the potential for glucocorticoid insufficiency, hyperglycemia and other endocrine effects. A particular concern in children and adolescents is the risk of decreased linear growth during treatment. Labels for systemic corticosteroids do not specify any limitations on the age.

Topical corticosteroids (TCS) are the first-line pharmacologic treatment for AD and represent the cornerstone of anti-inflammatory treatment of AD in all age groups (Eichenfield et al. 2014b). Numerous TCS, in various dosage forms and potencies, are available for the treatment of AD, and some are specifically indicated for pediatric use. For example, fluticasone propionate lotion, 0.05%, a medium potency TCS, is indicated for relief of the inflammatory and pruritic manifestations of atopic dermatitis in patients 3 months of age and older. According to product labels, TCS may be sufficiently absorbed to lead to systemic adverse effects. Additionally, pediatric patients may be more susceptible to systemic toxicity doses due to their larger skin surface to body mass ratios. Local adverse effects include skin atrophy, striae, telangiectasias, and hypopigmentation. Chronic and/or prolonged use of topical corticosteroids, i.e., longer than 3 weeks continuously, may show decreased efficacy (tachyphylaxis).

There are two topical PDE-4 inhibitors approved for the treatment of mild to moderate AD. Crisaborole ointment, 2%, is approved for the treatment of pediatric patients 3 months of age and older, while roflumilast cream, 0.15% is approved for the treatment of patients 6 years and older. While the adverse events related to crisaborale are limited to application site pain, there is relatively low efficacy as compared to vehicle. Roflumilast cream, 0.15% has relatively low efficacy as well. Adverse reactions for roflumilast described in labeling include headache, nausea, application site pain, diarrhea, and vomiting.

Topical calcineurin inhibitors (pimecrolimus cream, 1%; tacrolimus ointment, 0.03% and 0.1%) are second-line therapies indicated for the short-term, non-chronic treatment of AD when other topical prescription treatments have failed or are inadvisable. More specifically pimecrolimus cream, 1% is approved for mild to moderate AD patients 2 years and older; tacrolimus ointment, 0.03% carries boxed warnings advising that the safety of its long-term use has not been established. More specifically, the boxed warnings describe rare cases of malignancy (e.g., skin and lymphoma) that have been reported in patients treated with TCIs; a causal relationship has not been established. Tacrolimus ointment, both 0.03% and 0.1% for adults, and only 0.03% for children aged 2 to 15 years, is indicated as *second-line therapy* for the short-term and non-continuous chronic treatment of moderate to severe atopic dermatitis 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.

Ruxolitinib cream, 1.5% is a Janus kinase inhibitor (JAKi) indicated for the topical short-term and non- continuous chronic treatment of mild to moderate AD in non-immunocompromised adult and pediatric patients (12 years of age and older) whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Use is limited to 20% BSA and no more than 60 gm of ruxolitinib cream, 1.5% in 1 week and no more 100 gm in 2 weeks. In addition, it cannot be prescribed in conjunction with other systemic immunomodulators (e.g., dupilumab). There is also a boxed warning (see below for systemic JAKis).

FDA-approved systemic treatments for atopic dermatitis include biologics and JAKis, which are

typically considered second-and third-line therapies, respectively, when disease is not adequately controlled with topical prescription and systemic therapies, respectively, or when those therapies are not advisable. Typically, subjects who are treated with systemic therapies have moderate to severe AD. All the biologics are administered as a subcutaneous injections and may be used without or without topical corticosteroids.

Dupilumab is an IL-4 receptor antagonist approved for the treatment of adult and pediatric patients age 6 months and older with moderate-to-severe AD. Tralokinumab is an IL-13 antagonist approved for the treatment of moderate-to-severe AD in adults and pediatric patients 12 years of age and older. Lebrikizumab is an IL-13 inhibitor indicated for the treatment of adults and pediatric patients 12 years of age and older who weigh at least 40 kg with moderate-to-severe AD.

The systemic JAKis approved for AD are all administered orally. In this class of drugs are upadacitinib and abrocitinib, both indicated for the treatment of adults and pediatric patients 12 years of age and older with moderate to severe atopic dermatitis. JAKis (including topical ruxolitinib) carry boxed warnings for serious infections, mortality, malignancy, major adverse cardiovascular events, and thrombosis. As a result, oral JAKis are considered third-line therapy for refractory moderate to severe AD disease that is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable. JAKis are not recommended for use in combination with other JAK inhibitors, biologic immunomodulators, or with other immunosuppressants.

Nonpharmacologic care is critical to AD management and includes attention to bathing practices and the regular use of moisturizers, which are available in several delivery systems, such as creams, ointments, oils, lotions. Moisturizers are directed at the xerosis and transepidermal water loss that are central elements of the disease. They may also relieve pruritus, lessen erythema and fissuring, 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 important and required, irrespective of the severity of disease. The use of moisturizers during maintenance may stave off flares and may lessen the amounts of pharmacologic agents needed to control the disease (Eichenfield et al. 2014b).

**Table 1. Topical Treatments for Atopic Dermatitis**

| Product Class (all topical) | Drug products | Relevant Indication/ Age group | Year of Approval | Efficacy Information | Important Safety and Tolerability Issues |
|---|---|---|---|---|---|
| Corticosteroid (TCS) | Examples: Hydrocortisone Desonide Triamcinolone | Relief of the inflammatory and pruritic manifestations of corticosteroid responsive dermatoses | Varies | Considered first-line therapy for atopic dermatitis | Potential for systemic absorption; local adverse effects include skin atrophy, striae, telangiectasias, and hypopigmentation; tachyphylaxis |
| Calcineurin inhibitor (TCIs)* | Pimecrolimus cream, 1% | Mild to moderate AD in adults and children 2 years of age and older | 2001 | Second-line therapy for mild to moderate AD | Boxed warning: Rare cases of malignancy (e.g., skin and lymphoma) has been reported in patients treated with TCIs, although causal relationship has not been established; Application site burning or stinging |
| | Tacrolimus ointment, 0.03% | Moderate to severe atopic dermatitis in adults and children 2 years of age and older | 2000 | Second-line therapy* for moderate to severe AD | |
| Phosphodiesterase -4 (PDE-4) inhibitor | Crisaborale ointment (Eucrisa) | Mild to moderate atopic dermatitis in adult and pediatric patients 3 months of age and older | 2016, 2020 | 31.4-32.8% success in IGA compared to 18-25.4% vehicle | Application site burning or stinging |
| | Roflumilast (Zoryve) cream, 0.15% | Mild to moderate atopic dermatitis in adult and pediatric patients 6 years of age and older | 2024 | 28.9-32% success in IGA compared to 12-15.2% vehicle | Application site pain |
| JAK-1/2 inhibitor* | Ruxolitinib (Opzelura) cream, 1.5% | Mild to moderate atopic dermatitis adult and pediatric patients 12 years of age and older | 2021 | 51.3-53.8% success in IGA compared to 7-15.1% vehicle | Boxed warning for serious infections, higher rate of all-cause mortality, lymphoma and other malignancies, MACE, thombosis; Systemic absorption observed; although not cumulative |
| Aryl hydrocarbon receptor (AhR) modulating agonist | Tapinarof (Vtama) cream, 1% | Atopic dermatitis in adults and pediatric patients 2 years of age and older | 2024 | 45-46% success in IGA compared to 14-18% vehicle | Folliculitis, contact dermatitis |

**Source: Clinical Reviewer.**

*For short-term and non-continuous chronic treatment in non-immunocompromised patients who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable

APPEARS THIS WAY ON ORIGINAL

# 3 Regulatory Background

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

OPZELURA (ruxolitinib) cream, 1.5%, was approved on September 21, 2021, by the FDA for the indication of topical treatment of mild-moderate atopic dermatitis in patients 12 years of age and older, under the 505 (b)(1) pathway, and for the topical treatment of nonsegmental vitiligo (NSV) in adults and pediatric patients 12 years and older on July 18, 2022. Pediatric exclusivity for the moiety was issued (expiration January 18, 2026). The dosing regimen for both indications is to apply a thin layer to affected areas twice daily. It is packaged and dispensed as a 60 g and 100 g tube.

## 3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant developed ruxolitinib cream, 1.5% for topical treatment of AD under IND 077101 and submitted their marketing application under Efficacy Supplement-7 for new drug application (NDA) 215309 (505(b)(1) regulatory pathway). Milestone interactions with the Applicant included the following:

- **24 February 2017** – Initial submission of Protocol INCB 18424-102, an open-label study to assess the safety, tolerability, and PK of ruxolitinib cream in subjects 2 to <17 years of age. This study was placed on clinical hold under 21 CFR 312.42(b)(1)(iv): Insufficient information to assess risks to human subjects.
    - In **July 2017**, the Sponsor submitted juvenile animal toxicity data and a risk assessment for the maximal clinical dose, as well as a protocol amendment to include only AD subjects 12-17 years. The submitted data was sufficient to allow for a removal of the clinical hold to allow for the study to proceed in AD subjects 12-17 years.

- **16 April 2018** – Type C meeting (Written Response Only, WRO) to discuss a proposed amendment of Protocol INCB 18424-102 to include AD subjects ages 2 to <12 years. The Sponsor submitted additional juvenile toxicity data in rats which identified bone toxicity as a unique juvenile toxicity. The FDA requested human AUC values from another a related study in adults with AD.
    - **May 2018** – The Sponsor submitted the requested data and a proposed amendment of Protocol INCB 18424-102 to include AD subjects ages 2 to <12 years. The amended protocol was placed on partial clinical hold under 21 CFR §312.42(b)(1)(i): Human subjects are or would be exposed to an unreasonable and significant risk of illness or injury. The FDA directed the Sponsor to propose appropriate safety monitoring for early detection of bone effects in pediatric subjects.

- **16 November 2018** – The Sponsor submitted a Clinical Hold Response and Amendment

2 to Protocol ICNB 18424-102. The Sponsor proposed to monitor for early detection of possible bone changes in pediatric subjects by implementing monitoring rules based on the following markers of bone metabolism: procollagen type 1 N-terminal propeptide (P1NP, preferred), bone specific alkaline phosphatase (BSAP), and carboxy-terminal collagen crosslinks (CTx), as well as evaluate a lower concentration of ruxolitinib cream (0.75%). DDD obtained consults from the Division of Bone, Reproductive, and Urologic Products (DBRUP) and Division of Pediatric and Maternal Health (DPMH). The DBRUP consultant "agree(d) with the sponsor's proposal for monitoring of bone biomarkers in the initial study of children <12 years old, including the criteria for added monitoring and/or treatment modification based on excessive P1NP suppression, as outlined in the briefing package (for the EOP2 meeting)". The consultant recommended that blood sampling for these markers be conducted in the morning, after an overnight fast. Height should be measured during the 4-week study, and "in longer-term pediatric studies, assessment of linear growth at least every 6 months during treatment and follow-up. If, after evaluation of short-term bone biomarker data, there is continued concern about possible bone toxicity of ruxolitinib, bone imaging and/or densitometry should be strongly considered for inclusion in longer-term studies of children <12 years old."

  - 13 December 2018 – Partial clinical hold was removed to allow for INCB 18424-102 to proceed with study in AD subjects 2 to <12 years.

- **12 December 2018** – The Sponsor submitted the initial Pediatric Study Plan (iPSP) for atopic dermatitis, requesting a deferral for pediatric assessment in ages 2 to <12 years.
  - **27 March 2019** – The Pediatric Review Committee (PeRC) agreed with the Sponsor's plan to request partial waiver below the age of 3 months, deferral of study in subjects 3 to <24 months (with clarification of studies required); deferral of study in subjects 2 to <12 years (after removal of partial clinical hold); and inclusion of subjects 12 years and older in the adult phase 3 studies.
  - **1 April 2019** – These comments were conveyed to the Sponsor, including the FDA comment that an open-label design would not allow for adequate assessment of efficacy in AD subjects 2 to <12 years, and include an open-label, long-term safety study.

- **22 May 2019** – The Sponsor submitted a revised iPSP with the requested changes, which was discussed further during the Pre-NDA meeting for atopic dermatitis on 13 May 2020. DDD provided further comments on the revised iPSP, which the Sponsor re-submitted on 22 May 2020.
  - 23 June 2020 – The PeRC agreed with the revised iPSP.
  - 15 July 2020 – An iPSP Agreement Letter was sent to the Sponsor.

- **10 March 2021** – Type C meeting to discuss studies in pediatric AD subjects ages 2 to <12 years
  - After obtaining consults from the Division of General Endocrinology (DGE) and DPMH, DDD agreed with the Sponsor's proposal to record height and weight at

screening and weeks 24 and 52 in the phase 3 study (INCB 18424-305). In addition to growth measurements, DDD also recommended obtaining additional biomarker data in the maximal use study INCB 18424-109 in which higher levels of drug exposure could be assessed, and for a longer duration of treatment (8 vs. 4 weeks). Other recommendations included targeting at least 10 completers in this age group with sufficient number of subjects within the lowest age range and rolling over subjects from the maximum use study into the phase 3 trial and assess bone biomarkers.

- These recommendations were incorporated into Amendment 1 to Protocol INCB 18424-305 (phase 3 in AD subjects ages 2 to <12 years, submitted 10 May 2021) and Protocol INCB 18424-109 (Maximal Use study in AD subjects ages 2 to <12 years, submitted 25 June 2021).

- **21 September 2021** – Opzelura approved for the indication of topical treatment of mild-moderate atopic dermatitis in patients 12 years of age and older. The following PMRs for ages 2 to <12 were issued:

    - **PMR 4147-1** – 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 trial should enroll 250 subjects ages ≥ 2 to < 12 years with atopic dermatitis of at least 3 months duration, a baseline Investigator's Global Assessment (IGA) score of 2 to 3, and % body surface area (BSA) involvement (excluding scalp) of 3% to 20%.
        - Final Protocol Submission: Submitted 05/2021
        - Trial Completion: 08/2023
        - Final Report Submission: 02/2024
    - **PMR 4147-2** – Conduct a maximal use pharmacokinetic (PK) study in pediatric subjects with atopic dermatitis ages ≥ 2 years to < 12 and target at least 16 completers.
        - Final Protocol Submission: 06/2021
        - Study Completion: 06/2023
        - Final Report Submission: 12/2023

- **8 March 2023** – Submission of Amendment 6 to INCB 18424-305
    - Added 2 key secondary endpoints: The proportion of participants with a ≥ 4-point improvement in Itch NRS score from baseline to Day 7 (Week 1) and from baseline to Day 3. The rationale for adding these endpoints is to include an alpha-controlled assessment of early itch reduction with ruxolitinib cream.

- **1 November 2023** – Pre-sNDA meeting for atopic dermatitis in 2 to <12 years
    - The FDA stated that the complete datasets for studies INCB 18424-109 (MUsT study) and INCB 18424-305 (phase 3 study) must be submitted in the

original sNDA submission.

### 3.3.Foreign Regulatory Actions and Marketing History

Ruxolitinib (Opzelura) 1.5% cream has been approved in the following areas for the noted indications:

- European Union – Nonsegmental vitiligo (April 2023)
- Canada – AD and vitiligo (October 2024)
- France – Vitiligo (January 2024)
- Japan – Incyte has a strategic alliance with Maruho to develop, manufacture, and commercialize ruxolitinib cream for autoimmune and inflammatory dermatologic indications.

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

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

The overall quality of the clinical information contained in this submission was adequate. Studies 305 and 109 were conducted at sites in the U.S. and Canada. Because of the history of recent approvals of ruxolitinib cream, 1.5% for the indication of the topical treatment of atopic dermatitis in adults and pediatric patients 12 years and older and no deviation from the good clinical practice or concerns with any sites identified by the statistical reviewer (Kathleen Fritsch, PhD), the Division did not request that the Office of Scientific Investigations conduct clinical inspections of any sites.

### 4.2.Product Quality

A claim for categorical exclusion of the requirement to file an environmental assessment was provided in section 1.12.14. The provided categorical exclusion of the requirements of an environmental impact assessment under 21 CFR 25.31(b) is acceptable from the CMC standpoint.

There is no proposed changed to the CMC-related Sections 3, 11 or 16 of the Prescribing Information (PI) in NDA-215309-SUPPL-7 and the Prescribing Information (PI) is acceptable from the CMC standpoint. There is no proposed changed to the CMC-related sections of the Medication Guide in NDA-215309-SUPPL-7 and the Medication Guide is acceptable from the CMC standpoint.

The supplement, NDA 215309/S-007, for Opzelura (ruxolitinib) cream, 1.5%, is recommended for approval from the standpoint of Chemistry, Manufacturing and Controls (CMC) team. Refer to CMC review in Panorama dated, May 5, 2025.

(b) (4)

## 4.3.Clinical Microbiology

Not applicable.

## 4.4.Devices and Companion Diagnostic Issues

Not applicable.

# 5 Nonclinical Pharmacology/Toxicology

In this NDA efficacy supplement, the applicant proposes to extend the indication for OPZELURA cream, 1.5%, to a new patient population, pediatric patients 2 to < 12 years of age with atopic dermatitis. There are no new nonclinical data in this efficacy supplement. A juvenile rat toxicity study has been reviewed in the original NDA review. The applicant proposed minor labeling changes in Section 8.4 (the juvenile animal toxicity data subsection). This NDA efficacy supplement is approvable from a pharmacology/toxicology perspective. There is no recommended nonclinical PMC/PMR for this NDA supplement. Refer to the nonclinical review entered into DARRTS on 03/01/2025 for detailed information.

# 6 Clinical Pharmacology

## 6.1.Executive Summary

Ruxolitinib cream, 1.5% (OPZELURA) is a topical formulation of ruxolitinib phosphate that was approved in 2021 for the treatment of atopic dermatitis (AD) in subjects 12 years of age and older and in 2022, the same product was approved for the treatment of nonsegmental vitiligo in subjects 12 years of age and older. At the time of original approval for the indication of AD, three PREA post-marketing requirements (PMRs) were issued as shown below.

**4147-1:** 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 trial should enroll 250 subjects ages ≥ 2 to < 12 years with atopic dermatitis of at least 3 months duration, a baseline Investigator's Global Assessment (IGA) score of 2 to 3, and % body surface area (BSA) involvement (excluding scalp) of 3% to 20% (Study INCB 18424-305).

**4147-2:** Conduct a maximal use pharmacokinetic (PK) study in pediatric subjects with atopic dermatitis ages ≥ 2 years to < 12 and target at least 16 completers.

**4147-3:** Conduct an open-label safety study in 100 subjects ages ≥ 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.

The purpose of this supplement is to fulfill PMR 4147-1 and PMR 4147-2 and extend the indication of AD in subjects down to 2 years of age.

Ruxolitinib is an inhibitor of the JAK family of protein tyrosine kinases enzymes. Specifically, it inhibits JAK1 and JAK2 enzymes. In 2011, ruxolitinib tablets (JAKAFI) were approved for the treatment of myelofibrosis and polycythemia vera.

The safety and effectiveness ruxolitinib cream were assessed from three trials - a phase 3 pivotal study [INCB 18424-305], a phase 1 maximum-use study [INCB 18424-109], and a phase 1 pilot study [INCB 18424-102] in pediatric participants with AD to support extension of this indication in subjects down to 2 years of age.

The phase 3 trial and the maximum-use trial fulfill post-marketing requirements for evaluating ruxolitinib cream in pediatric participants 2 to < 12 years of age with AD (PMR 4147-1 and PMR 4147-2). The recommended strength of ruxolitinib cream in adult patients with AD is 1.5%, administered BID and applied to up to 20% BSA. The clinical pharmacology review evaluated pharmacokinetic (PK) data obtained from these three studies.

**Recommendation:** The Office of Clinical Pharmacology (OCP) has reviewed this sNDA submission and found it acceptable for approval from a clinical pharmacology standpoint, provided that a mutually satisfactory agreement can be reached between the Applicant and Agency regarding the labeling language. Furthermore, OCP considers that PMR 4147-1 and 4147-2 are considered as fulfilled and the Applicant be released from these two PMRs.

## 6.2.Summary of Clinical Pharmacology Assessment

### 6.2.1. Pharmacology and Clinical Pharmacokinetics

Ruxolitinib cream is a Janus kinase (JAK) inhibitor specifically inhibiting JAK1 and JAK2 enzymes. It 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.

**Clinical Pharmacokinetics in Pediatric Subjects Aged 2 years to < 12 Years with AD Under Maximal Use Conditions**

In the current submission, the Applicant evaluated PK of ruxolitinib in three clinical trials, which includes a phase 3 pivotal trial [INCB 18424-305], a Phase 1 maximum-use trial (MUsT) [INCB 18424-109], and a phase 1 pilot study [INCB 18424-102] in pediatric subjects aged 2 years to < 12 Years with AD. Application of ruxolitinib 0.75% and 1.5% cream BID resulted in a mean (STD) ruxolitinib plasma Css of 15.7 (31.0) and 29.7 (60.7) nM and 53.6 (70) and 76.5 (89.9) when applied to a mean %BSA of 11.3% (Study INCB 18424-305) and 13.6% (Study INCB 18424-102), respectively.

This mean (STD) ruxolitinib Css was increased to 98.2 (148) nM during the maximum-use trial when each participant was treated with a 1.5% already marketed cream applied to a mean %BSA of 63% (INCB 18424-109). There was an apparent correlation between ruxolitinib Css and

total affected %BSA such that participants with affected BSA > 50% showed higher plasma ruxolitinib concentrations (mean [STD] of 168 [187] nM) compared with those with affected BSA ≤ 50% (mean [STD] of 28.4 [19.8] nM).

The mean ± STD Cmax and AUC in the MUsT were 109 ± 122 nM and 1308 ± 1464 h*nM in subjects 2 to < 7 years (n=12) and 84.1 ± 183 nM and 1009 ± 2196 h*nM in subjects 7 to < 12 (n=15) years of age respectively. Based on cross-study comparison, when these observed exposures (AUC) from MUsT study were compared to the exposure observed after 5 mg oral dose at steady state, where the mean $AUC_{0-12}$ was 862 h*nM; the observed $AUC_{0-12}$ following topical administration was approximately 52% and 17% higher in 2 to < 7 years and 7 to < 12 years of age, respectively when compared to adult exposures after 5 mg oral tablet. The mean Cmax following topical administration was lower compared to oral 5 mg dose. The Cmax following topical administration was 109 nM and 84.1 nM in subjects 2 to < 7 years and 7 to < 12 years of age, respectively, while the Cmax for the 5 mg oral dose was 205 nM. It should be noted that the above comparison of systemic exposures between topical and oral administrations are based on cross-study comparison.

### 6.2.2. General Dosing and Therapeutic Individualization

**General Dosing**

In the current submission, the Applicant proposed a dose of 1.5% ruxolitinib cream to be applied as a thin layer twice daily to affected areas of up to 20% body surface area. The exposure (AUC) observed in MUsT study exceeds the exposure (AUC) observed after 5 mg oral tablet, which is approximately 50% greater in subjects 2 to >7 years and 17% great in subjects 7 to < 12 years for 1.5% cream when applied BID and Max use condition. In order to minimize the risk of systemic exposure and potentially minimize the adverse events of ruxolitinib cream, 1.5% in 2 to < 12 year old pediatric subjects, the review team is recommending that ruxolitinib cream be applied as a thin layer twice daily to affected areas of up to 20% body surface area with limitations of 30g per week (or 60g per 2 weeks) for subjects 2 to < 12 years. The review team proposed dosing is as follows:

- *For 2 to < 12 years of age: Apply OPZELURA cream, 1.5%, applying as a thin layer twice daily to up to 20% BSA. Do not use more than 60g per every 2 weeks.*

**Therapeutic Individualization**

N/A

**Outstanding Issues**

None

## 6.3.Comprehensive Clinical Pharmacology Review

### 6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Ruxolitinib is a Janus kinase (JAK) inhibitor approved for the treatment of atopic dermatitis and nonsegmental vitiligo, when applied topically. The PK of ruxolitinib cream has been previously characterized in healthy subjects, adult and pediatric subjects with AD aged 12 years and older, adult and pediatric subjects with nonsegmental vitiligo aged 12 years and older.

In the current submission, the pharmacokinetics of ruxolitinib were evaluated in adequate and well-controlled trials in pediatric subjects ages 2 to less than 12 years including 357 subjects from 2 to 11 years (Study INCB 18424-109 and INCB 18424-305) and 68 pediatric subjects ages 2 to 17 years (Study INCB 18424-102) with mild to moderate atopic dermatitis. Findings from each study is discussed in detail in below sections.

**Maximal usage trial (MUsT):** Study INCB 18424-109 was an open-label, maximum-use study that assessed the pharmacokinetics in 27 subjects 2 to 11 years of age with atopic dermatitis with a mean ± SD BSA involvement of 58.9 ± 20.6% (range 35% to 92%) following BID application of ruxolitinib 1.5% cream.

The study duration was for 28 days, and 25 subjects were able to complete up to Day 56 (the treatment-extension period of treating active lesions only). A total of 17 subjects (58.6%) in the study were aged 2 to < 7 years and 12 subjects (41.4%) were aged 7 to < 12 years. Blood plasma samples for the determination of ruxolitinib concentrations after topical applications of ruxolitinib 1.5% cream BID were collected. The range of the total affected %BSA at baseline treated during the 4-week maximum-use period ranged from 35% to 92%, with treated lesion areas of 1980 to 14,300 $cm^2$. The mean ± SD daily dose of the cream was 8.5 ± 6.3 g. The summary of baseline population characteristics and ruxolitinib steady-state plasma pharmacokinetic parameters by age group are listed in Table 2. Plasma concentrations of ruxolitinib after topical application were quantifiable in all subjects. The mean ± SD steady state plasma concentration ($C_{ss}$) and projected area under the concentration time curve from 0 to 12 hours post dose ($AUC_{0\text{-}12h}$) for ruxolitinib were 84.1 ± 183 nM and 1009.2 ± 2196 h*nM, respectively in subjects 7 years to < 12 years (n=12) and 109 ± 122 nM and 1308 ± 1464 h*nM, respectively in subjects 2 years to < 7 years of age (n=15). No apparent accumulation was observed after daily application of ruxolitinib 1.5% cream BID for 28 days in pediatric participants with AD. Participants with affected BSA > 50% showed higher plasma ruxolitinib concentrations (mean [STD] of 168 [187] nM) compared with participants with affected BSA ≤ 50% (mean [STD] of 28.4 [19.8] nM). A large variability was observed in ruxolitinib PK concentrations, and it was consistent with what was observed with the adult and adolescents PK data. Subject demographics are shown in Table 3.

**Table 2. Summary of Baseline Population Characteristics and Ruxolitinib Steady-State Plasma Pharmacokinetic Parameters by Age Group in Study INCB 18424-109**

| Age Group | N | Total BSA Affected at Baseline (%) | BSA at Baseline ($m^2$) | Lesion Area ($cm^2$) | $C_{ss,p}$ (nM) | Active Pharmaceutical Ingredient Dose (mg) |
|---|---|---|---|---|---|---|
| 35% to ≤ 50% BSA affected | | | | | | |
| 2 to < 7 years | 5 | 40.4 ± 4.10<br>39.0 (35.0, 45.0) | 0.684 ± 0.0807<br>0.683 (0.564, 0.789) | 2780 ± 556<br>2760 (1980, 3470) | 22.2 ± 12.6<br>20.7 (9.64, 42.9) | 37.7 ± 21.5<br>32.9 (21.0, 75.0) |
| 7 to < 12 years | 9 | 41.3 ± 4.86<br>40.5 (35.0, 48.0)<br>[n = 8] | 1.28 ± 0.178<br>1.26 (1.06, 1.68)<br>[n = 8] | 5320 ± 1200<br>4790 (4550, 8050)<br>[n = 8] | 32.4 ± 23.1<br>27.8 (9.24, 62.0)<br>[n = 8] | 77.7 ± 55.6<br>52.5 (21.8, 174)<br>[n = 8] |
| 2 to < 12 years | 14 | 40.9 ± 4.43<br>39.0 (35.0, 48.0)<br>[n = 13] | 1.05 ± 0.336<br>1.20 (0.564, 1.68)<br>[n = 13] | 4350 ± 1610<br>4560 (1980, 8050)<br>[n = 13] | 28.4 ± 19.8<br>20.7 (9.24, 62.0)<br>[n = 13] | 62.3 ± 48.7<br>37.5 (21.0, 174)<br>[n = 13] |
| > 50% BSA affected | | | | | | |
| 2 to < 7 years | 10 | 74.8 ± 13.8<br>79.7 (52.0, 90.0) | 0.746 ± 0.0957<br>0.724 (0.613, 0.903) | 5610 ± 1360<br>5870 (3390, 8070) | 152 ± 130<br>128 (28.1, 436) | 80.8 ± 45.2<br>76.7 (27.0, 180) |
| 7 to < 12 years | 3 | 83.8 ± 7.16<br>80.3 (79.0, 92.0) | 1.25 ± 0.485<br>1.01 (0.928, 1.81) | 10,300 ± 3530<br>9270 (7450, 14,300) | 222 ± 356<br>18.3 (14.4, 634) | 92.0 ± 109<br>39.0 (19.5, 218) |
| 2 to < 12 years | 13 | 76.9 ± 12.9<br>80.3 (52.0, 92.0) | 0.862 ± 0.307<br>0.750 (0.613, 1.81) | 6690 ± 2780<br>6160 (3390, 14,300) | 168 ± 187<br>99.4 (14.4, 634) | 83.4 ± 59.5<br>75.0 (19.5, 218) |
| Overall | | | | | | |
| 2 to < 7 years | 15 | 63.4 ± 20.2<br>67.0 (35.0, 90.0) | 0.725 ± 0.0930<br>0.714 (0.564, 0.903) | 4660 ± 1780<br>4720 (1980, 8070) | 109 ± 122<br>43.3 (9.64, 436) | 66.4 ± 43.4<br>66.0 (21.0, 180) |
| 7 to < 12 years | 12 | 52.9 ± 20.5<br>43.0 (35.0, 92.0)<br>[n = 11] | 1.27 ± 0.264<br>1.26 (0.928, 1.81)<br>[n = 11] | 6690 ± 2990<br>5490 (4550, 14,300)<br>[n = 11] | 84.1 ± 183<br>18.3 (9.24, 634)<br>[n = 11] | 81.6 ± 67.7<br>46.5 (19.5, 218)<br>[n = 11] |
| 2 to < 12 years | 27 | 58.9 ± 20.6<br>50.0 (35.0, 92.0)<br>[n = 26] | 0.957 ± 0.330<br>0.848 (0.564, 1.81)<br>[n = 26] | 5520 ± 2530<br>5050 (1980, 14,300)<br>[n = 26] | 98.2 ± 148<br>40.6 (9.24, 634)<br>[n = 26] | 72.8 ± 54.3<br>52.5 (19.5, 218)<br>[n = 26] |

N = number of participants; n = number of observations
Note: Values are presented as mean ± STD, median (min, max).
Source: DMB-23.166 Tables 16.1.1.4, 16.1.1.4.1, and 16.1.1.4.2.

**Source: Applicant, Table 9, INCB 18424-109 CSR**

**Table 3. Summary of Subject Demographics in Maximal Usage Trial (MuST)**

| Variable | Ruxolitinib 1.5% Cream BID (N = 29) |
|---|---|
| Age (years) | |
| Mean (STD) | 6.0 (3.01) |
| Median (min, max) | 5.0 (2, 11) |
| Age group, n (%) | |
| 2 to < 7 years | 17 (58.6) |
| 7 to < 12 years | 12 (41.4) |
| Sex, n (%) | |
| Male | 13 (44.8) |
| Female | 16 (55.2) |
| Race, n (%) | |
| American Indian or Alaskan Native | 1 (3.4) |
| Asian | 2 (6.9) |
| Black or African American | 11 (37.9) |
| Other | 1 (3.4) |
| White | 14 (48.3) |
| Ethnicity, n (%) | |
| Hispanic or Latino | 12 (41.4) |
| Not Hispanic or Latino | 17 (58.6) |

Source: Table 1.2.

**Source: Applicant, Table 5, INCB 18424-109 CSR**

The observed mean systemic exposure (mean AUCtau) in the 2-6 yr old age group and 7-11 yr old age group was approximately 52% and 17% higher, respectively, when compared to that of the 5 mg oral tablet in adults. The comparison of observed mean steady state exposure parameters (Css and AUCtau) for different age group in adults, adolescents, and children under maximum use conditions, when compared to adult exposures after 5 mg oral tablet is detailed in Table 4 below.

**Table 4. The PK in Adult, Adolescents, and Children after Topical Application and Oral Administration**

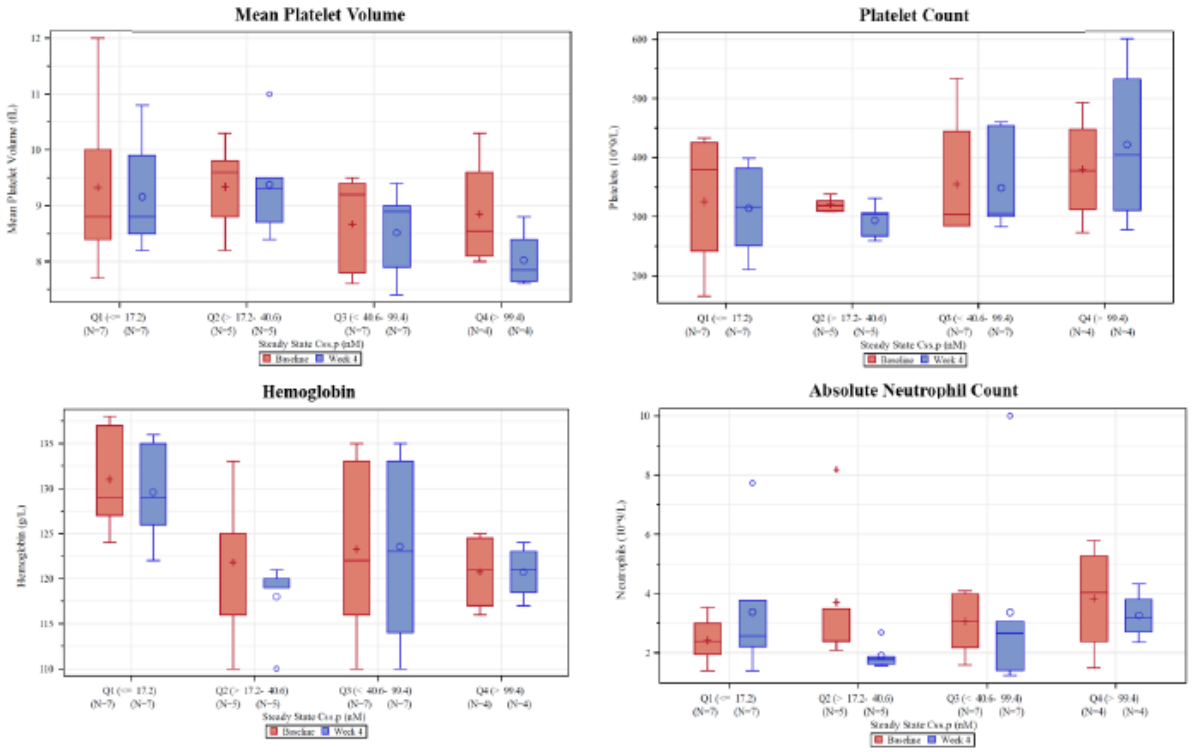
| Age (years) | Mean Css (nM) | Mean AUCtau (h*nM) | Fold change Css (topical/oral) | Fold change AUCtau (topical/oral) |
|---|---|---|---|---|
| Adult (oral) - 5 mg – SD* | 205 | 862 | Not applicable | Not applicable |
| Adult (topical MUsT study)** | 449 | 3200 | 2.19 | 3.73 |

| | | | | |
|---|---|---|---|---|
| Adolescents (13 < 17 years) - MUsT study ** | 110 | 801 | 0.54 | 0.93 |
| Children (2 < 7 years) - MUsT study*** | 109 | 1308 | 0.53 | 1.52 |
| Children (7 < 12 years) - MUsT study *** | 84.1 | 1009 | 0.41 | 1.17 |

**Source: Clinical Pharmacology Reviewer**
***Jakafi Label, ** Table 5 MUsT Study INCB 18424-103, *** MUsT Study INCB 18424-109**

Summary of safety: The changes in hemoglobin, neutrophil count, platelet count, and mean platelet volume values for all the Css quartiles during the maximum-use period were also measured and reported to be minor. Results for concentration–hematology parameter analyses are shown in Figure 1. There was no apparent concentration-dependent pattern (either increase or decrease) in hemoglobin, neutrophil count, mean platelet volume, or platelet count values during the maximum-use period. For additional information on safety, see Section 8.2.

**Figure 1. Plasma Ruxolitinib Concentration–Hematology Laboratory Test Relationship During the Maximum-Use Period**




Source: DMB-23.166 Figures 6.2.1.1, 6.2.2.1, 6.2.3.1, and 6.2.4.1.

**Source: Applicant, Figure 3, INCB 18424-109 CSR**

**Phase 3 trial:** Study INCB 18424-305 was a phase 3, randomized, double-blind, vehicle controlled (VC) trial that included a long-term safety (LTS) period for pediatric subjects aged 2 to < 12 years with AD. A total of 330 subjects were randomized 2:2:1 to blinded treatment with either ruxolitinib 0.75% cream BID, ruxolitinib 1.5% cream BID, or vehicle cream BID, with stratification by baseline IGA score (2 [mild] or 3 [moderate]) and age (2 to <7 and 7 to <12) for a total treatment duration of 8 weeks for VC period. Inclusion criteria for subjects included the following: AD involvement of 3-20% BSA, IGA-AD score of 2 or 3, AD present for at least 3 months, and for ages 6-11 years old, a baseline itch NRS score ≥4.

The majority of participants (87.3%) completed treatment through Week 8. Male and female subjects were equally distributed (female were 54.2%), and the study population was largely composed of White (54.5%) and Black or African American (32.1%) participants. Subjects had a mean %BSA affected by AD at baseline of 10.45% (range: 3.0%-20.0%). The study product was applied in a thin layer to cover all affected areas twice daily. The mean daily dose of the cream was approximately 4 g (4.35 g for 0.75% BID and 3.87 g for 1.5% BID applications groups respectively) and hence, the weekly dose of the cream would be approximately 30 g for each dose strength. Summary of drug usage in the VC period is shown in Table 5 below.

**Table 5. Summary of Study Drug Exposure During Vehicle-Controlled Period**

| Variable | Vehicle Cream BID (N = 65) | Ruxolitinib 0.75% Cream BID (N = 134) | Ruxolitinib 1.5% Cream BID (N = 130) | Total (N = 329) |
|---|---|---|---|---|
| Duration of treatment (days) | | | | |
| n | 65 | 134 | 130 | 329 |
| Mean (STD) | 47.1 (18.60) | 54.0 (12.00) | 54.1 (11.81) | 52.7 (13.72) |
| Median | 56.0 | 56.0 | 56.0 | 56.0 |
| Min, max | 1, 72 | 1, 70 | 1, 79 | 1, 79 |
| Total amount of cream applied (g) | | | | |
| n | 65 | 134 | 130 | 329 |
| Mean (STD) | 124.69 (78.002) | 140.50 (116.115) | 138.17 (102.745) | 136.45 (104.122) |
| Median | 112.90 | 109.20 | 108.95 | 110.86 |
| Min, max | 10.7, 414.8 | 6.3, 859.1 | 9.2, 485.9 | 6.3, 859.1 |
| Average daily amount of cream applied (g) | | | | |
| n | 65 | 134 | 130 | 329 |
| Mean (STD) | 3.91 (8.794) | 4.35 (13.893) | 3.87 (12.651) | 4.08 (12.504) |
| Median | 2.63 | 2.06 | 2.00 | 2.16 |
| Min, max | 0.5, 72.3 | 0.2, 144.5 | 0.3, 144.2 | 0.2, 144.5 |

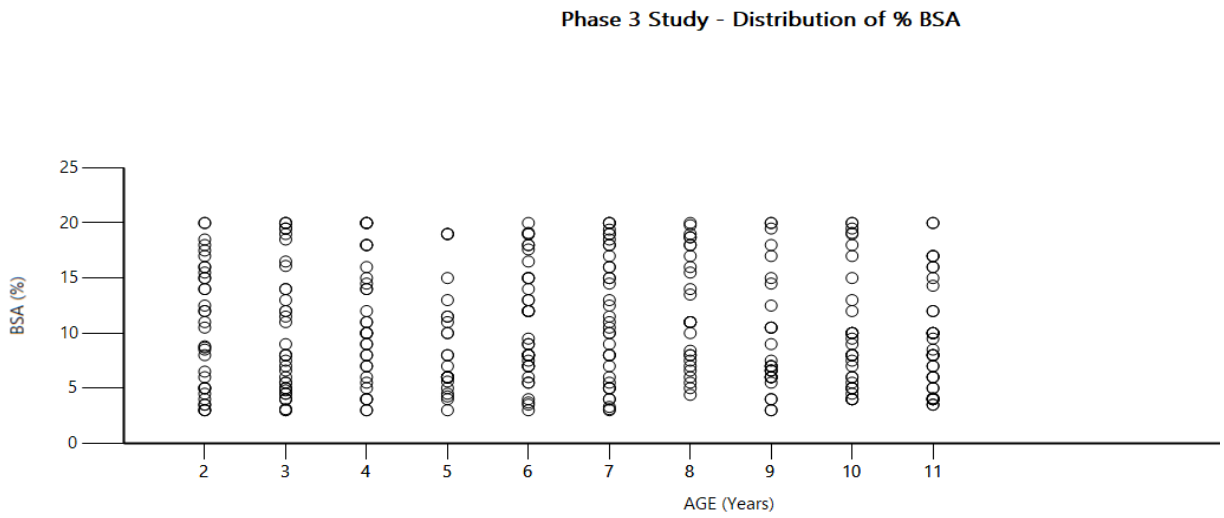
Note 1: Duration of treatment is defined as the duration from first cream application to last application.
Note 2: Average daily amount of cream applied = total amount of cream applied / (duration of treatment – interrupted days).
Note 3: If a tube was not returned, then it was assumed in the analysis that the whole tube was used.
Source: Table 3.1.1.1.

**Source: Applicant, Table 9, INCB 18424-305 CSR**

The primary efficacy endpoint was the proportion of subjects who have achieved an IGA of 0 (clear) or 1 (almost clear) with at least a 2-grade reduction from baseline at Week 8. Approximately 50% of the overall study population consisted of subjects aged 2 to ≤ 7 years of age and males and female participants are equally distributed among each age group in both 0.75% and 1.5% treatment groups.

Distribution of baseline %BSA: The mean ± SD %BSA involvement was 10.6 % ± 5.60% (range: 3%-20%) treated with ruxolitinib 1.5% cream BID, was similar among each treatment groups (9.97 in 0.75% vs 11.18 in 1.5%). The %BSA is equally distributed among each group, where out of total 330 subjects, 78 (26%) had % affected BSA between 15 and 20%, whereas 65 (20%) subjects had % affected BSA between 10 and 15%, whereas rest participants (n=187) had %BSA between 3 and 10 (Figure 2). This data supports the application of ruxolitinib cream up to 20% BSA in pediatric subjects 2 to < 12 years of age for each dose strength.

**Figure 2. Distribution of % BSA in Phase 3 Trial Across Age**

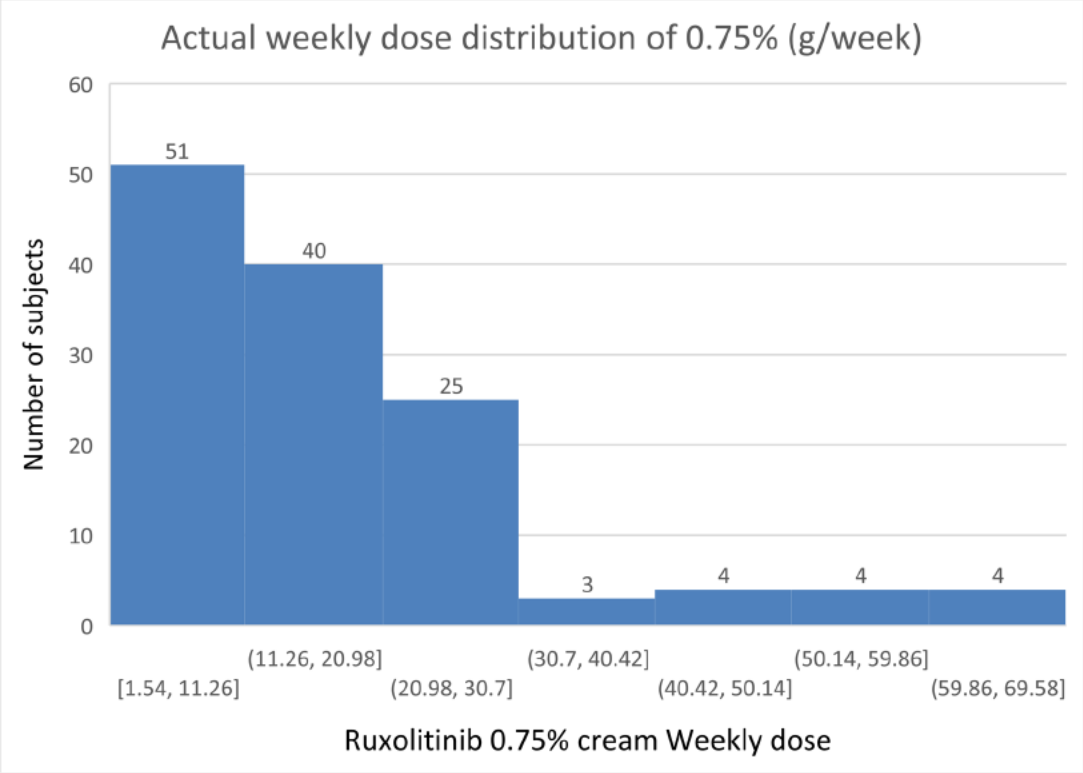



**Source: Clinical Pharmacology Reviewer, using baseline % BSA value, INCB 18424-305.**

Extent of Exposure: Cumulative exposure through Week 52 for participants in the ruxolitinib 0.75% and 1.5% cream BID treatment groups were similar among ruxolitinib 0.75% or 1.5% cream BID throughout the study, with a median duration of treatment of 341.0 and 346.5 days, respectively. The median of actual average amount of ruxolitinib 0.75% or 1.5% cream for each subject applied daily over the 52 weeks was 2.02 and 1.86 g, respectively. The weekly dose distribution for both ruxolitinib 0.75% or 1.5% cream (Figure 3), shows that approximately 90 percentiles of subjects in each treatment group receive up to 30 grams per week of ruxolitinib 0.75% or 1.5% cream respectively. This data supports the maximum weekly dose recommendation of 30 grams for both ruxolitinib 0.75% or 1.5% treatment groups.

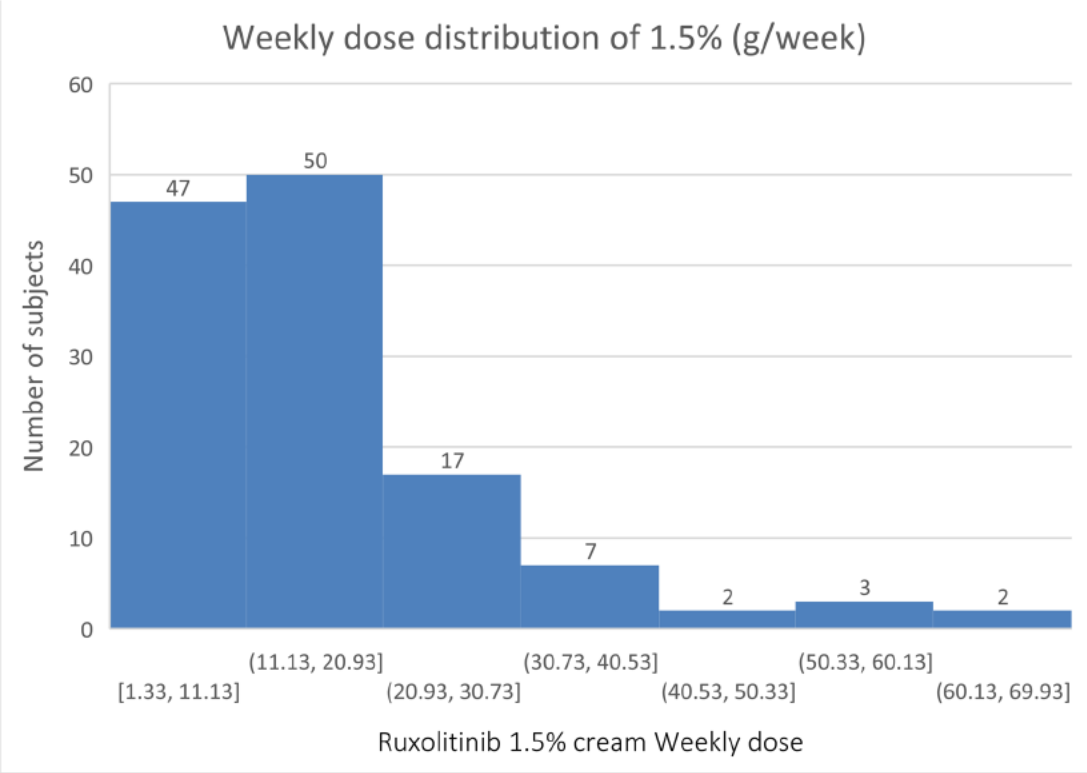
**Figure 3. Weekly dose distribution of 0.75% (g/week) (A), and 1.5% (g/week) (B)**

A: 0.75% Cream BID




**Source: Clinical Pharmacology Reviewer, where weekly exposure is calculated based on the daily exposure as presented by participant for the VC period, for the LTS period, and from baseline through Week 52 in Listings 2.5.1, 2.5.2, and 2.5.3, respectively of Study INCB 18424-305.**

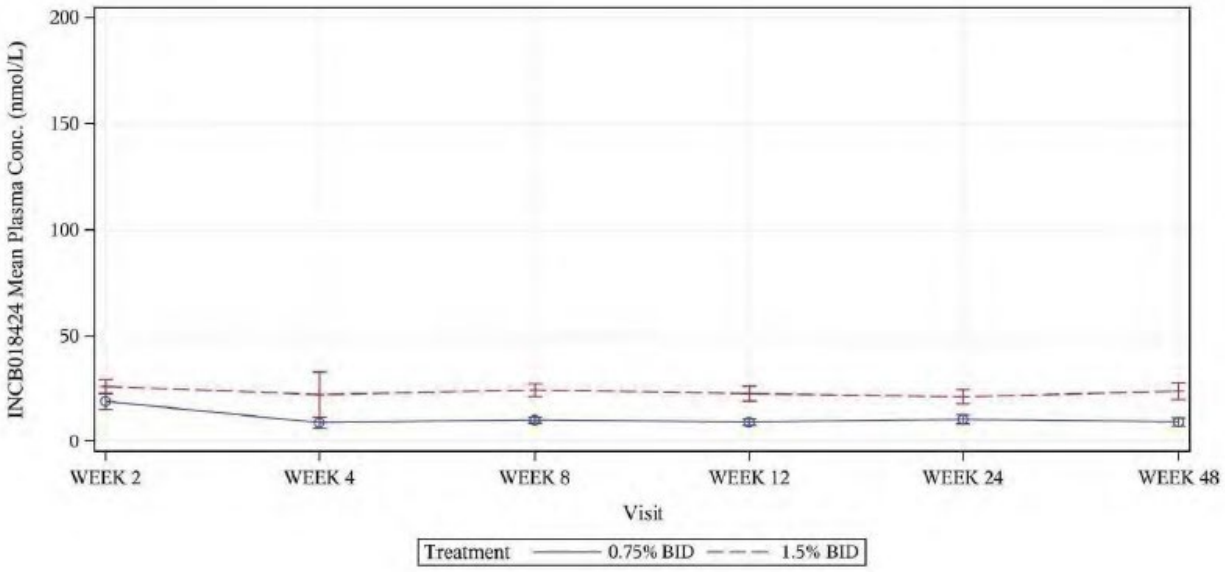
B: 1.5 % Cream BID




**Source: Clinical Pharmacology Reviewer, where weekly exposure is calculated based on the daily exposure as presented by participant for the VC period, for the LTS period, and from baseline through Week 52 in Listings 2.5.1, 2.5.2, and 2.5.3, respectively of Study INCB 18424-305.**

PK plasma samples were collected before drug application (trough) at either Week 2 or Week 4 (not both) and at Week 8, Week 12, Week 24, and Week 48. Plasma ruxolitinib concentrations were low and variable (> 100% GCV), which was attributed to, at least in part, a broad range of %BSA treated (range: 3%-20%). There was no apparent accumulation in ruxolitinib concentrations between Weeks 2 and 8 during the VC period when constant affected %BSA was treated; however, there was a dose-dependent increase in plasma ruxolitinib concentrations. Application of ruxolitinib 0.75% cream BID and 1.5% cream BID resulted in a mean (STD) plasma ruxolitinib Css of 15.7 (31.0) nM and 29.7 (60.7) nM respectively. Figure 4 shows the plot of pre-dose plasma concentrations following 0.75% BID and 1.5% BID applications which shows that the mean systemic exposure following 1.5% strength is higher than 0.75% strength. Figure 5 shows the box plots of pre-dose plasma ruxolitinib concentrations by age groups which indicates that the systemic exposure was higher in the lowest age range of 2 to 4 years compared to subjects 10 to 11 years.

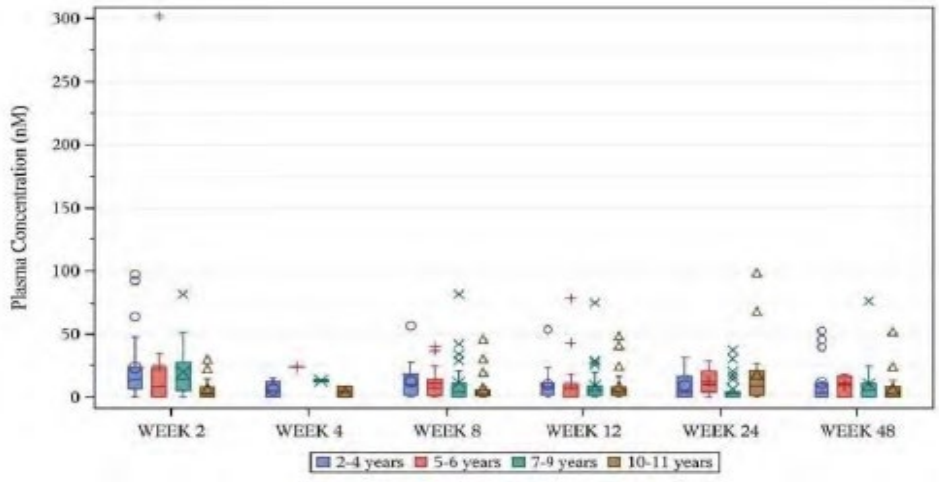
**Figure 4. Plot of Trough Level Plasma Concentrations for Phase 3 Trial**




**Source: Applicant, Table 5, INCB 18424-305 CSR**

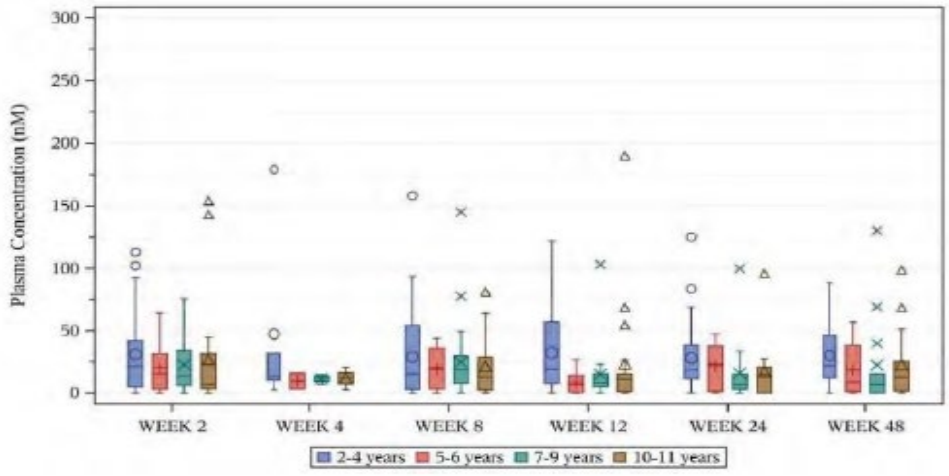
**Figure 5. Box Plots of Plasma Ruxolitinib Concentrations by Age Group**

A: 0.75% Cream BID




**Source: Applicant, Figure 6 A, INCB 18424-305 CSR**

B: 1.5% Cream BID




**Source: Applicant, Figure 6 B, INCB 18424-305 CSR**

Efficacy and safety results: Both 0.75% and 1.5% cream showed efficacy. Based on drug usage data, the review team has recommend to apply OPZELURA cream, 1.5% twice daily to affected areas of up to 20% body surface area for pediatric patients with limitations of 30g per week (or 60g per 2 weeks) for subjects 2 to < 12 years. See Section 8 for details.

**Pilot study:** Study INCB 18424-102 was an open-label, descending-age, and increasing-strength study to evaluate the safety, tolerability, and PK of ruxolitinib cream applied BID for 4 weeks in pediatric subjects aged 2 to < 18 years with AD (8%-20% BSA and an IGA score of at least 2).

A total of 71 subjects were treated in 1 of 6 cohorts, defined by age and ruxolitinib cream strength: Cohort 1 (12 to < 18 years, ruxolitinib 0.5% cream BID), Cohort 2 (12 to < 18 years, ruxolitinib 1.5% cream BID), Cohort 3 (7 to < 12 years, ruxolitinib 0.75% cream BID), Cohort 4 (7 to < 12 years, ruxolitinib 1.5% cream BID), Cohort 5 (2 to < 7 years, ruxolitinib 0.75% cream BID), and Cohort 6 (2 to < 7 years, ruxolitinib 1.5% cream BID).

Sixty-four participants (90.1%) completed treatment, and 62 participants (87.3%) completed the study. Sparse plasma sampling for assessment of ruxolitinib concentrations were obtained at scheduled visits and/or timepoints throughout the study. The plasma Css of ruxolitinib increased in a less-than-proportional manner as the formulation strength increased based on comparisons within each of the age groups of 12 to < 18 years, 7 to < 12 years, and 2 to < 7 years. Furthermore, ruxolitinib Css increased sub proportionally with respect to the ruxolitinib cream API dose across all age groups, consistent with historical data in adolescents and adults with AD. There appeared to be minimal to no accumulation in plasma ruxolitinib concentrations at 2 hours post application by Week 2/Day 10 in Cohorts 1, 2, and 3, while Cohorts 4 to 6 did not have sufficient data to assess the accumulation due to a protocol amendment to remove PK sampling at 2 hours post application on Week 2/Day 10 to shorten the required visit time for younger participants.

Summary of observed PK for each subgroup from Study INCB 18424-102 are listed below in Table 7. A high level of interindividual variability observed in the ruxolitinib Css which is not unusual for topically administered dermatological products.

The overall incidences of TEAEs were highest among ≥ 12- to 17-year-olds (50.0% and 45.5% for Cohorts 1 and 2, respectively) and did not vary according to ruxolitinib cream strength. See Section 8.2 for additional information on safety.

**Table 6. Summary of observed PK Ruxolitinib (nM) by Visit and/or Timepoint**

| Cohort | N | %BSA Treated (%) | Day 1 | Week 2 or Day 10 | | | Week 4 |
|---|---|---|---|---|---|---|---|
| | | | 2 Hours | Preapplication | 2 Hours | Combined | Anytime[a] |
| Cohort 1<br>≥ 12 to 17 years<br>0.5% BID | 9 | 12.8 ± 4.26<br>(10.6) | 28.1 ± 36.3<br>(12.9, 319%) | 30.1 ± 39.6<br>(14.4, 212%) | 27.5 ± 36.8<br>(13.3, 203%) | 28.8 ± 37.1<br>(13.8, 195%)<br>[n = 18] | 11.7 ± 12.5<br>(8.17, 99.8%) |
| Cohort 2<br>≥ 12 to 17 years<br>1.5% BID | 11 | 14.1 ± 4.25<br>(11.7) | 76.8 ± 82.3<br>(41.6, 220%) | 40.9 ± 44.0<br>(29.6, 91.8%) | 45.7 ± 45.9<br>(33.2, 93.8%) | 43.3 ± 44.0<br>(31.3, 90.2%)<br>[n = 22] | 44.6 ± 66.4<br>(24.2, 153%)<br>[n = 10] |
| Cohort 3<br>≥ 7 to < 12 years<br>0.75% BID | 10 | 14.8 ± 3.78<br>(15.9) | 87.6 ± 125<br>(49.0, 142%)<br>[n = 9] | 82.2 ± 127<br>(38.8, 190%)<br>[n = 9] | 66.7 ± 86.4<br>(41.2, 128%)<br>[n = 9] | 74.4 ± 105<br>(40.0, 150%)<br>[n = 18] | 32.6 ± 36.5<br>(18.1, 264%) |
| Cohort 4<br>≥ 7 to < 12 years<br>1.5% BID | 13 | 11.5 ± 4.38<br>(11.1) | 34.5 ± 61.6<br>(8.39, 760%)<br>[n = 12] | 124 ± 126<br>(67.4, 188%)<br>[n = 11] | 95.7 ± 136<br>(47.5, 206%)<br>[n = 4] | 117 ± 125<br>(61.4, 182%)<br>[n = 15] | 60.1 ± 87.1<br>(24.2, 297%)<br>[n = 10] |
| Cohort 5<br>≥ 2 to < 7 years<br>0.75% BID | 12 | 11.4 ± 4.61<br>(10.4) | 77.7 ± 103<br>(25.2, 597%) | 36.7 ± 29.8<br>(16.9, 546%)<br>[n = 11] | — | 36.7 ± 29.8<br>(16.9, 546%)<br>[n = 11] | 64.3 ± 112<br>(11.8, 1170%)<br>[n = 11] |
| Cohort 6<br>≥ 2 to < 7 years<br>1.5% BID | 13 | 14.1 ± 4.14<br>(13.5) | 50.5 ± 112<br>(8.80, 793%) | 56.7 ± 75.2<br>(30.6, 183%) | 26.9 ± 24.4<br>(20.7, 103%)<br>[n = 3] | 51.1 ± 68.9<br>(28.5, 163%)<br>[n = 16] | 37.3 ± 33.1<br>(16.0, 581%)<br>[n = 11] |

N = number of participants; n = number of observations.
Note: Summary values are mean ± SD (median) for %BSA treated and mean ± SD (geometric mean, GCV%) for concentrations.
[a] On account of the protocol amendment history and the fact of steady-state plasma ruxolitinib lacking an apparent excursion at 2 hours postapplication, all PK samples collected at Week 4 were regarded as "anytime PK" and summarized by cohorts. Refer to DMB-20.140, Section 3.2 for additional details.
Source: DMB-20.140 Table 3.

**Source: Applicant, Table 11, INCB 18424-102 CSR**

### 6.3.2. Clinical Pharmacology Questions

**Is the proposed dosing regimen of 1.5% BID appropriate in pediatric participants 2 to < 12 years of age?**

The Applicant proposed dose includes the application of a thin layer of ruxolitinib 1.5% cream twice daily to affected areas of up to 20% body surface area and it is recommended not to use more than 60 grams per (b) (4). The observed mean systemic exposure (mean AUCtau) in the 2-6 year old group and 7-11 year old group was approximately 52% and 17% higher respectively, when compared to that of the 5 mg tablet (label). Due to known AEs of the JAK inhibitor class of drugs, the review team recommends using 1.5% ruxolitinib cream to be applied as a thin layer

twice daily to affected areas maximum up to 20% body surface area with limitations of maximum 30g per week (or 60g per 2 weeks).

Clinical pharmacology study included MUsT which is a study to support systemic safety and may not support efficacy as the drug is administered directly at the target site (skin). See Section 8 for further information on efficacy.

**What is the systemic exposure of ruxolitinib in subjects 2 to 12 years of age with AD?**

Mean plasma ruxolitinib Css in participants aged 2 to < 7 years (n = 15) and aged 7 to < 12 years (n = 12) is 109 nM and 84.1 nM respectively after ruxolitinib 1.5% applied BID under maximum use conditions.

In the phase 3 trial, the mean plasma ruxolitinib Css in participants aged 2 to < 7 years (n = 59) and aged 7 to < 12 years (n = 63) after ruxolitinib 0.75 % cream applied BID in less than 20% BSA is 19.4 nM and 11.8 nM respectively. The mean plasma ruxolitinib Css in participants aged 2 to < 7 years (n = 56) and aged 7 to < 12 years (n = 56) after ruxolitinib 1.5 % cream applied BID in less than 20% BSA is 36 nM and 22.7 nM respectively.

**How does the systemic exposure in subjects 2 to 12 years old compare with older subjects?**

The systemic exposure (Cmax and AUC) after topical application under MUsT conditions in adults is approximately 2 to 4-fold higher compared to that observed in pediatric subjects 2 to < 17 years of age. When compared to the exposures after 5 mg oral tablet, the observed mean systemic exposure (mean AUCtau) in the 2 to < 7 and 7 to < 12 years group was approximately 52% and 17% higher after topical application of 1.5% cream under maximum use conditions respectively. The comparison of observed mean steady state exposure parameters (Css and AUCtau) for different age group in adults, adolescents, and children in maximum use conditions, when compared to adult exposures after 5 mg oral tablet is detailed in Table 4 above.

**Is there an effect of dose, age and % BSA on the systemic exposure?**

Age, [redacted], race, and body size (BSA) were not significant predictors of PK variability following the topical application of ruxolitinib cream in participants aged 2 to < 12 years with AD with up to 20% BSA). Participants with affected BSA ≥ 50% showed 6-fold higher steady state plasma ruxolitinib concentrations (mean of 168 nM) when compared to those with affected BSA < 50% (mean of 28.4 nM). In the phase 3 trial, the systemic exposure within the lowest age range (2- to 4-year-old) appears to be higher compared to subjects 10 to 11 years old for 1.5% BID treatment group, which is not the same for 0.75% BID treatment group.

Sources of Clinical Data and Review Strategy

# 7 Sources of Clinical Data and Review Strategy

## 7.1.Table of Clinical Studies

The primary evaluation of the efficacy of ruxolitinib cream supporting the extension of ruxolitinib cream in pediatric participants 2 to < 12 years of age with AD is based on data from the phase 3, randomized, vehicle-controlled Study INCB 18424-305 in pediatric participants aged 2 to < 12 years with AD eligible for topical therapy.

Efficacy was also evaluated as exploratory endpoints in Studies INCB 18424-109 and INCB 18424-102. Study INCB 18424-109 was a phase 1 study to determine the safety and tolerability, systemic exposure, and efficacy of ruxolitinib 1.5% cream under maximum-use conditions in children ages 2 to < 12 years with AD. Study INCB 18424-102 was a phase 1, pilot PK study to determine the safety, tolerability, and plasma PK profile of ruxolitinib cream in participants aged 2 to < 18 years with AD. A tabular summary of the clinical studies that evaluated the efficacy of ruxolitinib cream in pediatric participants with AD eligible for topical therapy to support Supplement 007 for NDA 215309 is presented in Table 7. The summary of acceptance criteria and validation parameters of the bioanalytical method for the determination of ruxolitinib concentrations in human plasma are listed in section 19.4

**Table 7. Listing of Clinical Trials Relevant to Assessment of Efficacy and Safety of Ruxolitinib Cream, 1.5%**

| Study Identifier Number of Study Centers Locations | First Participant Treated Study Status, Date Total Enrollment/Goal | Study Objective(s) | Study Design and Type of Control | Test Product(s), Treatment Regimen(s), and Route of Administration | Number of Participants by Arm Entered/Completed | Diagnosis of Participants | Duration of Treatment |
|---|---|---|---|---|---|---|---|
| INCB 18424-305<br>50<br>Canada, US | 19 JUL 2021<br>Completed,<br>08 APR 2024 (LPLV)<br>330/315 | Efficacy, safety, tolerability, and PK | Phase 3, randomized, double-blind, VC study | VC period:<br>Vehicle cream BID; topical<br>Ruxolitinib 0.75% cream BID, ruxolitinib 1.5% cream BID; topical<br>LTS period:<br>Ruxolitinib 0.75% cream BID, ruxolitinib 1.5% cream BID; topical | VC period:<br>• Vehicle BID: 65/49<br>• 0.75% BID: 134/122<br>• 1.5% BID: 131/117<br>LTS period:<br>• Vehicle BID to 0.75% BID: 25/19<br>• Vehicle BID to 1.5% BID: 24/18<br>• 0.75% BID: 119/78<br>• 1.5% BID: 114/83 | Pediatric participants (2 to < 12 years of age) with AD, 3% to 20% BSA involvement (excluding the scalp), and an IGA score of 2 or 3 | VC period: 8 weeks<br>LTS period: 44 weeks; participants treated AD flares during the LTS period |
| INCB 18424-109<br>12<br>US | 16 DEC 2021<br>Completed,<br>07 AUG 2023 (LPLV)<br>29/24 | Safety, tolerability, PK, and efficacy | Phase 1, open-label, maximum-use study | Ruxolitinib 1.5% cream BID; topical | Maximum-use period: 29/28<br>Treatment-extension period: 26/25<br>LTS period: 22/14 | Pediatric participants (2 to < 12 years of age) with extensive AD, ≥ 35% BSA involvement (excluding the scalp), and an IGA score ≥ 3 | Maximum-use period: 4 weeks<br>Treatment-extension period: 4 weeks<br>LTS period: 44 weeks<br>Participants treated AD flares during the treatment-extension and LTS periods |
| INCB 18424-102<br>17<br>US | 21 SEP 2017<br>Completed,<br>07 OCT 2020 (LPLV)<br>71/60 | Safety, tolerability, PK, and efficacy | Phase 1, open-label, descending age, increasing treatment strength study | Ruxolitinib 0.5% cream BID, ruxolitinib 0.75% cream BID, ruxolitinib 1.5% cream BID; topical | • Cohort 1 (0.5% BID, 12 to < 18 years): 10/9[a]<br>• Cohort 2 (1.5% BID, 12 to < 18 years): 11/9[a]<br>• Cohort 3 (0.75% BID, 7 to < 12 years): 10/10<br>• Cohort 4 (1.5% BID, 7 to < 12 years): 14/12<br>• Cohort 5 (0.75% BID, 2 to < 7 years): 12/9<br>• Cohort 6 (1.5% BID, 2 to < 7 years): 14/13 | Pediatric participants (2 to < 18 years of age) with AD, 8% to 20% BSA involvement, and an IGA score ≥ 2 | 4 weeks |

[a] Only data from participants 2 to < 12 years of age (Cohorts 3 to 6) are summarized in this SCS.

**Source: Applicant, Summary of Clinical Safety.**

## 7.2.Review Strategy

**Data Sources**

The data sources used for the evaluation of the efficacy and safety of ruxolitinib cream, 1.5%, included the Applicant's clinical study reports, datasets, clinical summaries, and proposed labeling. The submission was submitted in electronic common technical document format and was entirely electronic. Both Study Data Tabulation Model datasets and Analysis Data Model datasets were submitted. The analysis datasets used in this review are archived at:

Study INCB 18424-102: \\CDSESUB1\EVSPROD\nda215309\0086\m5\datasets\incb18424-102\analysis\adam\datasets\

Study INCB 18424-109: \\CDSESUB1\EVSPROD\nda215309\0086\m5\datasets\incb18424-109\analysis\adam\datasets\

Study INCB 18424-305: \\CDSESUB1\EVSPROD\nda215309\0086\m5\datasets\incb18424-305\analysis\adam\datasets\

**Data and Analysis Quality**

The statistical and clinical teams evaluated the efficacy and safety data. In general, the data submitted by the Applicant to support the safety and efficacy of ruxolitinib cream for the proposed indication appear to be adequate.

# 8 Statistical and Clinical and Evaluation

## 8.1.Review of Relevant Individual Trials Used to Support Efficacy

### 8.1.1. Study INCB 18424-305

**Study Design**

Study INCB 18424-305 (Study 305) is a randomized, double-blind, vehicle-controlled phase 3 trial in pediatric subjects 2 to <12 years of age with mild to moderate atopic dermatitis. The studies enrolled subjects who have been diagnosed with atopic dermatitis for at least 3 months and with 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. Participants aged 6 years to < 12 years were to have a baseline itch NRS score ≥ 4 (averaged across at least 4 of the 7 days immediately prior to the Day 1/baseline visit). Enrollment was to be capped such that no more than approximately 25% of randomized participants have a baseline IGA score of 2. At least 40% of the overall study population was to consist of children aged ≥ 2 years to 6

years. The study was designed to enroll approximately 315 subjects randomized 2:2:1 to ruxolitinib 1.5% cream, ruxolitinib 0.75% cream, or vehicle cream. Randomization was stratified by baseline IGA (2 vs. 3) and age (2-6 vs. 7-11 years). 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.

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 1:1 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. Participants whose AD lesions recurred and who were previously in an observation/no treatment cycle will restart treatment at home at the first sign of recurrence and record the date of the new treatment cycle.

**Study Endpoints**
Efficacy was assessed using the IGA scale (Table 10) and an Itch Numerical Rating Scale (NRS). Additional efficacy scales included Eczema Area and Severity Index Score (EASI), BSA, Skin Pain NRS, Patient-Oriented Eczema Measure (POEM), Children's Dermatology Life Quality Index/Infants' Dermatitis Quality of Life Index (CDLQI/IDQoL), Patient-Reported Outcomes Measurement Information System (PROMIS) Short Form – Sleep-Related Impairment (8a), EQ-5D-Y, and the Dermatitis Family Impact (DFI) questionnaire.

**Table 8. 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 24 of Statistical Analysis Plan for Study INCB 18424-305.**

The Itch NRS was assessed daily by subjects 6 years of age and older. The scale assessed the worst level of itching in the past 24 hours from 0 (no itch) to 10 (worst imaginable itch). During the double-blind period the recall period is 24 hours.

The primary efficacy endpoint was the proportion of subjects with IGA-TS at Week 8, defined as an IGA score of 0 or 1 with at least 2 grades reduction from baseline.

The key secondary endpoints (multiplicity-controlled) were

- Proportion of subjects with ≥ 4-point improvement in Itch NRS from baseline to Week 8
- Proportion of subjects with ≥ 4-point improvement in Itch NRS from baseline to Day 7
- Proportion of subjects with ≥ 4-point improvement in Itch NRS from baseline to Day 3

For the Itch NRS endpoint at Week 8, the baseline and Week 8 values were calculated 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. For the endpoints at Days 3 and 7, all assessments were based on the assessment from a single day (for baseline this was the last available score during the week prior to Day 1).

**Statistical Analysis Plan**

Analysis Populations

The primary analysis population was the ITT population, defined as all randomized subjects. For the Itch NRS endpoints, the primary analysis population was the ITT population in participants with baseline Itch NRS score ≥4. Only subjects 6 years of age and older completed the Itch NRS.

Primary Endpoint

The primary endpoint was analyzed with logistic regression with terms for treatment group and stratification factors (baseline IGA and age group), 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 from the logistic model and difference in response rates, based on the large sample normal approximation with continuity correction. All participants missing the Week 8 assessment and who discontinue study treatment at any time before Week 8, or discontinue from the study for any reason, were classified as non-responders in the analysis.

A longitudinal logistic regression analysis with repeated measures will be conducted as a supportive analysis. The binary response (IGA-TS) of each participant at Weeks 2, 4, and 8 will be included as the dependent variable. Treatment (1.5% BID, 0.75% BID, and vehicle BID), randomization stratification factors (baseline IGA score and age), visit, and treatment-by-visit interaction will be included as fixed effects. Site level intercept and participant nested in site level intercept will be included as random effects. The within-participant and within-site errors will be modeled by an unstructured variance-covariance matrix. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom for this model.

Multiple imputation with missing-at-random assumption will be used as an alternative method to handle missing data. A full conditional specification method that assumes the existence of a joint distribution for all variables will be used to impute the IGA score. A regression model including treatment group, stratification factor age group, and baseline and scheduled post-baseline IGA scores up to Week 8 will be specified for the fully conditional specification method. The imputation will be repeated 40 times to generate corresponding complete datasets in order to reflect the uncertainty around the true values. A Last Observation Carried Forward analysis will also be conducted as an alternative analysis.

A tipping point sensitivity analysis will be conducted to examine the potential effects of missing data. The missing binary IGA-TS response in each treatment group at Week 8 will be replaced by a range of values from the most conservative case to the most aggressive case. The most conservative case is that all the missing participants in active treatment groups are non-responders and all the missing participants in the vehicle group are responders, while the most aggressive case is the other way around. For each scenario, between-treatment comparisons will be performed using a chi-square test. If there are N missing responses in the 1.5% BID arm and M missing responses in the vehicle arm, the following process will be used to determine the tipping point and a similar process will be implemented for the 0.75% BID arm versus the vehicle arm:

- Missing responses in the 1.5% BID arm will be imputed with a range of values from 0 to N.
- Missing responses in the vehicle arm will be imputed with a range of values from 0 to M.
- Treatment comparisons between the 1.5% BID arm and the vehicle arm will be analyzed in each of the (N + 1) × (M + 1) imputed datasets using a chi-square test, which will result in a (N + 1) × (M + 1) table; columns will represent the number of responses imputed for the 1.5% BID arm and rows will represent the number of responses imputed for the vehicle arm. A separate table will be generated to compare the 0.75% BID arm with the vehicle arm following the same process.

Secondary Endpoints

The Itch NRS score for baseline will be determined by averaging the 7 daily NRS scores directly before Day 1 (Day –7 to Day –1) for all the by-visit summaries. The by-visit Itch NRS score for postbaseline visits will be determined by averaging the 7 daily NRS scores directly before the visit day. If 4 or more daily scores are missing (out of the 7), the Itch NRS score at the visit will be set to missing. The Itch NRS response endpoints will be analyzed using the same methods as the primary endpoint.

Type I Error Control

A graphical procedure with gatekeeping testing strategy was used to control the Type I error rate for the primary and key secondary analyses.

In Step 1, 2 families of 4 elementary hypotheses tests at Week 8 are grouped according to

treatment comparison between each ruxolitinib cream group and the vehicle cream group, where

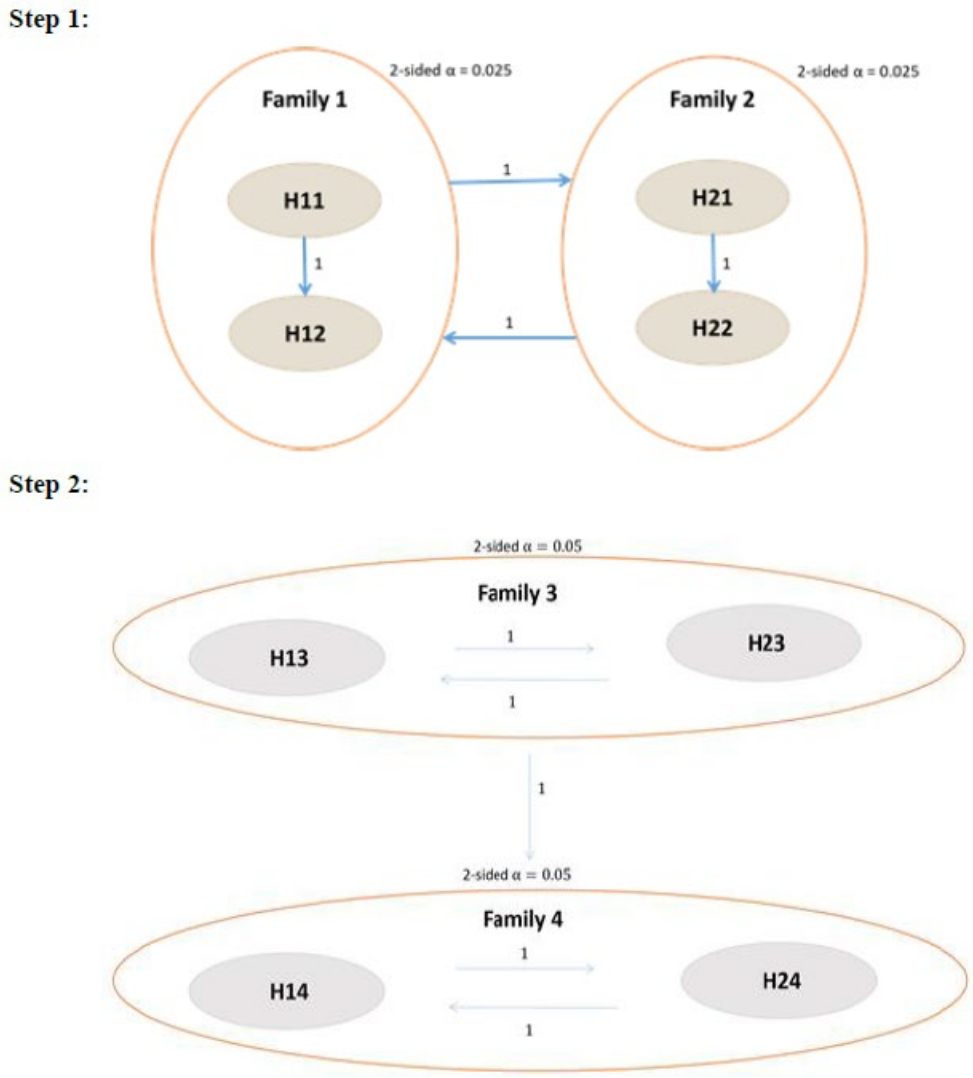
- Family 1 (1.5% BID vs vehicle):
  - H11: proportion of participants who achieve IGA-TS
  - H12: proportion of participants with a ≥ 4-grade improvement in Itch NRS score over baseline
- Family 2 (0.75% BID vs vehicle):
  - H21: proportion of participants who achieve IGA-TS
  - H22: proportion of participants with a ≥ 4-grade improvement in Itch NRS score over baseline

Step 2 has 2 families of 4 hypotheses tests:

- Family 3 (1.5% BID vs vehicle and 0.75% BID vs vehicle on Day 7 Itch NRS):
  - H13: proportion of participants with a ≥ 4-grade improvement in Itch NRS score over baseline to Day 7 (Week 1) between 1.5% BID and vehicle
  - H23: proportion of participants with a ≥ 4-grade improvement in Itch NRS score over baseline to Day 7 (Week 1) between 0.75% BID and vehicle
- Family 4 (1.5% BID vs vehicle and 0.75% BID vs vehicle on Day 3 Itch NRS):
  - H14: proportion of participants with a ≥ 4-grade improvement in Itch NRS score over baseline to Day 3 between 1.5% BID and vehicle
  - H24: proportion of participants with a ≥ 4-grade improvement in Itch NRS score over baseline to Day 3 between 0.75% BID and vehicle

In Step 1, within Family 1 and 2, the endpoints are tested in a fixed sequence at a 2-sided $\alpha$ = 0.025 level. The key secondary endpoint will be tested only if the associated primary endpoint is rejected. For any treatment strength, if the 2 related null hypotheses can be rejected, then the fixed sequence for the other treatment strength can be conducted at the 2-sided $\alpha$ = 0.05 level. If all null hypotheses in Family 1 and 2 are rejected, in Step 2, the endpoints in Family 3 (H13 and H23) will be tested using Bonferroni-Hochberg's procedure with overall 2-sided $\alpha$ = 0.05 level. If both hypotheses in Family 3 are rejected, the endpoints in Family 4 (H14 and H24) will be tested similarly using Bonferroni-Hochberg's procedure with overall 2-sided $\alpha$ = 0.05 level. See Figure 6.

**Figure 6. Type I Error Control**




**Source: Pg 15 of Statistical Analysis Plan for Study INCB 18424-305 .**

## Protocol Amendments

The final protocol was Amendment 6. Subjects were enrolled under Amendments 2-6. Each amendment included clarifications regarding study procedures. The more significant changes included the following:

- Amendment 2: The key change was to modify exclusion criteria related to certain laboratory tests and make them less restrictive.
- Amendment 4: The endpoint of EASI 75 at Week 8 was moved from a secondary endpoint to an exploratory endpoint.
- Amendment 5: The planned sample size was increased from 250 to 315 subjects. The sample size was increased because the study was under-enrolling the planned number of subjects 6 years of age and older with non-missing baseline Itch NRS scores. The

sample size was increased in attempt to ensure adequate enrollment for the analysis of the Itch NRS secondary endpoint.

- Amendment 6: Two key secondary endpoints were added: 4-point improvement in Itch NRS score from baseline to Day 7 and from baseline to Day 3.

### 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 ICH guidelines on drug development. All studies were closely monitored by the study sponsor's personnel or a contract organization for compliance to the Protocol and the procedures described in it." (p. 7 of Clinical Overview - Atopic Dermatitis (2 to < 12 Years)).

**Financial Disclosure**

See Section 19.2.

**Patient Disposition**

The study randomized 330 subjects to ruxolitinib cream 0.75%, ruxolitinib cream 1.5%, and vehicle. One subject randomized to ruxolitinib cream 1.5% did not receive any treatment and was excluded from the safety population. More subjects on the vehicle arm (25%) discontinued treatment during the 8-week vehicle-controlled period than on the two ruxolitinib arms (9% and 11% in the 0.75% and 1.5% cohorts, respectively). The most common reasons for treatment discontinuation from the ruxolitinib arms was loss to follow-up and withdrawal by subject. The most common reasons for treatment discontinuation from the vehicle arm were lack of efficacy, withdrawal by subject, and other protocol-specified criteria. Study discontinuation rates were similar to the treatment discontinuation rates. See Table 9.

**Table 9. Disposition during Vehicle-Controlled Period**

| | Ruxolitinib 0.75% Cream (N=134) | Ruxolitinib 1.5% Cream (N=131) | Vehicle Cream (N=65) | Total (N=330) |
|---|---|---|---|---|
| Randomized (ITT) | 134 | 131 | 65 | 330 |
| Treated (Safety) | 134 (100) | 130 (99) | 65 (100) | 329 (>99) |
| Discontinued treatment during vehicle-controlled period | 12 (9) | 14 (11) | 16 (25) | 42 (13) |
| Adverse event | 1 (1) | 1 (1) | 0 (0) | 2 (1) |
| Lack of efficacy | 0 (0) | 0 (0) | 3 (5) | 3 (1) |
| Lost to follow-up | 5 (4) | 5 (4) | 2 (3) | 12 (4) |
| Physician decision | 1 (1) | 1 (1) | 0 (0) | 2 (1) |
| Protocol violation | 0 (0) | 1 (1) | 0 (0) | 1 (<1) |

| | Ruxolitinib 0.75% Cream (N=134) | Ruxolitinib 1.5% Cream (N=131) | Vehicle Cream (N=65) | Total (N=330) |
|---|---|---|---|---|
| Prot.-specified WD criterion met | 1 (1) | 0 (0) | 3 (5) | 4 (1) |
| Withdrawal by subject | 4 (3) | 6 (5) | 8 (12) | 18 (5) |
| Discontinued study during vehicle-controlled period | 14 (1) | 16 (12) | 16 (25) | 46 (14) |
| Adverse event | 1 (1) | 1 (1) | 0 (0) | 2 (1) |
| Lack of efficacy | 0 (0) | 0 (0) | 2 (3) | 2 (1) |
| Lost to follow-up | 5 (4) | 5 (4) | 2 (3) | 12 (4) |
| Physician decision | 1 (1) | 1 (1) | 0 (0) | 2 (1) |
| Protocol violation | 0 (0) | 1 (1) | 0 (0) | 1 (1) |
| Prot.-specified WD criterion met | 2 (1) | 0 (0) | 3 (5) | 5 (2) |
| Withdrawal by subject | 5 (4) | 8 (6) | 9 (14) | 22 (7) |

**ITT=intent to treat, WD = withdrawal**
**Source: Pg 187-188 of clinical study report and reviewer analysis (adsl.xpt).**

Subjects who completed Week 8 assessments with no additional safety concerns were to continue into the 44-week long-term safety period. All subjects were treated intermittently with ruxolitinib 0.75% or 1.5% based on IGA response. The long-term safety period included 282 (85%) of the originally randomized subjects. During this period, approximately 30% of subjects discontinued before the end of the period. The most common reasons for treatment discontinuation during this period were loss to follow-up and withdrawal by subject. Study discontinuation rates were similar to the treatment discontinuation rates. See Table 10. Disposition during Long Term Safety Period.

**Table 10. Disposition during Long Term Safety Period**

| | Ruxolitinib 0.75% Cream (N=119) | Ruxolitinib 1.5% Cream (N=114) | Vehicle to Ruxolitinib 0.75% Cream (N=25) | Vehicle to Ruxolitinib 1.5% Cream (N=24) | Total (N=282) |
|---|---|---|---|---|---|
| Treated in LTS period | 119 | 114 | 25 | 24 | 282 |
| Discontinue treatment during LTS period | 41 (34) | 31 (27) | 6 (24) | 6 (25) | 84 (30) |
| Adverse event | 0 (0) | 2 (2) | 0 (0) | 0 (0) | 2 (1) |
| Lack of efficacy | 3 (3) | 2 (2) | 1 (4) | 0 (0) | 6 (2) |
| Lost to follow-up | 16 (13) | 8 (7) | 1 (4) | 6 (25) | 31 (11) |
| Non-compliance with study drug | 0 (0) | 1 (1) | 1 (4) | 0 (0) | 2 (1) |
| Other | 1 (1) | 0 (0) | 0 (0) | 0 (0) | 1 (<1) |
| Physician decision | 1 (1) | 1 (1) | 1 (4) | 0 (0) | 3 (1) |
| Prot.-specified WD criterion met | 1 (1) | 2 (2) | 1 (4) | 0 (0) | 4 (1) |
| Withdrawal by subject | 19 (16) | 15 (13) | 1 (4) | 0 (0) | 35 (12) |
| Discontinue study during LTS period | 48 (40) | 37 (32) | 7 (28) | 9 (38) | 101 (36) |
| Adverse event | 0 (0) | 1 (1) | 0 (0) | 0 (0) | 1 (<1) |

| | Ruxolitinib 0.75% Cream (N=119) | Ruxolitinib 1.5% Cream (N=114) | Vehicle to Ruxolitinib 0.75% Cream (N=25) | Vehicle to Ruxolitinib 1.5% Cream (N=24) | Total (N=282) |
|---|---|---|---|---|---|
| Lack of efficacy | 3 (3) | 2 (2) | 1 (4) | 0 (0) | 6 (2) |
| Lost to follow-up | 18 (15) | 9 (8) | 1 (4) | 6 (25) | 34 (12) |
| Non-compliance with study drug | 0 (0) | 1 (1) | 1 (4) | 0 (0) | 2 (1) |
| Other | 3 (3) | 3 (3) | 0 (0) | 0 (0) | 6 (2) |
| Physician decision | 1 (1) | 1 (1) | 1 (4) | 0 (0) | 3 (1) |
| Prot.-specified WD criterion met | 1 (1) | 2 (2) | 1 (4) | 0 (0) | 4 (1) |
| Withdrawal by subject | 22 (18) | 18 (16) | 2 (8) | 3 (13) | 45 (16) |

**LTS=long term safety, WD=withdrawal**
**Source: Pg 189-190 of clinical study report and reviewer analysis (adsl.xpt).**

### Protocol Violations/Deviations

Approximately 56% of subjects experienced major protocol violations during the vehicle-controlled period. The most common violations were related to subjects or investigators not recording efficacy assessments per the protocol. See Table 11. This included assessments not completed at the appropriate visit or non-compliance with daily diary collection. However, one source of efficacy assessment violations included 5 investigators (enrolling 40 subjects) who did not use the protocol-defined IGA scale to evaluate subjects at baseline. All scales used in the trial included the following 5 categories: 0=clear, 1=almost clear, 2=mild, and 3=moderate, 4=severe; however, two of the sites used a scale with 6 categories. The descriptions of these categories varied slightly across the versions used but were similar. The study enrolled subjects with mild (2) to moderate (3) disease at baseline.

**Table 11. Major Protocol Violations during Vehicle-Controlled Period**

| | Ruxolitinib 0.75% Cream (N=134) | Ruxolitinib 1.5% Cream (N=131) | Vehicle Cream (N=65) | Total (N=330) |
|---|---|---|---|---|
| **Major Violations** | 78 (58) | 76 (58) | 31 (48) | 185 (56) |
| Assessment - efficacy | 40 (30) | 32 (24) | 16 (25) | 88 (27) |
| Assessment - safety | 11 (8) | 10 (8) | 6 (9) | 27 (8) |
| Exclusion | 3 (2) | 2 (2) | 1 (2) | 6 (2) |
| Inclusion | 3 (2) | 1 (1) | 1 (2) | 5 (2) |
| Informed consent | 9 (7) | 13 (10) | 3 (5) | 25 (8) |
| Lab/endpoint data | 5 (4) | 5 (4) | 2 (3) | 12 (4) |
| Other | 1 (1) | 0 (0) | 1 (2) | 2 (1) |
| Overdose/misuse | 3 (2) | 9 (7) | 0 (0) | 12 (4) |
| Prohibited co-medication | 4 (3) | 6 (5) | 5 (8) | 15 (5) |
| Study drug | 14 (10) | 16 (12) | 1 (2) | 31 (9) |
| Visit window | 8 (6) | 12 (9) | 7 (11) | 27 (8) |

**Source: Pg 46 of clinical study report and reviewer analysis (addv.xpt).**

**Table of Demographic Characteristics**

The study enrolled subjects aged 2 to 11 years, with approximately half of the subjects aged 2 to 6 years, and half aged 7 to 11 years. Fifty-four percent of the subjects were female, and 55% were White, 32% were Black or African American, 6% were Asian, 7% were other races. Thirty percent of subjects were Hispanic or Latino. See Table 12.

**Table 12. Baseline Demographics**

| | Ruxolitinib 0.75% Cream (N=134) | Ruxolitinib 1.5% Cream (N=131) | Vehicle Cream (N=65) | Total (N=330) |
|---|---|---|---|---|
| **Age** | | | | |
| N | 134 | 131 | 65 | 330 |
| Mean (SD) | 6.6 (2.8) | 6.4 (2.9) | 6.3 (3.1) | 6.5 (2.9) |
| Median | 6.0 | 6.0 | 6.0 | 6.0 |
| Range | 2.0, 11.0 | 2.0, 11.0 | 2.0, 11.0 | 2.0, 11.0 |
| **Age Group**, n (%) | | | | |
| 2 to 6 years | 68 (51) | 66 (50) | 33 (51) | 167 (51) |
| 7 to < 12 years | 66 (49) | 65 (50) | 32 (49) | 163 (49) |
| **Sex**, n (%) | | | | |
| F | 73 (54) | 68 (52) | 38 (58) | 179 (54) |
| M | 61 (46) | 63 (48) | 27 (42) | 151 (46) |
| **Race**, n (%) | | | | |
| American Indian Or Alaska Native | 0 (0) | 1 (1) | 0 (0) | 1 (0) |
| Asian | 7 (5) | 11 (8) | 3 (5) | 21 (6) |
| Black Or African American | 45 (34) | 42 (32) | 19 (29) | 106 (32) |
| Native Hawaiian Or Other Pacific Islander | 1 (1) | 0 (0) | 1 (2) | 2 (1) |
| Not Reported | 1 (1) | 1 (1) | 0 (0) | 2 (1) |
| Other | 5 (4) | 8 (6) | 5 (8) | 18 (5) |
| White | 75 (56) | 68 (52) | 37 (57) | 180 (55) |
| **Ethnicity**, n (%) | | | | |
| Hispanic Or Latino | 32 (24) | 42 (32) | 26 (40) | 100 (30) |
| Not Hispanic Or Latino | 99 (74) | 89 (68) | 39 (60) | 227 (69) |
| Not Reported/Other | 3 (2) | 0 (0) | 0 (0) | 3 (1) |
| **Country**, n (%) | | | | |
| Canada | 5 (4) | 9 (7) | 0 (0) | 14 (4) |
| USA | 129 (96) | 122 (93) | 65 (100) | 316 (96) |

**Source: Pg 41 of clinical study report and reviewer analysis (adsl.xpt).**

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

The study enrolled subjects with mild to moderate atopic dermatitis. Approximately 24% of subjects were classified as mild at baseline and 76% as moderate. Itch daily diary assessments were collected in subjects 6 years of age and older. Approximately 97% of subjects had Itch NRS scores of at least 4 at baseline. See Table 13.

**Table 13. Baseline Disease Characteristics**

| | Ruxolitinib 0.75% Cream (N=134) | Ruxolitinib 1.5% Cream (N=131) | Vehicle Cream (N=65) | Total (N=330) |
|---|---|---|---|---|
| **Baseline IGA, n (%)** | | | | |
| 2 = MILD | 31 (23) | 31 (24) | 16 (25) | 78 (24) |
| 3 = MODERATE | 103 (77) | 100 (76) | 49 (75) | 252 (76) |
| **Baseline EASI Score** | | | | |
| N | 134 | 131 | 65 | 330 |
| Mean (SD) | 8.4 (6.1) | 8.9 (4.6) | 8.6 (5.5) | 8.6 (5.4) |
| Median | 6.6 | 8.6 | 7.8 | 7.7 |
| Range | 1.3, 39.6 | 1.6, 22.8 | 1.7, 35.2 | 1.3, 39.6 |
| **Total BSA involvement** | | | | |
| N | 134 | 131 | 65 | 330 |
| Mean (SD) | 10.0 (5.1) | 11.2 (5.6) | 10.0 (5.5) | 10.5 (5.4) |
| Median | 8.9 | 10.0 | 8.8 | 9.3 |
| Range | 3.0, 20.0 | 3.0, 20.0 | 3.0, 20.0 | 3.0, 20.0 |
| **Baseline Itch NRS in subjects 6 to < 12 years, n (%)** | **(N=85)** | **(N=77)** | **(N=38)** | **(n=200)** |
| Itch NRS <4 | 3 (4) | 0 (0) | 1 (3) | 4 (2) |
| Itch NRS ≥4 | 80 (94) | 76 (99) | 37 (97) | 193 (97) |
| Missing | 2 (2) | 1 (1) | 0 (0) | 3 (2) |

**Source: Pg 44 of clinical study report and reviewer analysis (adsl.xpt).**

**Efficacy Results – Primary Endpoint**

The primary endpoint (IGA-TS at Week 8) was analyzed with exact logistic regression with terms for treatment group and stratification factors (baseline IGA and age group). The analysis included confidence intervals for the difference in response rates, based on the large sample normal approximation with continuity correction. In addition, for labeling purposes the applicant calculated Mantel-Haenszel common risk difference confidence intervals in order to be consistent with the adult and adolescent trials. To control for multiplicity, the primary endpoint was tested at two-sided α=0.025. Both ruxolitinib 0.75% and 1.5% were superior to vehicle for the primary endpoint. See Table 14.

**Table 14. Primary Endpoint - IGA-TS at Week 8 (ITT)**

| | Ruxolitinib 0.75% Cream (N=134) | Ruxolitinib 1.5% Cream (N=131) | Vehicle Cream (N=65) |
|---|---|---|---|
| IGA-TS, n (%) | 49 (36.6) | 74 (56.5) | 7 (10.8) |
| Difference (95% CI)[a] | 25.8 (14.7, 36.9) | 45.7 (34.4, 57.1) | - |
| Difference (95% CI)[b] | 25.7 (14.6, 36.8) | 45.7 (34.7, 56.8) | |

| | Ruxolitinib 0.75% Cream (N=134) | Ruxolitinib 1.5% Cream (N=131) | Vehicle Cream (N=65) |
|---|---|---|---|
| P-value[c] | 0.0001 | <0.0001 | - |

**IGA-TS = Investigator's Global Assessment-Treatment Success, ITT = Intent to Treat, CI = Confidence Interval**
**[a] Normal Approximation**
**[b] Mantel-Haenszel Common Risk Difference**
**[c] Exact Logistic Regression**
**Source: Pg 73 and 322 of clinical study report and reviewer analysis (adeff.xpt).**

The IGA-TS results at Week 8 were consistent across age groups (2 to 6 years and 7 to 11 years). See Table 15.

**Table 15. IGA-TS at Week 8 by Age Group (ITT)**

| | Ruxolitinib 0.75% Cream (N=68) | Ruxolitinib 1.5% Cream (N=66) | Vehicle Cream (N=33) |
|---|---|---|---|
| **Aged 2 to 6 years**, n (%) | 24 (35.3) | 40 (60.6) | 5 (15.2) |
| Difference (95% CI)[a] | 20.1 (3.4, 36.8) | 45.5 (28.5, 62.4) | - |
| Difference (95% CI)[b] | 20.2 (3.6, 36.8) | 45.5 (29.0, 61.9) | - |
| P-value[c] | 0.0541 | <0.0001 | |
| | **Ruxolitinib 0.75% Cream (N=66)** | **Ruxolitinib 1.5% Cream (N=65)** | **Vehicle Cream (N=32)** |
| **Aged 7 to 11 years**, n (%) | 25 (37.9) | 34 (52.3) | 2 (6.3) |
| Difference (95% CI)[a] | 31.6 (17.2, 46.0) | 46.1 (31.3, 60.8) | - |
| Difference (95% CI)[b] | 31.3 (16.9, 45.7) | 46.0 (31.2, 60.9) | - |
| P-value[c] | 0.001 | <0.0001 | |

**IGA-TS = Investigator's Global Assessment-Treatment Success, ITT = Intent to Treat, CI = Confidence Interval**
**[a] Normal Approximation**
**[b] Mantel-Haenszel Common Risk Difference**
**[c] Exact Logistic Regression**
**Source: Pg. 364 of clinical study report and reviewer analysis (adeff.xpt).**

Sensitivity Analyses

As sensitivity analyses, missing data was also handled using multiple imputation and Last Observation Carried Forward. The treatment effects were similar under both sensitivity analyses. See Table 16. The applicant also conducted a tipping point analysis. The proportion of subjects with missing data was higher on the vehicle arm (25%) than the ruxolitinib arms (approximately 10%). For ruxolitinib 1.5%, all combinations of missing data response imputations led to statistically significant findings, including the scenario in which all vehicle subjects with missing data were imputed as responders and all ruxolitinib 1.5% subjects with missing data were imputed as non-responders. For ruxolitinib 0.75%, the analysis tipped into non-significance under certain scenarios. Example scenarios included when 50% (8/16) of vehicle subjects and 0% (0/12) of ruxolitinib 0.75% subjects with missing data were imputed as responders or when 63% (10/16) of vehicle subjects and 33% (4/12) of ruxolitinib 0.75%

subjects with missing data were imputed as responders. (See pg 323-324 of clinical study report.) As these scenarios are unrealistic as it is unlikely that the vehicle subjects who discontinued would have such high response rates, the Week 8 IGA-TS results are robust to the handling of missing data.

**Table 16. Sensitivity Analyses for IGA-TS at Week 8 (ITT)**

| | Ruxolitinib 0.75% Cream (N=134) | Ruxolitinib 1.5% Cream (N=131) | Vehicle Cream (N=65) |
|---|---|---|---|
| Multiple Imputation, % | 39.9 | 63.8 | 14.5 |
| Difference (95% CI)[a] | 25.4 (11.3, 39.5) | 49.3 (35.6, 63.0) | |
| P-value[b] | 0.0014 | <0.0001 | |
| LOCF, % | 39.1 | 62.2 | 12.5 |
| Difference (95% CI)[a] | 26.6 (14.5, 38.7) | 49.7 (37.6, 61.8) | |
| P-value[b] | 0.0004 | <0.0001 | |

**IGA-TS = Investigator's Global Assessment-Treatment Success, LOCF = Last Observation Carried Forward**
**[a] Normal Approximation**
**[b] Exact Logistic Regression**
**Source: Pg 74 of clinical study report and reviewer analysis (adeff.xpt).**

One key protocol violation involved 5 investigators (enrolling 40 subjects) who did not use the protocol-defined IGA scale to evaluate subjects at baseline. If the analysis is conducted using only the sites that used the correct IGA scale at baseline, the results are similar to the results using all subjects, and the corresponding p-values would still be statistically significant. Thus, the IGA scale protocol violation does not impact the conclusions and it is reasonable to present results for the full ITT population. See Table 17.

**Table 17. IGA-TS at Week 8 Excluding Sites with IGA Scale Protocol Violations**

| IGA-TS, n (%) | Ruxolitinib 0.75% Cream (N=134) | Ruxolitinib 1.5% Cream (N=131) | Vehicle Cream (N=65) |
|---|---|---|---|
| All Sites (ITT) | 49 (36.6) | 74 (56.5) | 7 (10.8) |
| Difference (95% CI)[b] | 25.8 (14.7, 36.9) | 45.7 (34.4, 57.1) | - |
| P-value[c] | 0.0001 | <0.0001 | - |
| | **(N=12)** | **(N=17)** | **(N=11)** |
| Non-Protocol IGA Sites[a] | 6 (50.0) | 11 (64.7) | 1 (9.1) |
| Difference (95% CI)[b] | 40.9 (7.9, 73.9) | 55.6 (27.3, 84.0) | - |
| P-value[c] | 0.1028 | 0.0163 | - |
| | **(N=122)** | **(N=114)** | **(N=54)** |
| Protocol IGA Sites | 43 (35.3) | 63 (55.3) | 6 (11.1) |
| Difference (95% CI)[b] | 24.1 (12.2, 36.1) | 44.2 (31.8, 56.5) | - |
| P-value[c] | 0.0011 | <0.0001 | - |

**IGA-TS = Investigator's Global Assessment-Treatment Success, CI = Confidence Interval**
**[a] Sites 102, 103, 111, 120, 155**
**[b] Normal Approximation**

**[c] Exact Logistic Regression**
**Source: Reviewer analysis (adeff.xpt).**

Subgroup Results

Treatment effects were generally consistent across age, sex, race, and ethnicity subgroups. The studies enrolled few subjects in the American Indian/Alaskan native and Native Hawaiian/Pacific Islander groups. See Table 18.

**Table 18. IGA-TS at Week 8 by Demographic Subgroups (ITT)**

| n (%) | Ruxolitinib 0.75% Cream (N=134) | Ruxolitinib 1.5% Cream (N=131) | Vehicle Cream (N=65) |
|---|---|---|---|
| **Age Group** | | | |
| 2 to 6 years (n=68, 66, 33) | 24 (35.3) | 40 (60.6) | 5 (15.2) |
| 7 to < 12 years (n=66, 65, 32) | 25 (37.9) | 34 (52.3) | 2 (6.3) |
| **Sex** | | | |
| F (n=73, 68, 38) | 27 (37.0) | 33 (48.5) | 4 (10.5) |
| M (n=61, 63, 27) | 22 (36.1) | 41 (65.1) | 3 (11.1) |
| **Race** | | | |
| Asian (n=7, 11, 3) | 2 (28.6) | 7 (63.6) | 1 (33.3) |
| Black Or African American (n=45, 42, 19) | 14 (31.1) | 23 (54.8) | 1 (5.3) |
| White (n=75, 68, 37) | 30 (40.0) | 39 (57.4) | 5 (13.5) |
| Other[a] | 3 (42.9) | 5 (50.0) | 0 (0) |
| **Ethnicity** | | | |
| Hispanic Or Latino (n=32, 42, 26) | 13 (40.6) | 21 (50.0) | 3 (11.5) |
| Not Hispanic Or Latino (n=99, 89, 39) | 36 (36.4) | 53 (59.6) | 4 (10.3) |

**IGA-TS = Investigator's Global Assessment-Treatment Success**
**[a] Includes American Indian or Alaska Native (n=0, 1, 0), Native Hawaiian or Other Pacific Islander (n=1, 0, 1), Not Reported (1, 1, 0), and Other (5, 8, 5)**
**Source: Pg 105 of clinical study report and reviewer analysis (adeff.xpt).**

### Data Quality and Integrity

No issues with data quality and integrity were identified during the review, other than the previously identified protocol violations. Clinical study site inspections were not requested for this supplement.

### Efficacy Results – Secondary and other relevant endpoints

The key secondary endpoint was Itch NRS response at Week 8. Itch NRS response was defined as at least a 4-point improvement from baseline and was evaluated in subjects 6 years of age and older with baseline Itch NRS score ≥ 4. Neither ruxolitinib 1.5% nor 0.75% was superior to vehicle for this endpoint. Thus, efficacy could not be established for this endpoint. Statistical testing terminated and no other secondary endpoints could be formally tested. See Table 19.

**Table 19. Itch NRS Response at Week 8 (ITT Subjects Age ≥ 6 Years and Baseline Itch NRS Score ≥ 4)**

| | Ruxolitinib 0.75% Cream (N=80) | Ruxolitinib 1.5% Cream (N=76) | Vehicle Cream (N=37) |
|---|---|---|---|
| Itch NRS response, n (%) | 30 (37.5) | 33 (43.4) | 11 (29.7) |
| Difference (95% CI)[a] | 7.8 (-10.4, 25.9) | 13.7 (-4.8, 32.2) | - |
| P-value[b] | 0.4198 | 0.1685 | - |

**NRS = Numeric Rating Score, CI = Confidence Interval**
**[a] Normal Approximation**
**[b] Logistic Regression**
**Source: Pg 75 of clinical study report and reviewer analysis (adqs.xpt).**

The trials conducted in adult and adolescent subjects with mild to moderate atopic dermatitis (INCB 18424-303 and INCB 18424-304) had Itch NRS response rates of approximately 41% for ruxolitinib 0.75%, 51% for ruxolitinib 1.5%, and 16% for vehicle. In subjects ages 6 to 11 years in Study INCB 1824-305, the response rates for the ruxolitinib arms were slightly lower, but the response rate for the vehicle arm was higher. Because the Itch NRS is a patient-reported outcome, it may be challenging for younger subjects to accurately record Itch NRS scores. The applicant did not submit data to support whether the tool was fit for purpose in this age group. The Itch NRS response results by age are presented in Table 20. Although the response rates are variable across these small samples, the response rates on the vehicle arm are consistently high across the younger subjects.

**Table 20. Itch NRS Response at Week 8 by Age (ITT in Subjects Age ≥ 6 Years and Baseline Itch NRS Score ≥ 4)**

| n (%) | Ruxolitinib 0.75% Cream (N=80) | Ruxolitinib 1.5% Cream (N=76) | Vehicle Cream (N=37) |
|---|---|---|---|
| **Age group (years)** | | | |
| 6 - 7 (n=26, 29, 14) | 7 (26.9) | 12 (41.4) | 7 (50.0) |
| 8 – 9 (n=27, 20, 7) | 13 (48.1) | 10 (50.0) | 3 (42.9) |
| 10 – 11 (n=27, 27, 16) | 10 (37.0) | 11 (40.7) | 1 (6.3) |

**NRS = Numeric Rating Score, ITT = Intent to Treat**
**Source: Reviewer analysis (adqs.xpt).**

The additional endpoints that the applicant included in the testing hierarchy were Itch NRS response at Day 7 and Itch NRS at Day 3. Because the prior tests in the hierarchy were not statistically significant, neither endpoint could be formally tested. However, similarly to the results at Week 8, the Itch NRS endpoints at Day 7 and Day 3 also did not achieve nominal significance for either dose relative to vehicle.

## 8.2.Review of Safety

### 8.2.1. Safety Review Approach

The primary review of safety for ruxolitinib cream, 1.5% and 0.75%, for the topical treatment of mild to moderate atopic dermatitis in patients 2 to <12 years of age focuses on data from a single phase 3 study, INCB 18424-305 (Study 305). Study 305 was a randomized, multicenter, double-blind, vehicle-controlled (VC), 8-week study in pediatric subjects ages 2 to <12 years old with mild to moderate AD. The Applicant also submitted long-term safety data for subjects who continued treatment for AD flares during the open-label, long-term safety (LTS) period for an additional 44 weeks (52 weeks total).

The phase 3 VC study population in Study 305 consisted of 330 subjects 2 to <12 years of age with mild to moderate AD for at least 3 months, defined as an IGA score of 2 (mild) to 3 (moderate) and BSA involvement (excluding scalp) of 3-20%. For subjects ages 6 to <12 years, the baseline itch Numerical Rating Scale (NRS) was ≥4. Subjects were randomized in a 2:2:1 ratio to treatment with ruxolitinib 1.5% cream (131 subjects), ruxolitinib 0.75% cream (134 subjects), or vehicle cream (65 subjects). One subject randomized to ruxolitinib 1.5% cream was not treated because of refusal for further blood draws.

The study population in the LTS period of Study 305 consisted of 282 subjects who were rolled over from Study 305 (49 vehicle, 119 ruxolitinib 0.75% cream, and 114 ruxolitinib 1.5% cream). In the LTS, subjects originally in the study drug treatment arms during the VC part of Study 305 continued to apply the same strength cream, while the 49 subjects who had been on vehicle during the VC portion of Study 305 were randomized 1:1 to either treatment with ruxolitinib 0.75% cream or ruxolitinib 1.5% cream. Of the 282 subjects who participated in the LTS, 144 subjects were assigned to apply ruxolitinib 0.75% cream and 138 subjects applied ruxolitinib 1.5% cream.

The Applicant also submitted the results from INCB 18424-109 (Study 109), a phase 2, maximal usage trial (MUsT), as supportive safety information. There were 3 periods to Study 109: a 4-week MUsT period, a 4-week treatment extension period, and a 44-week LTS period (52 weeks total). Twenty-nine pediatric subjects ages 2 to 12 with moderate-to-severe atopic dermatitis, defined as IGA ≥3 and ≥35% of the BSA (excluding the scalp), were enrolled into the 4-week MUsT phase. Of the 29 subjects, 17 (58.6%) of the subjects were ages 2 to <7 and 12 (41.4%) were ages 7 to <12. Twenty-six subjects continued into the treatment extension phase, and 22 continued into the LTS phase. All subjects were treated with ruxolitinib cream, 1.5%.

In both Study 305 and Study 109, subjects applied the study drug in a thin film twice daily (in the morning and in the evening ≥ 1 hour before bedtime, with applications ≥ 8 hours apart), to all areas identified for treatment at baseline even if they began to improve, throughout the first 4 weeks (maximum-use phase) of Study 109 and throughout the first 8 weeks (VC phase) of Study 305. If there were new areas to be treated, including expansion of existing areas or development of new areas, after consultation with the investigator, study cream was applied to

these areas in addition to the areas identified at the baseline visit (up to 20% BSA) for the remainder of the base period, and the percentage of BSA to be treated was recalculated and increased. Subjects whose additional new areas to be treated in addition to the areas identified at the baseline visit exceeded 20% BSA were discontinued from study treatment. In Study 109, during the treatment-extension period (Weeks 5-8), subjects applied ruxolitinib cream, 1.5% to active lesions only.

To continue ruxolitinib treatment during the 44-week LTS period (i.e., through Week 52) of both studies, subjects were enrolled only if they had AD BSA involvement up to 20% BSA. Treatment with ruxolitinib 0.75% or 1.5% cream BID was as needed, with cycles of re-treatment as needed. Upon entry into the LTS period and at each study visit (every 4 weeks) during the LTS period, the investigator assessed the AD lesions to determine whether the subject required treatment (IGA score ≥ 1) or could (re)enter the observation/no treatment cycle (IGA score = 0). Between study visits, subjects self-evaluated for recurrence of AD and treated skin areas with active lesions (not to exceed 20% BSA). If a lesion(s) cleared, participants continued treatment for 3 days after the lesion(s) disappeared. As before, subjects could treat new areas with the investigator's approval as long as there were no safety concerns regarding the additional application of study drug and the total treated BSA in the LTS period did not exceed 20%.

To determine the safety profile of ruxolitinib cream, 1.5% and 0.75%, the reviewer analyzed the following types of study data gathered from Studies 109 and 305: demographics of subjects, exposure, serious adverse events (SAEs), adverse events (AEs) leading to discontinuation, and treatment-emergent adverse events (TEAEs). In addition, the analysis also included a review of the safety assessments performed over the course of the studies to include vital signs, laboratory tests (hematology, chemistry), bone biomarker tests (bone-specific alkaline phosphatase, height and weight measurements for growth analyses (INCB 18424-109 and INCB 18424-305), and physical examinations. For Studies 109 and 305, investigators conducted safety assessments at Screening, Baseline (Week 1), and Weeks 2, 4, and 8. During the long-term safety period for both studies, safety assessments were performed every 4 weeks.

The Applicant submitted data from an additional study, INCB 18424-102, a 4-week pilot PK study in pediatric subjects ages 2 to 17 years, with AD BSA of 8-20% and an IGA score of ≥2 (specifically, 50 subjects ages 2 to <12 years in cohorts 3 to 6). The results of this study were primarily reviewed in the assessment of the bone biomarker data.

### 8.2.2. Review of the Safety Database

**Overall Exposure**

The safety database includes 329 subjects from Study 305 (130 subjects applying ruxolitinib 1.5%, 134 subjects applying ruxolitinib 0.75%, and 65 subjects applying vehicle) and in Study 109, 29 subjects. The safety population was defined to include all subjects who received at least one dose of the study drug. The number of subjects and duration of exposure to ruxolitinib 1.5% and 0.75% cream is presented in the Tables below.

**Table 21. Subjects with ≥24 and ≥48 Weeks Cumulative Exposure to Ruxolitinib Cream by Age Group**

| N1=Subjects at Baseline (Day 1) | Study 109 N1=29 | Study 305 N1=130 | Study 305 N1=134 | Study 305 N1=65 | |
|---|---|---|---|---|---|
| Initial treatment arm | Ruxolitinib 1.5% | Ruxolitinib 1.5% | Ruxolitinib 0.75% | Vehicle | |
| LTS treatment arm | Ruxolitinib 1.5% | Ruxolitinib 1.5% | Ruxolitinib 0.75% | Ruxolitinib 1.5% | Ruxolitinib 0.75% |
| **N2, subjects enrolled in LTS (Week 9)** | **22** | **114** | **119** | **24** | **25** |
| Length of exposure in initial treatment period | 8 weeks | 8 weeks | 8 weeks | None | None |
| Ages 2 to <7 years, n | 13 | 58 | 58 | 16 | 7 |
| Ages 7 to <12 years, n | 9 | 56 | 61 | 8 | 18 |
| **N3, subjects with ≥24 wks cumulative exposure** | **16 (72.7)** | **100 (87.7)** | **93 (78.2)** | **21 (87.5)** | **20 (80)** |
| Length of exposure in LTS period | ≥16 weeks | ≥16 weeks | ≥16 weeks | ≥24 weeks | ≥24 weeks |
| Ages 2 to <7 years, n | 10 (76.9) | 51 (87.9) | 41 (70.7) | 14 (87.5) | 4 (57.1) |
| Ages 7 to <12 years, n | 6 (66.7) | 49 (87.5) | 52 (85.2) | 7 (87.5) | 16 (88.9) |
| **N4, subjects with ≥48 wks cumulative exposure** | **14 (63.6)** | **75 (65.8)** | **70 (58.8)** | **16 (66.7)** | **16 (64)** |
| Length of exposure in LTS period | ≥40 weeks | ≥40 weeks | ≥16 weeks | ≥48 weeks | ≥48 weeks |
| Ages 2 to <7 years, n | 9 (69.2) | 36 (62.1) | 28 (48.3) | 10 (62.5) | 1 (14.3) |
| Ages 7 to <12 years, n | 5 (55.6) | 39 (69.6) | 42 (68.9) | 6 (75) | 15 (83.3) |

**Source: Reviewer, INCB 198424-109/-305 ADSL.**

Overall exposure to ruxolitinib cream, 1.5% and 0.75% BID in terms of frequency, duration, and target population were adequate for the evaluation of safety.

**Relevant characteristics of the safety population**

The demographics of the safety populations for the MUsT Study 109 and the phase 3 Study 305 were fairly comparable, with the majority of subjects being white and female, with a mean age of 6 to 6.6 years. Most subjects were non-Hispanic.

**Table 22. Demographics of Safety Populations in Studies 109 and 305, Initial Treatment Period (Weeks 1-8)**

| | Study 109 Ruxolitinib 1.5% N=29 | Study 305 Ruxolitinib 0.75% N=134 | Study 305 Ruxolitinib 1.5% N=130 | Study 305 Vehicle N=65 |
|---|---|---|---|---|
| **Age (years)** | | | | |
| Mean (SD) | 6 (3) | 6.6 (2.8) | 6.4 (3) | 6.3 (3.1) |
| Median | 6 | 6 | 6 | 6 |
| Range | 2-11 | 2-11 | 2-11 | 2-11 |
| **Age range** | | | | |
| 2 to <7 years | 17 (58.6) | 68 (50.7) | 66 (50.8) | 33 (50.8) |
| 7 to <12 years | 12 (41.4) | 66 (49.3) | 64 (49.2) | 32 (49.2) |
| **Sex** | | | | |
| Male | 13 (44.8) | 61 (45.5) | 63 (48.5) | 27 (41.5) |
| Female | 16 (55.2) | 73 (54.5) | 67 (51.5) | 38 (58.5) |
| **Race** | | | | |
| White | 14 (48.3) | 75 (56) | 68 (52.3) | 37 (56.9) |
| Black | 11 (37.9) | 45 (33.6) | 42 (32.3) | 19 (29.2) |
| Asian | 2 (6.9) | 7 (5.2) | 10 (7.7) | 3 (4.6) |
| American Indian | 1 (3.4) | 0 (0) | 1 (0.8) | 0 (0) |
| Hawaiian/Pacific Islander | 0 (0) | 1 (0.7) | 0 (0) | 1 (1.5) |
| Other[a] | 1 (3.4) | 5 (3.7) | 8 (6.2) | 5 (7.7) |
| Not reported | 0 (0) | 1 (0.7) | 1 (0.8) | 0 (0) |
| **Ethnicity** | | | | |
| Hispanic | 12 (41.4) | 32 (23.9) | 42 (32.3) | 26 (40) |
| Non-Hispanic | 17 (58.6) | 99 (73.9) | 88 (67.7) | 39 (60) |
| Other | 0 (0) | 1 (0.7) | 0 (0) | 0 (0) |
| Not reported | 0 (0) | 2 (1.5) | 0 (0) | 0 (0) |

**Source: Reviewer, INCB 198424-109/-305 ADSL.**

[a] Includes subjects who identified as being of mixed race.

The subjects of the LTS phases of Studies 109 and 305 were those who completed the initial 8 weeks of treatment in their respective studies and consented to continuation in the LTS phase. In some categories, the demographics varied significantly between groups in some respects. Although randomization of the subjects rolled over from the vehicle arm was 1:1, the mean and median age of those applying ruxolitinib 0.75% (7-8 years old) were higher than those for the subjects applying ruxolitinib 1.5% cream during the LTS (5-6 years old), resulting in a 1:2 ratio of younger (2-6 years) to

older (7-11 years) subjects to the ruxolitinib cream, 0.75% arm, and a 2:1 ratio of older to younger applying ruxolitinib cream, 1.5%. There was also an imbalance in the sex distribution due to a higher percentage of males in the ruxolitinib 1.5% cream arm of the VC period of Study 305 that continued in the LTS period compared to females.

**Table 23. Demographics of Safety Populations in Studies 109 and 305, LTS Period (Weeks 9-52)**

| | Study 109 Ruxolitinib 1.5% N=22 | Study 305 Ruxolitinib 0.75%- Ruxolitinib 0.75% N=119 | Study 305 Vehicle- Ruxolitinib 0.75% N=25 | Study 305 Ruxolitinib 1.5%- Ruxolitinib 1.5% N=114 | Study 305 Vehicle- Ruxolitinib 1.5% N=24 |
|---|---|---|---|---|---|
| **Age (years)** | | | | | |
| Mean (SD) | 6 (3) | 6.8 (2.8) | 7.5 (3.2) | 6.4 (3) | 5.8 (3) |
| Median | 5 | 7 | 8 | 6 | 5.5 |
| Range | 2-11 | 2-11 | 2-11 | 2-11 | 2-11 |
| **Age range** | | | | | |
| 2 to <7 years | 13 (59.1) | 58 (48.7) | 7 (28) | 58 (50.9) | 16 (66.7) |
| 7 to <12 years | 9 (40.9) | 61 (51.3) | 18 (72) | 56 (49.1) | 8 (33.3) |
| **Sex** | | | | | |
| Male | 9 (40.9) | 52 (43.7) | 10 (40) | 59 (51.8) | 12 (50) |
| Female | 13 (59.1) | 67 (56.3) | 15 (60) | 55 (48.2) | 12 (50) |
| **Race** | | | | | |
| White | 12 (54.5) | 69 (58) | 14 (56) | 61 (53.5) | 13 (54.2) |
| Black | 9 (40.9) | 37 (31.1) | 8 (32) | 35 (30.7) | 6 (25) |
| Asian | 1 (4.5) | 6 (5) | 0 (0) | 10 (8.8) | 2 (8.3) |
| American Indian | 0 (0) | 0 (0) | 0 (0) | 1 (0.9) | 0 (0) |
| Hawaiian/Pacific Islander | 0 (0) | 1 (0.8) | 1 (4) | 0 (0) | 0 (0) |
| Other[a] | 0 (0) | 5 (4.2) | 2 (8) | 6 (5.3) | 3 (12.5) |
| Not reported | 0 (0) | 1 (0.8) | 0 (0) | 1 (0.9) | 0 (0) |
| **Ethnicity** | | | | | |
| Hispanic | 10 (45.5) | 30 (25.2) | 10 (40) | 36 (31.6) | 8 (33.3) |
| Non-Hispanic | 12 (54.5) | 88 (73.9) | 15 (60) | 78 (68.4) | 16 (66.7) |
| Not reported | 0 (0) | 1 (0.8) | 0 (0) | 0 (0) | 0 (0) |

**Source: Reviewer, INCB 198424-109 ADSL 2/-305 LTS_ADSL.**
[a] Includes subjects who identified as being of mixed race.

**Adequacy of the safety database:**

The total subject exposure to ruxolitinib cream, 1.5% and 0.75%, applied twice daily for up to 8 weeks and the extension period for at least an additional 40 weeks (total exposure ≥48 weeks) provided adequate data for the evaluation of safety. The demographics of the phase 3 vehicle-controlled studies population were sufficiently representative of the target population. Therefore, the safety database submitted by the Applicant was deemed to be sufficient to characterize the safety profile of ruxolitinib cream, 1.5% and 0.75%, in pediatric subjects ages 2 to <12 years with mild to moderate atopic dermatitis.

### 8.2.3. Adequacy of Applicant's Clinical Safety Assessments

**Issues Regarding Data Integrity and Submission Quality**

Overall, the quality of the data submitted for the phase 3 vehicle-controlled Study 305 is adequate to characterize the safety and efficacy of ruxolitinib cream, 1.5% and 0.75%, for the topical treatment of atopic dermatitis in patients 2 to <12 years with mild to moderate AD. There were no significant deficiencies that would impede a thorough analysis of the data for Studies 109 and 305.

**Categorization of Adverse Events**

The Applicant defined an adverse event (AE) as "any untoward medical occurrence associated with the use of a drug in humans, whether or not it is considered drug-related," including any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) occurring after study drug initiation and temporally associated with the use of study cream". A treatment-emergent adverse event (TEAE) was any AE either reported for the first time or worsening of a pre-existing event after first application of study cream and no later than 30 days after the End-of-Study (EOS), End-of-Treatment (EOT), or Early Termination (ET) visit.

A serious adverse event (SAE) was defined as an AE that met any of the following criteria:

- Resulted in death.
- Was life-threatening.
- Required inpatient hospitalization or a prolongation of an existing hospitalization.
- Resulted in persistent or significant disability/incapacity (substantial disruption of a person's ability to conduct normal life functions).
- Resulted in a congenital anomaly or birth defect.
- Was considered by the investigator as an important medical event that was not immediately life-threatening or resulting in death or hospitalization but could have jeopardized the subject or required medical or surgical intervention to prevent one of the other outcomes listed in the above definition.

"Lack of efficacy" or "failure of expected pharmacological action" was not reported as an AE or serious adverse event (SAE). However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy were to be reported as an AE or SAE if they fulfilled the definition of an AE or SAE.

Each AE/SAE was categorized by system-organ class and the Medical Dictionary for Regulatory Activities (MedDRA) preferred term and evaluated to determine the severity (based on the National Cancer Institute CTCAE v5.0 using Grades 1 through 5), relatedness to the study drug, action taken with regard to the study cream, and the event outcome. For events not classified by CTCAE, the severity of the AE was graded according to the scale below to estimate the grade of severity. The investigator made an assessment of intensity for each AE and SAE reported during the study and assigned it to one of the following categories:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; treatment not indicated.
- Grade 2: Moderate; minimal, local, or noninvasive treatment indicated; limiting age-appropriate activities of daily living.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
- Grade 4: Life-threatening consequences; urgent treatment indicated.
- Grade 5: Fatal.

Any AEs/SAEs assessed as related to study participation (e.g., relationship to study cream or study procedure[s]) or related to study drug were recorded from the time a subject consented to participate in the study up to and including any follow-up contact. When an Investigator determined that an AE met the protocol definition of an SAE during the study, he/she notified the Sponsor using an SAE Report Form within 24 hours of the study site personnel's knowledge of the event, regardless of the Investigator assessment of the relationship of the event to study drug.

After the initial AE/SAE report, the Investigator was required to proactively follow each subject at subsequent visits/contacts. All SAEs and nonserious AEs were to be followed until resolution, until the condition stabilized, until the event was otherwise explained, or until the subject was lost to follow-up.

The Applicant presented standard AE analyses. The definitions of AE and SAE were acceptable. The classification system (CTCAE) used by investigators to describe the severity were acceptable. The coding of AEs in the sNDA submission appeared adequate and allowed for accurate estimation of AE risk.

**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 and 8 during the VC period. During the LTS period, lab testing was done monthly beginning at Week 12 through Week 52 and 30 days after the last application of study drug. This schedule of testing was acceptable.

### 8.2.4. Safety Results

The primary safety review will focus on the phase 3 Study 305, separated into the 8-week vehicle-controlled (VC) period and the 44-week, open-label, long-term safety (LTS) extension period, Week 9

up to Week 52. The results of Study 109, the MUsT study, are presented separately in Section 8.2.9, Additional Safety Explorations.

**Deaths**

There were no deaths reported from Study 305.

**Serious Adverse Events (SAEs)**

No SAEs were reported in the vehicle-controlled period of Study 305.

During the LTS period of Study 305, there were 3 SAEs, all in subjects applying ruxolitinib 1.5% cream. There were 2 episodes of asthma, in a 6-yo male and a 10-yo male, neither of which were attributed to ruxolitinib 1.5% cream, neither of which resulted in interruption in ruxolitinib treatment, and both cases considered unlikely related to the study drug by the reviewer. The third SAE, eczema herpeticum in a 2-yo male, is described below.

**NARRATIVES:**

- **Eczema herpeticum** in a 2-yo male (Subject (b) (6)) with moderate atopic dermatitis (baseline IGA 3, 14% BSA), hypersensitivity, and asthma. During the VC phase, the %BSA affected decreased from 14% to 1%. During the LTS, the %BSA affected fluctuated from a high of 17% (Week 20) to lows of 1.5-2% (Weeks 28-32). Per the protocol, during the LTS phase, ruxolitinib was only applied to affected areas; as such, the actual amount applied varied, but estimated by the Applicant to be an average weekly amount of 18.47 g over the LTS phase.
    - On Study Day (SD) 296 (between Weeks 40 and 44), the subject was diagnosed by primary care with a nonserious TEAE of molluscum, and prescribed tretinoin 0.1% for treatment of the molluscum on the abdomen, axillae, and thighs.
    - SD 309 (Week 44) – AD was active in areas treated at baseline; %BSA was 9%. The areas where the molluscum was located were not affected by AD and not being treated with ruxolitinib. Labs of white blood cells taken at this time were normal or high: leukocytes 9.2 x $10^9$/L (normal 6-17.5 x $10^9$/L); neutrophils 2.6 x $10^9$/L (normal 1.8-7.7 x $10^9$/L); and lymphocytes 6.1 x $10^9$/L (normal 1-4.8 x $10^9$/L).
    - SD 317 (Week 45) – The subject's mother stopped the subject's oral antihistamines in advance of an allergy appointment the following week. She also interrupted the ruxolitinib application, although the reason why isn't clear. Day 317 was the last day of ruxolitinib application.
    - Between SDs 318-321, the subject developed a dry, itchy rash involving the genitalia, arms, legs, and neck, also described as red and "picked over" with pustules. This rash was unlike the molluscum or AD, and the mother thought it might be "an allergic rash to the retinoin". On SD 321, the subject developed a fever of 102.7F. The mother reported that that rash "looked like MRSA" and treated the rash empirically with mupirocin at home.
    - On SD 322, when the subject was seen by the primary care provider, he was prescribed cephalexin. The rash did not improve, became more painful, and spread to the entire

body, with the worst parts on the scrotum, right elbow, and left neck. On SD 324, the subject was subsequently diagnosed with eczema herpeticum (confirmed with PCR) and hospitalized. The physical examination was notable for punched-out lesions and ulcerations on an erythematous base with areas of crusting; molluscum was still present on the abdomen. The subject was treated with acyclovir and morphine (for pain). By SD 326, the rash had improved enough that the subject was discharged from the hospital. By SD 348, the subject had recovered from the eczema herpeticum. The investigator assessment was that the eczema herpeticum was not related to the ruxolitinib.

*Reviewer's Comment: Eczema herpeticum (EH) is a serious condition that may occur in patients with severe atopic dermatitis, where the skin barrier is disrupted. In this subject, other known risk factors for EH,[1] including younger age, presence of molluscum, and allergic comorbidities (asthma and allergies) were present. In this subject, other factors may have been contributory to EH: Irritation of the skin by tretinoin (a common side effect) which was used to treat the molluscum which was possibly mistaken as an "allergic reaction"; concomitant secondary bacterial infection and/or an initial misdiagnosis of the eczema herpeticum, delaying treatment; and the co-occurrence/overlap of these severe rashes on the body, complicating the ability of being able to distinguish one rash from another.*

*Attribution of ruxolitinib in causality of this case of EH is challenging. Ruxolitinib cream was not being applied when the eczema herpeticum may have possibly first appeared (~Day 320, Week 45); however, there had been some amount of ruxolitinib applied (albeit %BSA fluctuated) without interruption until 4 days prior to the appearance of any "rash" other than AD or molluscum. There was no evidence of immunosuppression demonstrated by the most recent WBC results prior to the onset of EH. In addition, this subject had other confounding risk factors that, in the absence of ruxolitinib, are known to be risk factors for EH. In weighing together the circumstances surrounding this case of EH, it is unlikely that ruxolitinib 1.5% cream was related to this SAE.*

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

Overall, the rate of discontinuation due to adverse events was minimal during the VC period (1 subject in the ruxolitinib 0.75% arm discontinued due to pain/discomfort during application of the cream). Rather, the most common reasons for discontinuation were due to lack of efficacy/worsening of AD and withdrawal by subject/guardian. A primary cause of withdrawal (~50%) was due to blood draws.

**Table 24. Discontinuations in Study 305, VC Phase**

| | Ruxolitinib cream, 1.5% N=130 | Ruxolitinib cream, 0.75% N=134 | Vehicle cream N=65 |
|---|---|---|---|
| **Study Status** | | | |
| Completed study | 117 (90) | 122 (91) | 49 (75.4) |

[1] UpToDate, Eczema herpeticum, https://www.uptodate.com/contents/eczema-herpeticum, 16 Sep 2024

| | | | |
|---|---|---|---|
| Discontinued study | 13 (10) | 12 (9) | 16 (24.6) |
| **Reasons for Discontinuation** | | | |
| Adverse event | 0 (0) | 1 (0.7) | 1 (1.5) |
| Lack of efficacy | 1 (0.8) | 1 (0.7) | 7 (10.8) |
| Lost to follow-up | 5 (3.8) | 5 (3.7) | 2 (3.1) |
| Withdrawal by subject/guardian | 5 (3.8) | 3 (2.2) | 5 (7.7) |
| Physician decision | 1 (0.8) | 1 (0.7) | 0 (0) |
| Protocol specified withdrawal criterion | 0 (0) | 0 (0) | 1 (1.5) |
| Protocol violation | 1 (0.8) | 1 (0.7) | 0 (0) |

**Source: Reviewer, INCB 198424-109 ADSL 2/-305 ADSL.**

During the LTS period of Study 305, the rates of discontinuation were highest in the subjects that had been on ruxolitinib 0.75% through the VC period and the LTS phase. Similar to what was seen during the VC period, the most common discontinuations during the LTS phase were classified as Lost to Follow-Up or Withdrawal by Subject/Guardian, with the number of blood draws and study visits presenting the biggest barrier to continuation.

There was a total of 4 subjects (0.1%) with AEs leading to drug/study discontinuation during the LTS phase. There was one subject (0.8%), a 5-yo male with an upper arm fracture, who was applying ruxolitinib 0.75% cream. There were 3 subjects (2.6%) applying ruxolitinib 1.5% cream during the LTS at the time of discontinuation: a 2-yo male with Grade 3 eczema herpeticum (previously discussed under SAEs); an 8-yo male with Grade 2 impetigo, and a 7-yo female with a Grade 1 autoimmune hepatitis (abnormal liver enzymes) who was discontinued at the investigator's discretion (see discussion in Section 8.2.5 Analysis of Submission-Specific Safety Issues). None of these AEs were considered related to ruxolitinib use.

**Table 25. Discontinuations During the LTS Period of Study 305**

| | **Study 305 Ruxolitinib 1.5%-Ruxolitinib 1.5% N=114** | **Study 305 Vehicle-Ruxolitinib 1.5% N=24** | **Study 305 Ruxolitinib 0.75%-Ruxolitinib 0.75% N=119** | **Study 305 Vehicle-Ruxolitinib 0.75% N=25** |
|---|---|---|---|---|
| **Study Status** | | | | |
| Completed study | 77 (67.5) | 15 (62.5) | 71 (59.7) | 18 (72) |
| Discontinued study | 37 (32.5) | 9 (37.5) | 48 (40.3) | 7 (28) |
| **Reasons for Discontinuation** | | | | |
| Adverse event | 3 (2.6) | 0 (0) | 1 (0.8) | 0 (0) |
| Lack of efficacy | 2 (1.8) | 0 (0) | 5 (4.2) | 1 (4) |
| Lost to follow-up | 9 (7.9) | 6 (25) | 18 (15.1) | 1 (4) |
| Withdrawal by subject/guardian | 18 (15.8) | 3 (12.5) | 19 (16) | 2 (8) |

| | | | | |
|---|---|---|---|---|
| Physician decision | 0 (0) | 0 (0) | 1 (0.8) | 1 (4) |
| Protocol specified withdrawal criterion | 2 (1.8) | 0 (0) | 1 (0.8) | 1 (4) |
| Protocol violation | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Non-compliance with study drug | 1 (0.9) | 0 (0) | 0 (0) | 1 (4) |
| Other | 2 (1.8) | 0 (0) | 3 (2.5) | 0 (0) |

**Source: Reviewer, INCB 198424-305 ADSL.**

*Reviewer Comment: Discontinuation due to AEs of subjects applying either strength of ruxolitinib cream, 1.5% or 0.75%, over the long-term extension of this study was low. I agree with the investigators' assessments that these AEs were unlikely related to ruxolitinib 1.5% or 0.75% use.*

*Notably, the discontinuation rates in those applying 0.75% cream arm (40.3%) were higher than the rate in those applying the higher strength ruxolitinib, 1.5% (32.5-37.5%). Considering that the reason for withdrawal was due to requirements of the study (blood draws and study visits) and given the lower efficacy rate compared to the 1.5% strength, it could be possible that parents/guardians may not have perceived sufficient benefit (e.g., efficacy) from the lower strength ruxolitinib to compensate for the study burdens.*

**Significant Adverse Events**

During the VC period of Study 305, there were four Grade 3 AEs occurring in 2 subjects, both in the 7-11 year age group and applying ruxolitinib 1.5% cream. One subject, a 10-yo female, had a Grade 3 "worsening of atopic dermatitis" which led to discontinuation of treatment. The other subject, a 7-yo male, experienced bilateral tonsil hypertrophy, bilateral adenoid hypertrophy, and sleep apnea, all Grade 3. All of these AEs were considered unrelated to ruxolitinib 1.5% cream, as there were no changes in drug dosing and the subjects recovered and continued in the study. All of these AEs are considered unlikely related to the study drug by the reviewer.

During the LTS phase, the incidence rates of Grade 3 AEs in those applying ruxolitinib 1.5% and 0.75%. None of these AEs were assessed by the investigators as related to ruxolitinib.'

**Table 26. Grade 3 AEs during Study 305, LTS Phase**

| | **Study 305 Ruxolitinib 1.5%-Ruxolitinib 1.5% N=114** | **Study 305 Vehicle-Ruxolitinib 1.5% N=24** | **Study 305 Ruxolitinib 0.75%-Ruxolitinib 0.75% N=119** | **Study 305 Vehicle-Ruxolitinib 0.75% N=25** |
|---|---|---|---|---|
| **Any Grade 3 AE** | 3 (2.6) | 0 (0) | 3 (2.5) | 0 (0) |
| Asthma | 2 (1.8) | 0 (0) | 1 (0.8) | 0 (0) |
| Eczema herpeticum | 1 (0.9) | 0 (0) | 0 (0) | 0 (0) |

| | | | | |
|---|---|---|---|---|
| Post concussion syndrome | 0 (0) | 0 (0) | 1 (0.8) | 0 (0) |
| Hand fracture | 0 (0) | 0 (0) | 1 (0.8) | 0 (0) |

**Source: Reviewer, INCB 198424-305 ADAE.**

*Reviewer Comment: I agree that the Grade 3 AEs during the VC period and LTS period of Study 305 are unlikely to be related to the study drug.*

**Changes in Drug Dosing**

Overall, there were few drug interruptions and drug withdrawals due to AEs in Study 305. However, the most common cause in the active treatment arms was due to application site pain/irritation, which were all assessed as possibly related to ruxolitinib application. One subject in the ruxolitinib 1.5% arm had drug interruption due to lymphopenia; however, this AE was considered unlikely related to ruxolitinib as the subject's low lymphocyte count was at baseline (see narrative for Subject (b) (6) in Section 8.2.5).

**Table 27. Changes in Drug Dosing in Study 305, VC Period**

| | Ruxolitinib cream, 1.5% N=130 | Ruxolitinib cream, 0.75% N=134 | Vehicle cream N=65 |
|---|---|---|---|
| **Drug interruption** | 1 (0.8) | 4 (3) | 2 (3.1) |
| Application site pain/irritation | 0 (0) | 2 (1.5) | 0 (0) |
| Application site infection | 0 (0) | 0 (0) | 1 (1.6) |
| Abdominal pain | 0 (0) | 1 (0.7) | 0 (0) |
| Maculopapular rash | 0 (0) | 1 (0.7) | 0 (0) |
| Lymphopenia | 1 (0.8) | 0 (0) | 0 (0) |
| Contact dermatitis | 0 (0) | 0 (0) | 1 (1.6) |
| **Drug withdrawal** | 1 (0.8) | 1 (0.7) | 0 (0) |
| Application site pain | 0 (0) | 1 (0.7) | 0 (0) |
| Atopic dermatitis (worsening) | 1 (0.8) | 0 (0) | 0 (0) |

**Source: Reviewer, INCB 198424-305 ADAE.**

During the LTS period, rates of drug interruption were higher than the VC period in both treatment groups. Compared to the VC period, there were no changes in drug dosing due to application site reactions, suggesting that application site irritation may be more prominent in the first few weeks of treatment but becomes more tolerable with longer-term use. Infections of the skin (impetigo, molluscum, eczema coxsackium) and respiratory tract (nasopharyngitis, mononucleosis) resulted in drug interruption during treatment; however, all subjects were able to restart the drug after their AEs resolved, without further episodes. Of these infections, only the Grade 2 eczema coxsackium in Subject (b) (6), a 2 yo male with moderate AD, was assessed as possibly related to ruxolitinib 1.5% cream use.

**Table 28. Changes in Drug Dosing in Study 305, LTS Period**

| | Ruxolitinib cream, 1.5% N=138 | Ruxolitinib cream, 0.75% N=144 |
|---|---|---|
| **Drug interruption** | 5 (3.6) | 8 (5.6) |
| Skin infection/impetigo | 1 (0.7) | 2 (1.4) |
| ALT increased | 0 (0) | 1 (0.7) |
| Nasopharyngitis | 0 (0) | 1 (0.7) |
| Infectious mononucleosis/LFT increased | 0 (0) | 1 (0.7) |
| Abdominal pain upper | 0 (0) | 1 (0.7) |
| Hand fracture | 0 (0) | 1 (0.7) |
| Molluscum contagiosum | 1 (0.7) | 0 (0) |
| Eczema coxsackium | 1 (0.7) | 0 (0) |
| Neutropenia | 1 (0.7) | 0 (0) |
| Breast swelling | 1 (0.7) | 0 (0) |
| **Drug withdrawal** | 1 (0.7) | 0 (0) |
| Impetigo | 1 (0.7) | 0 (0) |

**Source: Reviewer, INCB 198424-305 ADAE.**

Abnormalities in liver enzymes (ALT) were also a cause for drug interruption in two subjects applying ruxolitinib 0.75% cream.

**Narratives:**

- Subject (b) (6), 11 yo female with moderate AD on ruxolitinib 0.75% cream during the VC and LTS phases, with baseline ALT of 22 U/L (normal 5-20 U/L) and baseline AST of 28 U/L (normal 0-36 U/L). The subject had elevations of ALT 45 U/L and AST 51 U/L at Week 8. She was not retested until Week 12 when the ALT had decreased to 23 U/L and AST to 31 U/L. With the exception of Week 8, her ALT was in a consistent range of 18-25 U/L and her AST ranged from 28-34 U/L throughout the study.
- Subject (b) (6), 3 yo male with moderate AD, initially on vehicle during the VC period and then randomized to 0.75% cream during the LTS, had an ALT value of 19 at baseline. His ALT values ranged from 15-27 U/L throughout the study. However, the range of normal ALT changed from the VC period (5-30 U/L) to the LTS period (5-20 U/L). The reported Grade 1 increases in ALT occurred during Weeks 32-40 with the narrower range of ALT values.

*Reviewer Comment: In both cases, although they were reported as Grade 1 AE increases in liver enzymes, the ALT/AST values were high-normal/slight elevated at baseline and remained consistent within a narrow range of values. The elevations, when they occurred, were mild and not sustained. By the end of study, all AST/ALT values were within the normal range. Except as noted, the other liver enzymes (e.g., bilirubin) remained in the normal range. Therefore, these elevations are unlikely due to ruxolitinib 0.75% cream application.*

**Treatment Emergent Adverse Events**

In the Study 305 VC period, 79 subjects (29.9%) of subjects applying ruxolitinib 1.5% or 0.75% cream experienced at least one AE: 45 (34.6%) in the ruxolitinib 1.5% group and 34 (25.4%) in the 0.75% group. These rates of affected subjects were very similar to those in the phase 3 studies TRUE-AD1 and TRUE-AD2 conducted in AD subjects 12 years and older. However, the safety profile varies from that of the adult/adolescent AD population. Whereas the AEs in adults/adolescents were primarily in the Infections/Infestations System Organ Class (SOC), the most common AEs seen in the 2-11 years AD population were more diverse and included COVID-19, application site reactions, pyrexia, asthma, and white blood cell decreased.

Upper respiratory tract infections occurred at high rates across all treatment arms, reflecting the elevated background risk of these infections in pediatric populations compared to adults. This pattern contrasts with the lower rates observed in TRUE-AD1 and TRUE-AD2 studies. For instance, nasopharyngitis rates in AD subjects 12 years and older who applied ruxolitinib 1.5% cream were comparatively lower at 3% in the phase 3 TRUE-AD1 and TRUE-AD2 studies. Incidence rates of respiratory infections were higher in the ruxolitinib 1.5% arm than in the ruxolitinib 0.75% arm.

**Table 29. TEAEs Occurring in ≥ 1% of Subjects Treated with Ruxolitinib 1.5% and at Higher Incidence than Vehicle in Study 305, VC Period**

| | **Ruxolitinib cream, 1.5% N=130** | **Ruxolitinib cream, 0.75% N=134** | **Vehicle N=65** |
|---|---|---|---|
| **Total TEAEs** | 76 | 61 | 22 |
| **Subjects, n (%)** | 45 (34.6) | 34 (25.4) | 16 (24.6) |
| Upper respiratory tract infection[a] | 20 (15.4) | 12 (9) | 7 (10.8) |
| COVID-19 | 6 (4.6) | 5 (3.7) | 2 (3.1) |
| Application site reaction[b] | 6 (4.6) | 5 (3.7) | 1 (1.5) |
| Pyrexia | 3 (2.3) | 5 (3.7) | 0 (0) |
| Asthma[c] | 2 (1.5) | 2 (1.5) | 0 (0) |
| White blood cell decreased[d] | 2 (1.5) | 0 (0) | 0 (0) |

**Source: Reviewer, INCB 18424-305 ADAE.**

[a] Upper respiratory tract infection includes Upper respiratory tract infection, nasopharyngitis, rhinorrhea, oropharyngeal pain, viral upper respiratory tract infection

[b] Application site reaction includes Application site pain, application site irritation, application site discomfort, application site erythema

[c] Asthma includes Asthma, wheezing

[d] White blood cell decreased includes White blood cell decreased, leukopenia

*Reviewer Comment: Some possible explanations for the differences noted in TEAEs from this pediatric population (2-<12 years of age) based on Study 305 compared to studies in the adolescent/adult AD population include a smaller sample size in a single phase 3 study 305 (500 per active treatment arm for the 2 adolescent/adult studies, TRUE-AD1/2, compared to 130-134 for Study 305), some AEs (such as pyrexia and skin sensitivity) in general are more prevalent in the younger pediatric population compared to adults, and the greater prevalence of COVID-19 overall when Study 305 was conducted.*

Because long-term, open-label extension studies are not powered to objectively assess for safety, there are limitations to interpretation of the safety data from Study 305 LTS period. Other factors that may contribute to an inability to draw meaningful conclusions were the small numbers of subjects, the lack of a vehicle-controlled arm, imbalances in randomization of the VC period vehicle subjects, and high discontinuation rates during the LTS period, particularly in those assigned to the 0.75% strength. To compensate for some of these factors, exposure-adjusted incidence rates (EAIRs) of TEAEs were calculated.

**Table 30. Exposure-Adjusted Incidence Rates (EAIRs) of TEAEs with ≥2% Difference Between Subjects Applying Ruxolitinib 1.5% Cream and Subjects Applying Ruxolitinib 0.75% Cream in Study 305, LTS Period**

| Incidence, n (EAIR) | **Ruxolitinib 1.5%-Ruxolitinib 1.5% N=114** | **Vehicle-Ruxolitinib 1.5% N=24** | **Ruxolitinib 0.75%-Ruxolitinib 0.75% N=119** | **Vehicle-Ruxolitinib 0.75% N=25** |
|---|---|---|---|---|
| PY of exposure | 95.3 | 16.2 | 93.9 | 17 |
| Any TEAE, n (%) | 54 (47.4) | 10 (41.7) | 52 (43.7) | 9 (36) |
| Upper respiratory tract infection[a] | 23 (26.7) | 4 (27.4) | 25 (29.9) | 6 (41.6) |
| Gastroenteritis[b] | 7 (7.5) | 1 (6.2) | 5 (5.4) | 1 (6) |
| Lower respiratory tract infection[c] | 6 (6.4) | 0 (0) | 8 (8.8) | 1 (6.2) |
| Neutropenia | 4 (4.3) | 0 (0) | 1 (1.1) | 0 (0) |
| Molluscum contagiosum | 3 (3.2) | 0 (0) | 0 (0) | 1 (6) |
| COVID-19[d] | 4 (4.3) | 2 (13.5) | 8 (8.8) | 2 (12.4) |
| Pyrexia | 1 (1.1) | 2 (13.2) | 6 (6.6) | 0 (0) |
| Cough | 1 (1.1) | 0 (0) | 4 (4.4) | 0 (0) |

**Source: Office of Computational Science Specialized Analysis Support Team, INCB 18424-305 ADAE.**

[a] Upper respiratory tract infection includes Upper respiratory tract infection, nasopharyngitis, rhinorrhea, oropharyngeal pain, viral upper respiratory tract infection, pharyngitis streptococcal, streptococcus test positive, respiratory tract congestion

[b] Gastroenteritis includes Gastroenteritis, gastroenteritis viral, gastroenteritis adenovirus

[c] Lower respiratory tract infection includes Bronchitis, influenza, pneumonia, pneumonia bacterial

[d] COVID-19 includes COVID-19, SARS-CoV-2 test positive

***Reviewer Comment:*** *These EAIRs of TEAEs during the LTS period reveal a slightly different safety profile of ruxolitinib cream with longer, intermittent use. Comparing the rates by strength, TEAEs with EAIRs higher in subjects using ruxolitinib 1.5% were gastroenteritis, neutropenia, and molluscum contagiosum, while subjects using ruxolitinib 0.75% cream had higher EAIRs in upper respiratory tract infections, lower respiratory tract infections, COVID-19, pyrexia, and cough. This paradoxical difference compared to the vehicle-controlled period creates uncertainty about safety differences between the ruxolitinib 1.5% and 0.75% strengths with long-term, intermittent use. The high discontinuation rate among ruxolitinib 0.75% users resulted in lower patient-years of exposure, which may have artificially inflated the impact of individual adverse events. This limitation restricts the ability to draw meaningful conclusions about long-term safety for either strength from the available open-label data in Study 305.*

**Adverse Reactions**

The determination of adverse drug reactions was based on a review of the most common TEAEs, serious TEAEs, ≥ Grade 3 TEAEs, and TEAEs leading to discontinuation or dose modification. Decisions on whether a relationship to study drug was plausible were based on the following factors:

- Frequency of reporting
- Whether the TEAE rate for the drug exceeds that for the vehicle
- Ruxolitinib strength-dependent trends in TEAE incidences
- Biological plausibility based on the mechanism of action of ruxolitinib
- Plasma ruxolitinib concentrations
- Timing relative to ruxolitinib cream application
- Alternative etiologies for occurrence of an AE, such as the disease under study, comorbidities, and prior/concomitant therapy

**Table 31. Adverse Reactions Occurring in ≥ 1% Pediatric Subjects 2 to 11 Years of Age Treated with Ruxolitinib 1.5% and 0.75% cream and >1% difference between Subjects receiving ruxoltinib cream and vehicle for Atopic Dermatitis through Week 8 (VC period) in Study 305**

| Subjects, n (%) | Ruxolitinib cream, 1.5% N=130 | Ruxolitinib cream, 0.75% N=134 | Vehicle N=65 |
|---|---|---|---|
| Upper respiratory tract infection[a] | 20 (15.4) | 12 (9) | 7 (10.8) |
| COVID-19 | 6 (4.6) | 5 (3.7) | 2 (3.1) |
| Application site reaction[b] | 6 (4.6) | 5 (3.7) | 1 (1.5) |
| Pyrexia | 3 (2.3) | 6 (4.5) | 0 (0) |
| White blood cell decreased[c] | 2 (1.5) | 0 (0) | 0 (0) |

**Source: Reviewer, INCB 18424-305 ADAE.**

[a] Upper respiratory tract infection includes Upper respiratory tract infection, nasopharyngitis, rhinorrhea, oropharyngeal pain, viral upper respiratory tract infection

[b] Application site reaction includes Application site pain, application site irritation, application site discomfort, application site erythema

[c] White blood cell decreased includes White blood cell decreased, leukopenia

Five common adverse drug reactions occurring during the VC period were identified based on these criteria: Upper respiratory tract infections, COVID-19, application site reactions (reported as burning, stinging, pain, and pain/discomfort at the application site), pyrexia, and white blood cell decreases (reported as leukopenia or white blood cell decreased) were identified as adverse drug reactions on the basis of the frequency of reporting during the VC period of the phase 3 study, higher incidences and IRs among participants on ruxolitinib cream versus vehicle cream, and the plausibility of a relationship to application of ruxolitinib cream.

See Section 8.2.5.1 Adverse Events of Special Interest for a more detailed description of application site reactions and Section 8.2.5 Analysis of Submission-Specific Safety Issues for other adverse reactions related to JAK inhibitors.

**Table 32. Exposure-Adjusted Incidence Rates of Adverse Reactions (EAIRs) with ≥2% Difference Between Subjects Applying Ruxolitinib 1.5% Cream and Subjects Applying Ruxolitinib 0.75% Cream in Study 305, LTS Period**

| Incidence, n (EAIR) | Ruxolitinib 1.5%-Ruxolitinib 1.5% N=114 | Ruxolitinib 0.75%-Ruxolitinib 0.75% N=119 | Vehicle-Ruxolitinib 1.5% N=24 | Vehicle-Ruxolitinib 0.75% N=25 |
|---|---|---|---|---|
| PY of exposure | 95.3 | 93.9 | 16.2 | 17 |
| Any AR | 54 (47.4) | 52 (43.7) | 10 (41.7) | 9 (36) |
| Upper respiratory tract infection[a] | 23 (26.7) | 25 (29.9) | 4 (27.4) | 6 (41.6) |
| Lower respiratory tract infection[b] | 6 (6.4) | 8 (8.8) | 0 (0) | 1 (6.2) |
| COVID-19[c] | 4 (4.3) | 8 (8.8) | 2 (13.5) | 2 (12.4) |
| Neutropenia | 4 (4.3) | 1 (1.1) | 0 (0) | 0 (0) |

**Source: Office of Computational Science Specialized Analysis Support Team, INCB 18424-305 ADAE.**

[a] Upper respiratory tract infection includes Upper respiratory tract infection, nasopharyngitis, rhinorrhea, oropharyngeal pain, viral upper respiratory tract infection, pharyngitis streptococcal, streptococcus test positive, respiratory tract congestion

[b] Lower respiratory tract infection includes Bronchitis, influenza, pneumonia, pneumonia bacterial

[c] COVID-19 includes COVID-19, SARS-CoV-2 test positive

With long-term, intermittent use of ruxolitinib cream, upper and lower respiratory tract infections and COVID-19 were common. The EAIR of neutropenia (rather than white blood cell decreased) was higher during the LTS period compared to the incidence rates seen during the VC period. For a more detailed discussion of neutropenia seen in Study 305, see Section 8.2.5 Analysis of Submission-Specific Safety Issues.

**Laboratory Findings**

Per the Study 305 protocol, clinical investigators were to record abnormal laboratory values as a test result in the eCFR as a diagnosis (e.g., anemia, thrombocytopenia) rather than a test abnormality (e.g., low hemoglobin, platelet count decreased). They were to report lab abnormalities as an AE if they considered the lab abnormality clinically meaningful; or if it had induced clinical signs or symptoms, required concomitant therapy, or required changes in study cream. Because the protocol allowed for this investigator discretion, both the ADAE and ADLB datasets were reviewed for abnormal values.

In Study 305, clinical safety laboratory evaluations were performed at screening/baseline, Week 2, Week 4, and Week 8 during the VC period and every 4 weeks starting Week 12 of the LTS period. Laboratory findings were assessed as a comparison between ruxolitinib cream, 1.5% and 0.75%, and vehicle at Weeks 2, 4, and 8 during the VC period, and by EAIRs during the LTS period. Cytopenias and abnormal liver enzymes are discussed in greater detail in Section 8.2.5 Analysis of Submission-Specific Safety Issues.

**Vital Signs**

No AEs related to changes in vital signs (including dyspnea, syncope, hypertension, hypotension,

bradycardia, tachycardia), with the exception of pyrexia, were reported in Study 305. The Applicant reported that most participants in Study 305 had normal vital signs at baseline and at study visits during the VC and LTS periods, and no meaningful trends in vital signs.

Of the 9 AEs of pyrexia (6 in the ruxolitinib 0.75% arm, 3 in the ruxolitinib 1.5% arm) reported in the VC period, all but 1 occurred in the 2-6 year age group. All of these incidents were short in duration (range 1-6 days), assessed as Grade 1 or 2, and did not result in dose changes. The subjects all recovered and remained in the study. During the LTS period, 7 subjects in the ruxolitinib 0.75% arm and 5 subjects in the ruxolitinib 1.5% arm experienced pyrexia. Similar to the VC period, the incidents of pyrexia in the LTS period were short in duration (range 1-5 days), assessed as Grade 1 or 2, and did not result in dose changes. The age distribution was split in the ruxolitinib 0.75% arm (4 subjects in the 2-6 yo group, 3 in the 7-11 yo group), while all the subjects in the ruxolitinib 1.5% arm were in the 2-6 yo group.

**Electrocardiograms (ECGs)**

There were no ECGs conducted during Study 305.

**QT**

There were no QT assessments conducted during Study 305.

**Immunogenicity**

Not applicable.

### 8.2.5. Analysis of Submission-Specific Safety Issues

#### 8.2.5.1 Adverse Events of Special Interest

Treatment-emergent AEs of special interest for the ruxolitinib cream development program include application site reactions and adverse events common in JAK inhibitors for the treatment of inflammatory conditions.

**Application site reactions**

Overall, the incidence rates of application site reactions (including application site pain, irritation, discomfort, and erythema) during the VC period of Study 305 were low (see Tables 28 and 30 above), and Grade 1 or 2 in severity. The majority of these AEs resolved without any changes in dose. One subject applying ruxolitinib 0.75% cream discontinued treatment due to Grade 2 application site pain, and 2 additional subjects in the ruxolitinib 0.75% cream required drug interruption before eventual resolution during the VC phase. During the LTS period, there were fewer AEs related to application site reactions to the skin.

**Adverse Events of Interest for JAK Inhibitors for the Treatment of Inflammatory Conditions**

During clinical trials conducted with systemic JAK inhibitors for the treatment of inflammatory conditions, there have been certain laboratory findings that appear to be shared by this class of drugs and are labeled as adverse reactions. These include thrombocytosis, cytopenias, lipid elevations, and liver enzyme elevations. While cross-comparisons with clinical trials for JAK inhibitors in other indications have limitations on the interpretation, a comparison of PK levels reported in Study 109 (the maximal usage study with ruxolitinib 1.5% cream) provides some context for assessing relative levels of systemic absorption of a topical product that is indicated for atopic dermatitis, a condition with a disrupted skin barrier, with chronic (8 weeks) application BID (see Section 4.5).

Studies in non-segmental vitiligo subjects and mild to moderate atopic dermatitis in ages 12 years and older have demonstrated systemic absorption, which justified the inclusion in the approved package insert (PI) for OPZELURA of a Boxed Warning advising of risks of serious infections, mortality, malignancy, major adverse cardiovascular events (MACE), and thrombosis. In addition to these potential risks, cytopenias (thrombocytopenia, anemia, and neutropenia) and lipid elevations are included in Section 5, Warnings and Precautions.

In this context, AEs of interest associated with the JAK inhibitor class were assessed in Study 305. Death, malignancies, MACE, and thrombosis were not reported. Lipids were not assessed in Study 305. Serious infections and laboratory abnormalities (specifically thrombocytosis, cytopenias, and liver enzyme elevations) are discussed below. In addition, due to uncertainties of the effect of topical ruxolitinib on bone growth originating from nonclinical studies, bone growth in the 2 to <12- year age group was assessed in Study 305.

**Serious Infections**

There were no TEAEs of tuberculosis, herpes zoster, or fungal infections reported in Study 305. Serious infections of COVID-19 and bacterial pneumonia were reported during the VC period of Study 305. These AEs are described below.

- **COVID-19:** A total of 13 cases of COVID-19 were reported during the VC period of Study 305. Six cases were reported in subjects treated with ruxolitinib 1.5% cream, 5 cases in subjects treated with ruxolitinib 0.75% cream, and 2 subjects treated with vehicle cream. Of the subjects treated with ruxolitinib cream, 3 in the 1.5% group and 2 in the 0.75% group were Grade 2. All subjects were able to recover within 13 days without a change in ruxolitinib dosing and continued in the study. The causality for all cases were assessed by the investigator as unlikely due to ruxolitinib.
- **Bacterial pneumonia:** There was a case of Grade 2 bacterial pneumonia reported in a 6-yo black, Hispanic male. The onset of bacterial pneumonia was on Day 12, the subject was treated and recovered by Day 20. The dose of ruxolitinib 1.5% cream was unchanged, and the bacterial pneumonia was assessed by the investigator as unlikely related to ruxolitinib. The subject completed the VC period of the study.

***Reviewer Comment:*** *In the cases above, the dosing of ruxolitinib cream was unchanged during their illness and the subjects recovered and continued in the study without further episodes. I agree with the investigators' assessments that these cases are unlikely related to ruxolitinib cream. However, based on the frequency of reporting during the VC period of the phase 3 study, higher incidences and IRs among participants on ruxolitinib cream versus vehicle cream, and the plausibility of a relationship to application of ruxolitinib cream, recommend labeling of COVID-19 under Adverse Reactions (see Table 30).*

Uncommon infections such as Grade 3 eczema herpeticum (previously discussed in Section 8.2.4 Serious Adverse Events) and Grade 2 eczema coxsackium (narrative below), both in 2-yo males with moderate AD applying ruxolitinib 1.5% cream, were also reported during the LTS period.

- **Subject** (b) (6) – 2 yo male with moderate AD (IGA 3, 5% BSA at baseline) on ruxolitinib 1.5% cream. The subject was randomized to ruxolitinib 1.5% cream during the VC period and continued into the LTS period. The % BSA affected at Week 8 (Day 55) was 0.5%, and the plasma PK concentration was 5.02 nM. The last dose of ruxolitinib cream prior to the TEAE was on Day 63 (during the LTS period) due to AD clearance. A Grade 2 TEAE of eczema coxsackium was reported starting on Day 66 and continued through Day 74. The investigator assessed the ruxolitinib cream use as possibly related and the dosing of ruxolitinib 1.5% cream was not restarted until Day 89 (after the subject was treated and recovered) when the AD flared. The subject continued to apply ruxolitinib 1.5% cream intermittently for the rest of the study (52 weeks) without further AEs.

***Reviewer Comment:*** *Patients with AD, especially children under the age of 5, are at higher risk for contracting infections, including disseminated viral infections when there is skin barrier disruption. In the case of eczema coxsackium, the %BSA affected immediately before the AE was minimal (0.5%) and ruxolitinib had already been stopped per protocol (<1 %BSA) when the eczema coxsackium was diagnosed. The investigator assessed ruxolitinib as possibly related; however, there was no corresponding action with the study drug because the drug had already been temporarily discontinued due to clearance of AD. The study drug was not restarted until approximately 2 weeks after the infection cleared. This reviewer would assess this TEAE as unlikely related to ruxolitinib use, because enterovirus (hand-foot-mouth disease) is most common in children under 5, pediatric patients with AD are at higher risk for disseminated viral infections, and the plasma PK level and %BSA affected was minimal at the time of diagnosis.*

**Thrombocytosis**

There were no TEAEs of thrombocytosis or abnormal lab values of elevated platelets reported in Study 305.

**Cytopenias**

Pediatric hematology lab values show considerable age-related variability, with values for children changing considerably from infancy to adulthood.

***Anemia***

There were no reported TEAEs of anemia and no Grade 3 or 4 episodes of decreased hemoglobin. Evaluation of grade shifts between the treatment arms demonstrates minimal differences.

**Table 33. Shift Summary of Hemoglobin Concentration Values in CTCAE Grade, Study 305, VC Period**

| Treatment Group | Baseline[a] | | Worst Postbaseline Value, n (%)[b] | | | | |
|---|---|---|---|---|---|---|---|
| | Grade | n (%) | Grade 0 | Grade 1 | Grade 2 | Grade 3 | Missing |
| Vehicle cream BID (N = 65) | Grade 0 | 62 (95.4) | 52 (83.9) | 1 (1.6) | 0 | 0 | 9 (14.5) |
| | Grade 1 | 1 (1.5) | 0 | 1 (100.0) | 0 | 0 | 0 |
| | Grade 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Grade 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Missing | 2 (3.1) | 2 (100.0) | 0 | 0 | 0 | 0 |
| | Total | 65 (100.0) | 54 (83.1) | 2 (3.1) | 0 | 0 | 9 (13.8) |
| Ruxolitinib 0.75% cream BID (N = 134) | Grade 0 | 131 (97.8) | 118 (90.1) | 2 (1.5) | 1 (0.8) | 0 | 10 (7.6) |
| | Grade 1 | 2 (1.5) | 0 | 1 (50.0) | 1 (50.0) | 0 | 0 |
| | Grade 2 | 1 (0.7) | 0 | 0 | 1 (100.0) | 0 | 0 |
| | Grade 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Missing | 0 | 0 | 0 | 0 | 0 | 0 |
| | Total | 134 (100.0) | 118 (88.1) | 3 (2.2) | 3 (2.2) | 0 | 10 (7.5) |
| Ruxolitinib 1.5% cream BID (N = 130) | Grade 0 | 125 (96.2) | 112 (89.6) | 5 (4.0) | 0 | 0 | 8 (6.4) |
| | Grade 1 | 5 (3.8) | 2 (40.0) | 2 (40.0) | 1 (20.0) | 0 | 0 |
| | Grade 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Grade 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Missing | 0 | 0 | 0 | 0 | 0 | 0 |
| | Total | 130 (100.0) | 114 (87.7) | 7 (5.4) | 1 (0.8) | 0 | 8 (6.2) |

Note: Grade 0 = below Grade 1 and any grade in the other direction.
[a] Percentages were calculated using the baseline total as the denominator.
[b] For each row, the percentages were calculated using the number of participants with the given grade at baseline as the denominator; the worst value on study was the worst grade observed postbaseline for a given participant.
Source: INCB 18424-305 CSR Table 3.3.3.1.

**Source: Applicant, Summary of Clinical Safety.**

***Thrombocytopenia***

There were no Grade 3 or 4 episodes of decreased platelets. Evaluation of grade shifts of platelet counts between the treatment arms demonstrates minimal differences. One 3 yo male in the roxuolitinib 0.75% group had a single incident of thrombocytopenia during the VC period (see below for case narrative).

**Narrative:**

- Subject (b) (6), 3-yo male with mild AD (IGA 2) in the ruxolitinib 0.75% group had a single incident of Grade 2 thrombocytopenia during the VC period. His baseline platelet count was 297 x $10^9$/L, then decreased to 66 x $10^9$/L at Week 2. He was not retested until Week 8, when his platelet count was 236 x $10^9$/L. The range of his platelet counts for the rest of the study through Week 52 was 236-462 x $10^9$/L. This decrease in platelets was not reported as a TEAE.

***Reviewer Comment:*** *The isolated incident of a Grade 2 decrease in platelets in a subject with otherwise normal platelet counts suggests that this may have been a lab error.*

**Table 34. Shift Summary of Platelet Count Values in CTCAE Grade, Study 305, VC Period**

| Treatment Group | Baseline[a] | | Worst Postbaseline Value, n (%)[b] | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Grade | n (%) | Grade 0 | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Missing |
| Vehicle cream BID (N = 65) | Grade 0 | 62 (95.4) | 53 (85.5) | 0 | 0 | 0 | 0 | 9 (14.5) |
| | Grade 1 | 1 (1.5) | 1 (100.0) | 0 | 0 | 0 | 0 | 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 (3.1) | 2 (100.0) | 0 | 0 | 0 | 0 | 0 |
| | Total | 65 (100.0) | 56 (86.2) | 0 | 0 | 0 | 0 | 9 (13.8) |
| Ruxolitinib 0.75% cream BID (N = 134) | Grade 0 | 132 (98.5) | 120 (90.9) | 1 (0.8) | 1 (0.8) | 0 | 0 | 10 (7.6) |
| | Grade 1 | 2 (1.5) | 1 (50.0) | 1 (50.0) | 0 | 0 | 0 | 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 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Total | 134 (100.0) | 121 (90.3) | 2 (1.5) | 1 (0.7) | 0 | 0 | 10 (7.5) |
| Ruxolitinib 1.5% cream BID (N = 130) | Grade 0 | 128 (98.5) | 117 (91.4) | 3 (2.3) | 0 | 0 | 0 | 8 (6.3) |
| | Grade 1 | 2 (1.5) | 2 (100.0) | 0 | 0 | 0 | 0 | 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 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Total | 130 (100.0) | 119 (91.5) | 3 (2.3) | 0 | 0 | 0 | 8 (6.2) |

[a] Percentages were calculated using the baseline total as the denominator.
[b] For each row, the percentages were calculated using the number of participants with the given grade at baseline as the denominator; the worst value on study was the worst grade observed postbaseline for a given participant.
Source: INCB 18424-305 CSR Table 3.3.3.1.
**Source: Applicant, Summary of Clinical Safety.**

***Neutropenia***

For assessment of neutropenia and lymphopenia in the pediatric AD population of Study 305 (both TEAEs and lab results), the Division of Non-Malignant Hematology (DNH) was consulted.

Because the reference ranges for "normal" vary considerably in the pediatric population, DNH provided the following tables for reference:

**Table 35. Cut-Offs for CTCAE Grade of Decreased Neutrophil and Lymphocyte Counts**

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Neutrophil count decreased | < 1.5 x 10e9 /L | <1.5 - 1.0 x 10e9 /L | <1.0 - 0.5 x 10e9 /L | <0.5 x 10e9 /L |
| Lymphocyte count decreased | <0.8 x 10e9 /L | <0.8 - 0.5 x 10e9 /L | <0.5 - 0.2 x 10e9 /L | 0.2 x 10e9 /L - |

**Source: Division of Non-malignant Hematology (DNH) consult**

**Table 36. Age-Specific Leukocyte Differential**

| | Total Leukocytes[a] | | Neutrophils[b] | | | Lymphocytes | | | Monocytes | | Eosinophils | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age | Mean | Range[c] | Mean | Range[c] | %[d] | Mean | Range[c] | %[d] | Mean | %[d] | Mean | %[d] |
| Birth | 18.1 | 9.0 to 30.0 | 11.0 | 6.0 to 26.0 | 61 | 5.5 | 2.0 to 11.0 | 31 | 1.1 | 6 | 0.4 | 2 |
| 12 h | 22.8 | 13.0 to 38.0 | 15.5 | 6.0 to 28.0 | 68 | 5.5 | 2.0 to 11.0 | 24 | 1.5 | 5 | 0.5 | 2 |
| 24 h | 18.9 | 9.4 to 34.0 | 11.5 | 5.0 to 21.0 | 61 | 5.8 | 2.0 to 11.5 | 31 | 1.1 | 6 | 0.5 | 2 |
| 1 wk | 12.2 | 5.0 to 21.0 | 5.5 | 1.5 to 10.0 | 45 | 5.0 | 2.0 to 17.0 | 41 | 1.1 | 9 | 0.5 | 4 |
| 2 wk | 11.4 | 5.0 to 20.0 | 4.5 | 1.0 to 9.5 | 40 | 5.5 | 2.0 to 17.0 | 48 | 1.0 | 9 | 0.4 | 3 |
| 1 mo | 10.8 | 5.0 to 19.5 | 3.8 | 1.0 to 9.0 | 35 | 6.0 | 2.5 to 16.5 | 56 | 0.7 | 7 | 0.3 | 3 |
| 6 mo | 11.9 | 6.0 to 17.5 | 3.8 | 1.0 to 8.5 | 32 | 7.3 | 4.0 to 13.5 | 61 | 0.6 | 5 | 0.3 | 3 |
| 1 y | 11.4 | 6.0 to 17.5 | 3.5 | 1.5 to 8.5 | 31 | 7.0 | 4.0 to 10.5 | 61 | 0.6 | 5 | 0.3 | 3 |
| 2 y | 10.6 | 6.0 to 17.5 | 3.5 | 1.5 to 8.5 | 33 | 6.3 | 3.0 to 9.5 | 59 | 0.5 | 5 | 0.3 | 3 |
| 4 y | 9.1 | 5.5 to 15.5 | 3.8 | 1.5 to 8.5 | 42 | 4.5 | 2.0 to 8.0 | 50 | 0.5 | 5 | 0.3 | 3 |
| 6 y | 8.5 | 5.0 to 14.5 | 4.3 | 1.5 to 8.0 | 51 | 3.5 | 1.5 to 7.0 | 42 | 0.4 | 5 | 0.2 | 3 |
| 8 y | 8.3 | 4.5 to 13.5 | 4.4 | 1.5 to 8.0 | 53 | 3.3 | 1.5 to 6.8 | 39 | 0.4 | 4 | 0.2 | 2 |
| 10 y | 8.1 | 4.5 to 13.5 | 4.4 | 1.8 to 8.0 | 54 | 3.1 | 1.5 to 6.5 | 38 | 0.4 | 4 | 0.2 | 2 |
| 16 y | 7.8 | 4.5 to 13.0 | 4.4 | 1.8 to 8.0 | 57 | 2.8 | 1.2 to 5.2 | 35 | 0.4 | 5 | 0.2 | 3 |
| 21 y | 7.4 | 4.5 to 11.0 | 4.4 | 1.8 to 7.7 | 59 | 2.5 | 1.0 to 4.8 | 34 | 0.3 | 4 | 0.2 | 3 |

*[a]Numbers of leukocytes are in thousands/mcL (10[9]/L).*
*[b]Neutrophils include band cells at all ages and a small number of metamyelocytes and myelocytes in the first few postnatal days.*
*[c]Ranges are estimates of 95% confidence limits.*
*[d]Percentages refer to differential counts.*
*Reprinted from Albritton[26] with permission.*

**Source: Mehta, et al. 1997.**

***Reviewer Comment:*** *In Table 34 above, Grade 1 neutropenia and Grade 1 lymphopenia do not specify a range of values, so by default any decrease of neutrophils below 1.5 x $10^9$/L is at least Grade 2. Table 35 highlights commonly-accepted ranges, whereas the ranges of normal as recorded in the ADLB differ slightly. For example, the lowest value of the "normal" range for lymphocytes for ages 2 to 11 is 1.5-3.0 x $10^9$/L for 2-10 year-olds, whereas the Applicant's low-normal value for lymphocytes in 2-6 years is 4.0 x $10^9$/L. However, when assigning Toxicity Grades to abnormal neutrophil and lymphocyte values, the Applicant used the values shown in Table 34.*

In Study 305, the mean change in neutrophil counts during the VC period were slight, ranging from -0.5 x $10^9$/L in subjects using ruxolitinib 0.75% to -0.1 x $10^9$/L in subjects using ruxolitinib 1.5%, while the subjects on vehicle were unchanged.

**Table 37. Mean and Median Neutrophil Counts ($10^9$/L), Study 305, VC Period**

| Treatment Group | N | Mean (SD) | Median (Min,Max) | Mean (SD) Change from Baseline |
|---|---|---|---|---|
| 0.75% BID | | | | |
| Baseline | 134 | 3.7 (1.8) | 3.5 (0.8, 10.6) | |
| Week 2 | 109 | 3.4 (1.7) | 3.1 (0.9, 10.3) | |
| Week 8 | 109 | 3.3 (1.5) | 3.0 (0.9, 8.3) | -0.5 (1.9) |
| 1.5% BID | | | | |
| Baseline | 130 | 3.3 (1.7) | 3.0 (1.3, 15.9) | |
| Week 2 | 105 | 3.0 (1.4) | 2.8 (1.1, 9.2) | |
| Week 8 | 108 | 3.3 (1.7) | 2.9 (0.7, 9.9) | -0.1 (2.0) |
| Vehicle BID | | | | |
| Baseline | 63 | 3.3 (1.6) | 2.9 (0.8, 8.6) | |
| Week 2 | 48 | 3.5 (1.7) | 3.4 (0.8, 10.0) | |
| Week 8 | 43 | 3.4 (1.7) | 3.2 (1.0, 8.9) | 0.0 (1.7) |

**Source: DNH Consult.**

An analysis of mean change from baseline by age group showed no clear trends, with the 0.75% strength producing the greatest change from baseline in the 2–6-year age group and the 1.5% strength producing the greatest change from baseline in the 7-11-year age group.

**Table 38. Mean and Median Neutrophil Counts (10^9/L) by Age Group, Study 305, VC Period**

| | Ages 2 to 6 | | | | Ages 7 to < 12 | | | |
|---|---|---|---|---|---|---|---|---|
| Treatment Group | N | Mean (SD) | Median (Min, Max) | Change from Baseline | N | Mean (SD) | Median (Min, Max) | Change from Baseline |
| 0.75% BID | | | | | | | | |
| Baseline | 66 | 3.6 (1.7) | 3.5 (1.1, 10.6) | | 68 | 3.7 (1.9) | 3.3 (0.8, 9.6) | |
| Week 2 | 61 | 3.4 (1.4) | 3.2 (1.3, 7.4) | | 48 | 3.4 (2.0) | 3.0 (0.9, 10.3) | |
| Week 8 | 59 | 3.3 (1.3) | 3.2 (0.9, 7.2) | -0.4 (1.3) | 50 | 3.3 (1.7) | 2.9 (1.1, 8.3) | -0.2 (2.3) |
| 1.5% BID | | | | | | | | |
| Baseline | 64 | 3.3 (1.2) | 3.1 (1.3, 7.3) | | 66 | 3.4 (2.1) | 2.8 (1.3, 16.0) | |
| Week 2 | 49 | 3.1 (1.5) | 2.8 (1.3, 8.8) | | 56 | 3.0 (1.4) | 2.8 (1.1, 9.2) | |
| Week 8 | 53 | 3.3 (1.3) | 3.1 (0.7, 7.0) | 0.1 (1.6) | 55 | 3.3 (2.0) | 2.6 (0.9, 9.9) | -0.6 (2.4) |
| Vehicle BID | | | | | | | | |
| Baseline | 32 | 3.4 (1.5) | 3.1 (0.8, 8.6) | | 31 | 3.3 (1.6) | 2.7 (1.1, 8.0) | |
| Week 2 | 26 | 3.6 (1.5) | 3.4 (0.8, 6.8) | | 22 | 3.4 (1.9) | 3.2 (1.0, 10.0) | |
| Week 8 | 24 | 3.9 (1.3) | 2.9 (1.0, 6.5) | 0.2 (1.0) | 19 | 4.0 (1.9) | 3.6 (1.2, 8.9) | 0.5 (2.2) |

**Source: DNH consult.**

**Table 39. Shift Summary of Neutrophil Count Values in CTCAE Grade, Study 305, VC Period**

| Treatment Group | Baseline[a] | | Worst Postbaseline Value, n (%)[b] | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Grade | n (%) | Grade 0 | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Missing |
| Vehicle cream BID (N = 65) | Grade 0 | 59 (90.8) | 47 (79.7) | 0 | 3 (5.1) | 0 | 0 | 9 (15.3) |
| | Grade 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Grade 2 | 3 (4.6) | 1 (33.3) | 0 | 1 (33.3) | 1 (33.3) | 0 | 0 |
| | Grade 3 | 1 (1.5) | 0 | 0 | 1 (100.0) | 0 | 0 | 0 |
| | Grade 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Missing | 2 (3.1) | 2 (100.0) | 0 | 0 | 0 | 0 | 0 |
| | Total | 65 (100.0) | 50 (76.9) | 0 | 5 (7.7) | 1 (1.5) | 0 | 9 (13.8) |
| Ruxolitinib 0.75% cream BID (N = 134) | Grade 0 | 129 (96.3) | 116 (89.9) | 0 | 5 (3.9) | 0 | 0 | 8 (6.2) |
| | Grade 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Grade 2 | 4 (3.0) | 1 (25.0) | 0 | 0 | 2 (50.0) | 0 | 1 (25.0) |
| | Grade 3 | 1 (0.7) | 0 | 0 | 0 | 0 | 0 | 1 (100.0) |
| | Grade 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Missing | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Total | 134 (100.0) | 117 (87.3) | 0 | 5 (3.7) | 2 (1.5) | 0 | 10 (7.5) |

| Treatment Group | Baseline[a] | | Worst Postbaseline Value, n (%)[b] | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Grade | n (%) | Grade 0 | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Missing |
| Ruxolitinib 1.5% cream BID (N = 130) | Grade 0 | 126 (96.9) | 108 (85.7) | 1 (0.8) | 8 (6.3%) | 1 (0.8) | 0 | 8 (6.3) |
| | Grade 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Grade 2 | 4 (3.1) | 3 (75.0) | 0 | 0 | 1 (25.0) | 0 | 0 |
| | Grade 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Grade 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Missing | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Total | 130 (100.0) | 111 (85.4) | 1 (0.8) | 8 (6.2) | 2 (1.5) | 0 | 8 (6.2) |

**Source: Applicant, Summary of Clinical Safety.**

Per consultation with DNH, for low neutrophil counts, in the vehicle control group, 4 subjects (6.2%) shifted to worse low neutrophil grade. In total, 3 subjects (4.6%) shifted from normal neutrophil count to grade 2 and 1 subject (1.5%) shifted from grade 2 baseline to grade 3. In the ruxolitinib 0.7% cream group, 7 subjects (5.2%) shifted to worse low neutrophil grade. In total, 5 subjects (3.7%) shifted from normal neutrophil count to grade 2 and 2 subjects (1.5%) shifted from grade 2 baseline to grade 3. In the ruxolitinib 1.5% cream group, 11 subjects (8.4% shifted to worse low neutrophil grade. In total, 1 subject (0.8%) with normal neutrophil count at baseline shifted to grade 1, 8 subjects (6.2%) shifted to grade 2, and 1 subject (0.8%) shifted to grade 3, along with 1 (0.8%) subject with grade 2 at baseline that shifted to grade 3.

*Reviewer's comment: Per discussion with the DNH consultants, although a higher percentage of shifts were observed in the ruxolitinib 1.5% cohort compared to the ruxolitinib 0.75% and vehicle cohorts, it is notable that the vehicle cohort had a higher percentage of shifts compared to the ruxolitinib 0.75% cohort. The small number of subjects also preclude definitive conclusions regarding the differences in shifts amongst the cohorts. In addition, when analyzing shifts, the consultants also evaluated the absolute numbers and the actual absolute neutrophil count (ANC) change may have been small (e.g., a subject's ANC may have shifted from grade 1 of 1050 to grade 2 of 990) which may reflect normal fluctuations.*

Subjects applying ruxolitinib 1.5% cream during the VC period and experiencing a Grade 3 decrease in neutrophils:

- **Subject** (b) (6), a 4 yo black female with moderate AD (BSA 20%), baseline 1.3 x $10^9$/L neutrophil count (Grade 2). She experienced a Grade 3 to 0.9 x $10^9$/L decrease at Week 8. These were reported as TEAEs (worsening neutropenia, leukopenia, and platelets). At that time, her AD BSA was 10% and her ruxolitinib plasma concentration was 21.1 nM. She continued applying ruxolitinib as needed and by Week 12, her AD BSA was 5%. Despite her ruxolitinib plasma concentration being higher (70.9nM), her lab values had normalized (neutrophil count 1.8 x $10^9$/L, lymphocytes 4.0 x $10^9$/L, leukocytes 6.8 x $10^9$/L, platelets 311 x $10^9$/L). at Week 12. By the time she discontinued the study on Day 154 due to withdrawal of consent (scheduling and time constraints per mother), her AD BSA was 4% and all of her cell counts continued to improve (except for lymphocytes which decreased to 3.3 x$10^9$/L, still in the normal range). No other TEAEs were reported for this subject while in the study.

- **Subject** (b) (6), an 11 yo black male with moderate AD (3.5% BSA), baseline 1.6 x $10^9$/L neutrophil count. He experienced a Grade 2 decrease to 1.3 x $10^9$/L at Week 2, and a Grade 3 decrease to 0.7 x $10^9$/L at Week 8 (Day 54). The drug was interrupted. The AD % BSA was 1%. The repeat neutrophil count of 1.9 x $10^9$/L was normal on Day 58. It is unclear when dosing resumed, as the subsequent study visit was Day 114. The investigator assessed the neutropenia as unlikely related due to the low-normal baseline value, and the minimal amount of ruxolitinib being applied. The neutrophil count on Day 114 was 1.1 x $10^9$/L. No TEAEs were reported.

Subjects applying ruxolitinib 0.75% cream during the VC period and experiencing a Grade 3 decrease in neutrophils:

- **Subject** (b) (6), an 8 yo black female with mild AD (BSA 0-5%), screening (D-15) 0.9 x $10^9$/L (Grade 3) and baseline 1.1 x $10^9$/L neutrophil count (Grade 2). Her neutrophil count ranged from 0.8-1.3 x $10^9$/L for her entire time during the study (52 weeks). The subject also Grade 2 AEs of nasopharyngitis from D25-27 and streptococcal sore throat from D106-113. In both cases, the dose of ruxolitinib cream was unchanged. The Applicant reported that at D15, her neutrophil count was at its highest (1.3 x $10^9$/L, increased from baseline) with BSA 1% and ruxolitinib plasma concentration 10.5nM. In contrast, her neutrophil count was at its lowest (0.8 x $10^9$/L) on D85, during the LTS period when her BSA was 0% and she was not applying ruxolinitib cream (plasma level 1.99nM). The investigator assessed the neutropenia as possibly related, but the Applicant's conclusion was that there was no correlation between the use of ruxolitinib and the subject's pre-existing neutropenia (which remained between 0.9-1.3 x $10^9$/L the entire duration of the study).
- **Subject** (b) (6), a 6 yo black female with moderate AD (IGA 3, BSA 12%), her neutrophil count at screening 1.5 x $10^9$/L. On Day 1, at baseline before the drug was started, her neutrophil count had decreased to 1.1 x $10^9$/L (Grade 2). The nadir of her neutrophil count was at Week 2, when it was 0.9 x $10^9$/L (Grade 3). Her BSA was 7% and ruxolitinib plasma concentration was 12.1 nM. Because this neutropenia was not deemed a TEAE, there was no investigator or Applicant assessment of relatedness to ruxolitinib. By Week 8, her AD %BSA was 4% and her neutrophil count had returned to normal (1.5 x $10^9$/L). The drug dose was unchanged during the VC period.

During Study 305, there were 3 subjects with decreases in white blood cells reported by the Applicant as TEAEs, all in the ruxolitinib 1.5% cream group. During the VC period, one subject each was reported with neutropenia (of note, 1 subject in the vehicle group also reported a TEAE of neutropenia), leukopenia, and white blood cell decreased. The narratives of these subjects are presented below.

**Narratives:**

- **Subject** (b) (6), a 2-yo Black male with mild AD (IGA 2), applied ruxolitinib 1.5% cream during the VC and LTS periods. The subject had no reported medical history or prior/concomitant medications. During the VC period, the subject applied the cream BID to 6.5% BSA with plasma levels of 19.8nM at Week 2 and below quantifiable limits (BLQ) at Week 8. The Applicant reported that at most clinic visits during the 44-week LTS period the participant's AD was clear,

and never affected more than 2.5% BSA. At Day 15, the subject had a Grade 2 neutropenia when the neutrophil count dropped from 1.9 x $10^9$/L at baseline to 1.1 x $10^9$/L (lower limit normal 1.5 x $10^9$/L). It recovered to 1.6 x $10^9$/L by Day 20 on retest, without interruption of the study drug. The neutrophil count dropped to 1.2 x $10^9$/L (Grade 1 neutropenia) on SD 54. The subject's AD at this time was clear (0% BSA). Per the protocol for the LTS, the subject stopped applying cream due to clearance and restarted at Day 58 when the AD recurred (unknown BSA since it was between clinic visits). During the remainder of the LTS, the subject had intermittent episodes of clearance with no cream applied when his skin was clear, but had 1 episode of lymphopenia (Grade 1, SDs 116 to 162) and 1 episode of neutropenia (Grade 1, SDs 243 to 389) during the LTS phase. Drug dosage was unchanged for all of these AEs, and the subject recovered in all episodes. The subject completed the 52-wk study, and the neutrophils were at 3.9 $10^9$/L at the safety follow-up (1 mo after last dose). Other AEs reported: Hyperkalemia (Grade 1, SDs 82 to 162, recovered). The investigator assessed the study drug as possibly related to the episodes of neutropenia during the VC period, but unlikely related to the lymphopenia and neutropenia during the LTS period. The Applicant attributed these AEs to fluctuations in the neutrophil count in a subject with a baseline low-normal neutrophil count.

- **Subject** (b) (6), a 9 yo white female with mild AD (IGA 2) on ruxolitinib 1.5% cream during the VC period and continuing during the LTS period. At baseline, the subject's white blood cell count was 5.3 x $10^9$/L (reference range 5-14.5 x $10^9$/L). The subject experienced an episode of white blood cell decreased to 3.3 x $10^9$/L (neutrophils 1.5 x $10^9$/L, lymphocytes 1.5 x $10^9$/L, both normal) at the end of the VC period (Week 8, SD 57). Plasma concentrations were 29.0 nM at Day 15 and 15.5 nM at Day 58. The leukopenia (3.3-3.6 x $10^9$/L) continued into the LTS period until Week 16 (SD 114), when it was normal at 5.4 x $10^9$/L. The participant's AD was mostly clear at clinic visits during the LTS period, with a maximum of 2.0% affected BSA. There were no other episodes of leukopenia for the duration of the LTS period, except at the last study visit on SD 366, when the leukocytes were 3.7 x $10^9$/L. This result was not considered clinically significant by the investigator because there was no associated AE.
- **Subject** (b) (6), a 4 yo white male with moderate AD (IGA 3,20% BSA at baseline) and seasonal allergies on ruxolitinib 1.5% cream during the VC period. At baseline, prior to applying the drug, the subject had TEAE reported of lymphopenia (3.2 x $10^9$/L; reference range 4-10.5 x $10^9$/L), and experienced worsening lymphopenia (2.6 x $10^9$/L, Grade 2) at Week 2. Plasma levels of ruxolitinib were 4.80 nM at Week 2. The last application of the study drug was on Day 22 (Week 3). The drug was interrupted, and the subject's mother withdrew consent, stating that she no longer wanted the subject to participate in the study but did not specify a reason. At the time of withdrawal of consent, the lymphopenia was ongoing and further decreased to 2.4 x $10^9$/L when tested 14 days after discontinuation. During the study, the leukocytes and neutrophils remained in the normal range. No other AEs were reported. The investigator considered the lymphopenia to be pre-existing and unrelated to ruxolitinib 1.5% cream.
- **Subject** (b) (6), an 11 yo Hispanic female with mild AD (IGA 2) at baseline on ruxolitinib 1.5% cream during the VC period and continuing during the LTS period. At baseline, the subject's leukocytes were 5.8 x $10^9$/L (reference range 5-14.5 x $10^9$/L), On SD 14, the subject had Grade 1 leukopenia of 3.4 x $10^9$/L (and lymphopenia at 1.2 x $10^9$/L). The leukocytes (6.3 x $10^9$/L) and lymphocytes (2.4 x $10^9$/L) were back in the normal range on retest on SD 28. Neutrophils were normal for the duration of the study. The drug was unchanged. The investigator assessed the

study drug as unlikely related to the leukopenia.

***Lymphopenia***

**Table 40. Mean and Median Lymphocyte Counts ($10^9$/L), Study 305, VC Period**

| Treatment Group | N | Mean (SD) | Median (Min, Max) | Change from Baseline |
|---|---|---|---|---|
| 0.75% BID | | | | |
| Baseline | 134 | 3.0 (0.9) | 3.0 (1.2, 6.2) | |
| Week 2 | 109 | 3.0 (0.9) | 2.9 (1.4, 6.4) | |
| Week 8 | 109 | 3.0 (0.7) | 22.9 (0.5, 6.0) | 0.0 (0.8) |
| 1.5% BID | | | | |
| Baseline | 130 | 3.8 (1.1) | 3.0 (1.2, 7.6) | |
| Week 2 | 105 | 3.3 (1.3) | 3.4 (1.0, 7.5) | |
| Week 8 | 108 | 3.1 (1.3) | 2.8 (1.1, 7.2) | -0.1 (0.6) |
| Vehicle BID | | | | |
| Baseline | 63 | 3.0 (1.3) | 2.8 (0.9, 7.6) | |
| Week 2 | 48 | 3.2 (1.3) | 2.8 (1.5, 7.0) | |
| Week 8 | 43 | 3.1 (1.3) | 2.8 (1.1, 7.9) | -0.4 (1.1) |

**Source:** Reviewer generated, adapted from INCB 18424-305 CSR
**Abbreviations:** BID, twice a day; N, number of patients; SD, standard deviation; min, minimum;max, maximum

**Table 41. Mean and Median Lymphocyte Counts (10^9/L) by Age Group, Study 305, VC Period**

| Treatment Group | Ages 2 to 6 | | | | Ages 7 to < 12 | | | |
|---|---|---|---|---|---|---|---|---|
| | N | Mean (SD) | Median (Min, Max) | Change from Baseline | N | Mean (SD) | Median (Min, Max) | Change from Baseline |
| 0.75% BID | | | | | | | | |
| Baseline | 66 | 2.6 (0.7) | 2.5 (1.2, 4.7) | | 68 | 3.4 (1.0) | 3.4 (1.4, 6.2) | |
| Week 2 | 61 | 2.6 (0.6) | 2.6 (1.4, 4.1) | | 48 | 3.4 (1.1) | 3.3 (1.4, 6.4) | |
| Week 8 | 59 | 2.7 (0.7) | 2.7 (0.5, 4.4) | 0.0 (0.8) | 50 | 3.3 (1.0) | 3.3 (1.5, 6.0) | -0.1 (0.9) |
| 1.5% BID | | | | | | | | |
| Baseline | 64 | 2.7 (0.8) | 2.5 (1.2, 4.4) | | 66 | 3.6(1.3) | 3.5 (1.4, 7.6) | |
| Week 2 | 49 | 2.7 (1.0) | 2.5 (1.1, 6.5) | | 56 | 3.8 (1.4) | 3.8 (1.0, 7.5) | |
| Week 8 | 53 | 2.6 (0.8) | 2.5 (1.1, 4.9) | -0.1 (0.6) | 55 | 3.6 (1.5) | 3.6 (1.1, 7.2) | 0.0 (1.2) |
| Vehicle BID | | | | | | | | |
| Baseline | 32 | 2.4 (0.5) | 2.4 (0.9, 3.4) | | 31 | 3.7 (1.6) | 3.1 (1.0, 7.6) | |
| Week 2 | 26 | 2.5 (0.6) | 2.6 (1.5, 3.8) | | 22 | 4.0 (1.4) | 3.7 (1.6, 7.0) | |
| Week 8 | 24 | 2.4 (0.6) | 2.5 (1.1, 3.5) | 0.0 (0.4) | 19 | 4.0 (1.5) | 3.6 (2.4, 7.9) | 0.5 (1.1) |

**Source:** Reviewer generated, adapted from INCB 18424-305 CSR
**Abbreviations:** BID, twice a day; N, number of patients; SD, standard deviation; min, minimum;max, maximum

**Table 42. Shift Summary of Lymphocyte Count Values in CTCAE Grade, Study 305, VC Period**

| Treatment Group | Baseline[a] | | Worst Postbaseline Value, n (%)[b] | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Grade | n (%) | Grade 0 | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Missing |
| Vehicle cream BID (N = 65) | Grade 0 | 42 (64.6) | 34 (81.0) | 3 (7.1%) | 0 | 0 | 0 | 5 (11.9) |
| | Grade 1 | 21 (32.3) | 5 (23.8) | 12 (57.1) | 0 | 0 | 0 | 4 (19.0) |
| | 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 (3.1) | 2 (100.0) | 0 | 0 | 0 | 0 | 0 |
| | Total | 65 (100.0) | 41 (63.1) | 15 (23.1) | 0 | 0 | 0 | 9 (13.8) |
| Ruxolitinib 0.75% cream BID (N = 134) | Grade 0 | 101 (75.4) | 82 (81.2) | 11 (10.9) | 1 (1.0) | 0 | 0 | 7 (6.9) |
| | Grade 1 | 33 (24.6) | 6 (18.2) | 24 (72.7) | 0 | 0 | 0 | 3 (9.1) |
| | 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 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Total | 134 (100.0) | 88 (65.7) | 35 (26.1) | 1 (0.7) | 0 | 0 | 10 (7.5) |
| Ruxolitinib 1.5% cream BID (N = 130) | Grade 0 | 93 (71.5) | 72 (77.4) | 14 (15.1) | 0 | 0 | 0 | 7 (7.5) |
| | Grade 1 | 37 (28.5) | 5 (13.5) | 31 (83.8) | 0 | 0 | 0 | 1 (2.7) |
| | 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 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Total | 130 (100.0) | 77 (59.2) | 45 (34.6) | 0 | 0 | 0 | 8 (6.2) |

**Source:** Applicant Information Request Response 28 July 2025
**Abbreviations:** CTCAE, Common Terminology Criteria for Adverse Events; BID, twice a day

Looking at the tables above (especially the lymphocyte shift table), it appears that many subjects (23.1-34.6%) experienced Grade 1 fluctuations in their lymphocyte counts. However, examination of the actual lymphocyte lab data reveals that the vast majority of these "Grade 1 decreases" were values between 1.0-4.0 x $10^9$/L, which would be considered normal according to the CTCAE grades for lymphopenia (Grade 1 = <0.8 x $10^9$/L) in Table 34. Only 1 subject ( (b) (6)), an 8 yo female on ruxolitinib 0.75% cream experienced a Grade 2 decrease of 0.5 x $10^9$/L at Week 8, starting from a baseline of 2.2 x $10^9$/L. However, by Week 12, her lymphocyte improved to 2 x $10^9$/L by Week 12. For the rest of the study, her lymphocyte counts ranged from 1.4-2.3 x $10^9$/L.

The DNH consultant also assessed episodes of lymphopenia in Study 305. Per the reviewer, "the laboratory data did not reveal any clinically meaningful differences in mean change from baseline in lymphocyte count between treatment and vehicle arm and between treatment arms (0.75% cream vs. 1.5% cream) during the vehicle-controlled treatment period (Table 39) and the long-term portion of

the study. No clinically meaningful differences in mean change from baseline were identified between the younger (2 to 6) and older (7 to < 12) age groups (Table 40). Of the five participants in Study 305 that were identified as having lymphopenia TEAE, none led to drug discontinuation or interruption. Lymphopenia has typically been defined in older children as an absolute lymphocyte count of < 1.5 x $10^9$/L and <4.5 x $10^9$/L in infants (Régent et. al, 2012). None of the participants in this study met this definition. Furthermore, several participants had viral illnesses preceding or in close proximity to their low lymphocyte count making it difficult to attribute the AE to the study drug."

***Reviewer's Comment:*** *Of the subjects experiencing white blood cell count decreases during the VC period, the majority experienced decreases in neutrophil count. The neutrophil count decreases occurring in Study 305 (assessing by ADLB, not TEAEs) affected 8 (7.7%) subjects applying ruxolitinib 1.5% cream and 7 (5.2%) subjects applying ruxolitinib 0.75% cream. Both of these incidence rates were lower than that of the vehicle arm – 6 (9.2%) subjects. The TEAE incidence rates were even lower – 0.8% (1 subject) for the ruxolitinib 1.5%, 0% for the ruxolitinib 0.75% arm, and 1.5% (1 subject) for the vehicle arm. While both strengths of ruxolitinib cream resulted in a slight decrease on some subjects' neutrophil counts, there were no subjects who developed grade 4 neutropenia (ANC < 0.5 x $10^9$/L). Subjects who experienced more persistent decreases in neutrophils were most frequently those whose baseline readings for the white blood cells were low to low-normal. More importantly, subjects with the lowest neutrophil counts experienced no clinical manifestations of neutropenia (i.e., serious bacterial and/or fungal infections). There was no clear correlation of use of a particular strength or age group with a defined level of increased/decreased risk amongst the subjects with reported neutropenia. There also seems to be low correlation between episodes of neutropenia/lymphopenia, BSA involvement, frequency of medication application, and plasma PK concentrations. Therefore, this reviewer's opinion is that the current guidance in the PI regarding cytopenias described in Section 5 (Perform CBC monitoring as clinically indicated) is adequate to inform risk.*

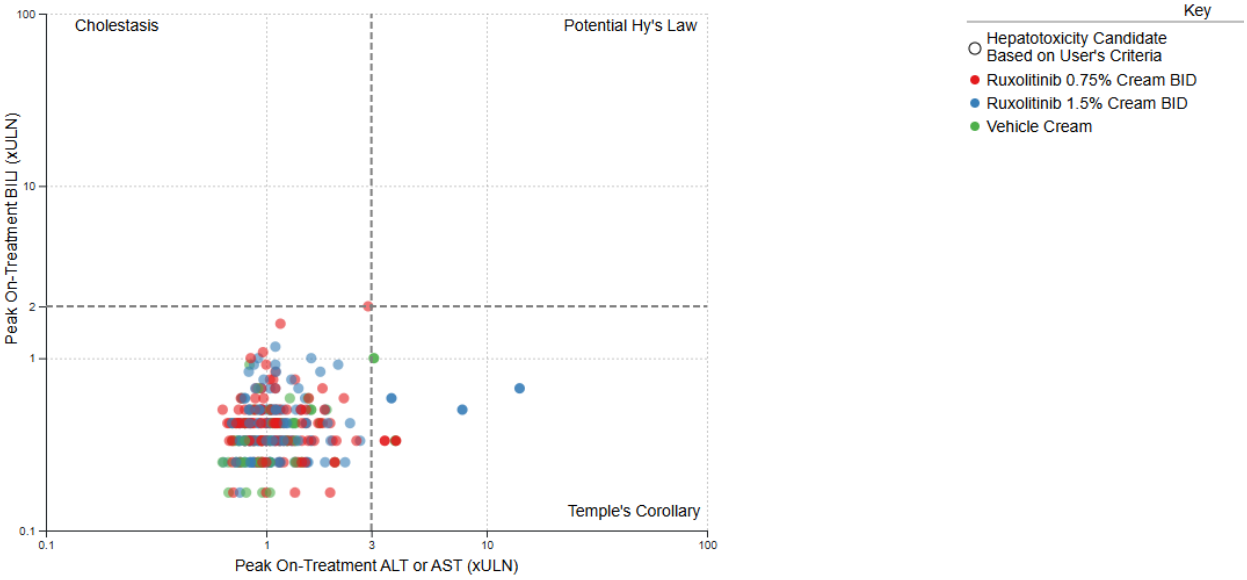
*This reviewer's conclusions are aligned with the specialist consult review of these laboratory results by the Division of Non-malignant Hematology (DNH). In their DAARTS review dated August 6, 2025, the reviewer stated, "The data provided does not raise a new concern of clinically significant neutropenia or lymphopenia, compared to what was observed in the adult studies," and "the clinical data did not demonstrate a significant difference in cytopenias observed between [the] two age groups or strengths." The DNH reviewer also noted the common fluctuation of neutrophil and lymphocyte counts for any person. Additionally, "The prevalence of neutropenia (absolute neutrophil count (ANC) < 1.5 x $10^9$/L) is reported to be 4.5% among Black individuals…Lower neutrophil counts linked with African ancestry is associated with a polymorphism in the DARC gene and…do not have an increased risk of infection." The reviewer further commented that "Lymphopenia has typically been defined in older children as an absolute lymphocyte count of < 1.5 x 10^9/L and <4.5 x 10^9/L in infants…None of the participants in this study met this definition [including Subject* (b) (6) *]." The DNH reviewer recommends no changes to the current OPZELURA label, i.e., that "current [published] labeling adequately addresses the risk of cytopenias and CBC monitoring should be based on the clinical picture." However, the DNH reviewer did recommend an additional statement in Section 14 that "participants with cytopenias at screening defined as hemoglobin < 10 g/dL, absolute neutrophil count (ANC) < 1000/µL, and platelet count < 100,000/ µL were excluded from the trials… [and] that the impact on blood counts of ruxolitinib 1.5% cream in this population has not been studied." I concur with these recommendations.*

**Liver Enzymes**

For assessment of abnormal liver enzymes in the pediatric AD population of Study 305 (both TEAEs and lab results), the Drug-Induced Liver Injury (DILI) team was consulted.

There were several subjects in Study 305 who experienced significant increases in ALT/AST: 2 subjects (1.6%) applying ruxolitinib 0.75% cream, 3 (2.4%) applying ruxolitinib 1.5% cream, and 2 subjects (3.5%) were applying vehicle cream. The Applicant did not attribute any of these liver enzyme elevations to ruxolitinib 0.75% or 1.5% cream application.

**Figure 7. Liver Enzyme Elevations in Subjects with Mild to Moderate AD, Study 305, VC Phase**




Source: OCS Analysis Studio, Hepatic Explorer.
Filters: None.
*Hepatotoxicity Candidates: ALT or AST >= 3*ULN; BILI >= 2*ULN (0-30 days forward); ALP < 2*ULN (0-999 days backward).
*Missing ULN values are imputed as the weighted mean of the present ULN values per lab test code per subject.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BILI, bilirubin; ULN, upper limit of normal.

Patients in Each Quadrant for Hepatocellular DILI Screening Plot

| Quadrant | Ruxolitinib 0.75% Cream BID N = 126 n (%) | Ruxolitinib 1.5% Cream BID N = 123 n (%) | Vehicle Cream N = 57 n (%) |
|---|---|---|---|
| Potential Hy's Law (right upper) | 0 (0%) | 0 (0%) | 0 (0%) |
| Cholestasis (left upper) | 1 (0.8%) | 0 (0%) | 0 (0%) |
| Temple's Corollary (right lower) | 2 (1.6%) | 3 (2.4%) | 2 (3.5%) |
| **Total** | **3 (2.4%)** | **3 (2.4%)** | **2 (3.5%)** |

Source: OCS Analysis Studio, Hepatic Explorer.
Abbreviations: DILI, drug-induced liver injury; N, number of patients in treatment arm; n, number of patients meeting criteria.

Narratives for subjects applying ruxolitinib 1.5% cream:

- **Subject** (b) (6), an 11 yo black female with mild AD (IGA 2, BSA 5%) and obesity (BMI: 32.0 kg/m2, 167.6 cm, 89.8 kg), applied ruxolitinib 1.5% cream BID during the VC and LTS periods. During the VC period, her ALT was 21 U/L (normal 5-20 U/L) and her AST 37 (normal 0-36 U/L) at baseline. At Week 2, there was a transient Grade 1 increase to ALT 35 U/L, with a decrease to ALT 14 U/L by Week 8. At the end of the VC, the subject's AD was clear, so she discontinued use of ruxolitinib 1.5% cream per protocol. During the LTS, the subject's AD remained clear, so she did not apply ruxolitinib 1.5% cream. Her plasma PK was 0.00 nM, taken at Week 40. During the LTS, the subject's ALT ranged from 12-18 U/L, with the exception of a period from Weeks 32-48, when her ALT peaked at 74 U/L (Grade 2) with a Grade 1 increase of her AST to 37 (normal 0-36) at Week 40. During this period of ALT elevation, the subject reportedly took several cold medications containing acetaminophen (paracetamol). Bilirubin levels were normal during the study.
- **Subject** (b) (6), a 7 yo Asian male with moderate AD (IGA 3, BSA 8%), asthma, allergic rhinitis, and obesity (BMI 22.5 kg/m2, 131.6 cm, 39 kg, >95$^{th}$ percentile) applied ruxolitinib 1.5% cream BID during the VC and LTS periods. During the VC period, his ALT was 31 U/L (Grade 1, normal 15-25 U/L) and AST 28 U/L (normal 0-41 U/L). On repeat testing, the ALT was 27 U/L. For the remainder of the VC and until Week 40 of the LTS period, both the ALT and AST were mostly in the normal range. At Week 40, the subject's ALT was 105 U/L (Grade 2), which the investigator attributed to taking cefdinir to treat a streptococcal pharyngitis infection for approx. 9 days prior to the lab draw. A repeat test at approximately Week 44 was 31 U/L. At Week 48, when the AD BSA was 1.5% and plasma PK concentration was 0 nM, both the ALT (353 U/L, Grade 3) and AST (121 U/L, Grade 1) were elevated. The investigator reported no clinical symptoms and attributed the elevated liver enzymes to obesity and non-alcoholic fatty liver disease (NAFLD). He was referred to his primary care provider, who recommended more activity and a change in dietary habits. At Week 52, with no change to ruxolitinib application, both his ALT and AST were 20 U/L.
- **Subject** (b) (6), a 7 yo black female with moderate AD (IGA 3, BSA 20%), asthma, allergies,

herpes simplex (all ongoing at study initiation), and obesity (BMI 21.6 kg/m2, 126.5 cm, 36.9 kg, 98$^{th}$ percentile) applied ruxolitinib 1.5% cream BID during the VC and LTS periods. The subject's BSA during the study was initially 20% but decreased to clear by Week 12, and ranged from 0-2% until Week 28, when it increased to 13.7%. It decreased to 1.1% by Week 32. The last plasma PK concentration level was 10nM at Week 24. The subject applied ruxolitinib cream BID continuously during the VC period and intermittently during the LTS period. The last day of ruxolitinib 1.5% cream application was Day 234 (Week 32).

At baseline, the subject's ALT was 42 U/L (normal 5-25 U/L) and AST 37 (normal 0-40). She had Grade 1 elevations at Week 2 in both ALT (58 U/L) and AST (60 U/L) that were in the normal range upon retest. At Week 16, the subject's ALT increased to 51 U/L, and by Week 24, both the ALT and AST continued to increase:

- Week 24 – ALT 85 U/L, AST 63 U/L
- Week 32 – ALT 100 U/L, AST 58 U/L [ruxolitinib discontinued]
- Unscheduled (approx Week 36) – ALT 194 U/L, AST 101 U/L
- Early termination (approx. Week 40) – ALT 327 U/L, AST 163 U/L

While the subject was on ruxolitinib 1.5% cream, her LDH was 280 U/L (normal 140-280 U/L) at baseline and remained at the high end of normal or mildly elevated 248-294 U/L) during her time in the study. She also had an elevated eosinophil/leukocyte ratio (a marker of inflammation) of 14.8% at screening and 9% at baseline before starting ruxolitinib. Prior to early termination (approx. Week 37), the subject was referred to a hepatologist for evaluation of her elevated liver enzymes. The workup revealed the following: negative for viral hepatitis (Hep A, B, C), negative for anti-smooth muscle antibody, negative for EBV; normal abdominal/liver ultrasound; normal abdominal CT scan; elevated ferritin, positive ANCA, positive ANA (1:40), and elevated INR. After ruxolitinib discontinuation, additional liver enzyme testing by the hepatologist showed that the ALT/AST elevations continued, with the last known values of ALT 260 U/L and AST 146 U/L at approx. what would have been approx. Week 44. A subsequent liver biopsy was consistent with autoimmune hepatitis. The pathologist noted the history of treatment with ruxolitinib and stated in the report that an overlap of histologic findings exists, and clinical correlation is needed.

With the results of the workup, the hepatologist considered the possibility of drug (ruxolitinib)-induced liver injury, but ultimately diagnosed the subject's condition as autoimmune hepatitis due to the pre-existing elevation of liver enzymes prior to drug administration and the stability of these labs during the period of highest drug application (during the VC period).

Narratives for subjects applying ruxolitinib 0.75% cream:

- **Subject** (b) (6), a 4 yo white male with mild AD (IGA 2, BSA 7%), attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and developmental delay applied ruxolitinib 0.75% cream BID during the VC and LTS periods. At baseline, the subject's ALT was 17 U/L (normal 0-20 U/L) and AST was 36 U/L (normal 0-47 U/L). The subject had transient elevations of both AST (highest 69 U/L, Grade 2, at Week 2; others were 21 U/L and 23 U/L) and ALT (55 U/L, Grade 1, at Week 2). At Week 2, the %BSA affected was 1.5% and the plasma ruxolitinib concentration was 20.2 nM. Otherwise, they were in the normal range. None of these liver enzyme elevations were reported as AEs or attributed to ruxolitinib cream use. The Applicant

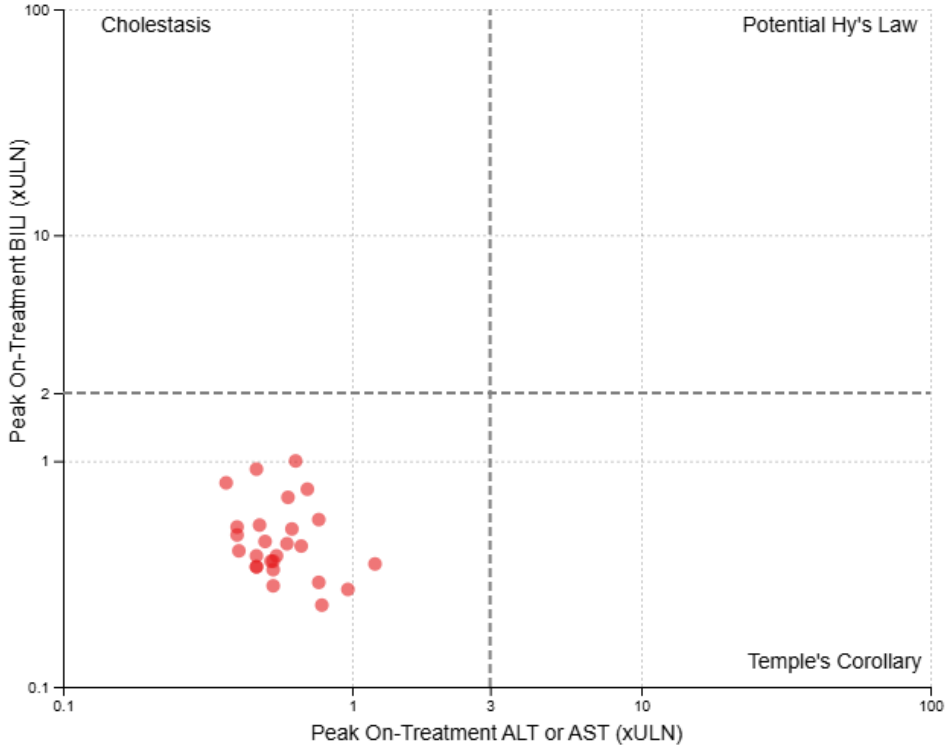
noted that transient liver enzyme elevations have been reported as a post-marketing AE in the label for methylphenidate, one of the subject's concomitant medications to treat ASD, and believes this medication is a more likely etiology.

- **Subject** (b) (6), a 4 yo white female with moderate AD (IGA 3, BSA 10%) and obesity (BMI 23.8 kg/m2) applied ruxolitinib 0.75% cream BID during the VC and LTS periods. At baseline, her ALT was 25 U/L (normal 5-25 U/L). Her AST remained in the normal range during the study. The subject applied ruxolitinib 0.75% cream BID through the VC and continuing through Week 12, when her plasma ruxolitinib concentration was 9.61 nM (peak 27.6 nM at Week 8). During this time, her liver enzymes were normal. By Week 16, her involved BSA was 4%. At Week 32, her ALT was 97 U/L (Grade 2), and upon repeat testing a week later, was 34 U/L (Grade 1). At Week 40, her ALT was 37 U/L (Grade 1). During this time, her involved BSA ranged from 1-4%, with the only plasma PK taken at Week 48 when it was 39.8nM. The investigator attributed the Week 32 Grade 2 increase to hemolysis of the blood sample, due to corresponding increases in the AST, ALP, and potassium levels from the same sample and to the drop closer to baseline upon testing one week later.

***Reviewer Comment:*** *In all of the cases described above (except for Subject* (b) (6) *with autoimmune hepatitis), the prescribed application schedule (BID during the VC period, as needed during the LTS period) for ruxolitinib 0.75% or 1.5% cream was maintained despite the lab abnormalities.*

During Study 109 (the max use study), there were no reports of liver enzyme elevations. See Figure 8.

**Figure 8. Liver Enzyme Elevations in Subjects with Moderate to Severe AD, Study 109**




Source: OCS Analysis Studio, Hepatic Explorer.
Filters: FASFL = "Y".
*Hepatotoxicity Candidates: ALT or AST >= 3*ULN; BILI >= 2*ULN (0-30 days forward); ALP < 2*ULN (0-999 days backward).
*Missing ULN values are imputed as the weighted mean of the present ULN values per lab test code per subject.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BILI, bilirubin;
ULN, upper limit of normal.

Key

○ Hepatotoxicity Candidate Based on User's Criteria

● Ruxolitinib 1.5%

***Reviewer Comment:*** *The incidence of liver enzyme elevation in subjects applying ruxolitinib 1.5% or 0.75% was lower than that of vehicle (2.4%, 1.6%, 3.5% respectively). In addition, in each of the cases noted above, there was no correlation between the lab elevations and % BSA affected/amount of ruxolitinib applied, and plasma PK concentrations, as the subjects were applying no to minimal ruxolitinib around the time of enzyme elevation. In several cases, there was a long latency between the last application of ruxolitinib cream and the liver enzyme elevations. In the cases of concurrent use of ruxolitinib, application was not interrupted, and the liver enzymes returned to the normal range. Also, there were concurrent confounding factors in each of the cases (e.g., cold medications containing acetaminophen, upper respiratory infections, obesity, or pre-existing lab abnormalities at baseline) that provide a more likely explanation than ruxolitinib as related. Finally, although the subject numbers were low, there were no reports of liver enzyme elevations during the length of Study 109 (52 weeks), the max use study in subjects with moderate to severe AD and %BSA involvement of >35% (some as high 92% BSA involvement at baseline). These reviewer's conclusions align with that of those of the Drug-Induced Liver Injury (DILI) team, who was consulted for specialist evaluation of liver enzyme*

*evaluations in Studies 109 and 305. The DILI team stated that there was "substantially lower systemic exposure with topical compared to oral [i.e., JAKAFI] administration," and "lack of reactive metabolite formation supports the lack of a substantial liver injury risk for this supplemental NDA. Therefore, concerns for hepatotoxicity should not hold up approval." The DILI team further recommends "no additional liver injury language beyond current discussion of hepatitis B and C risk" in the current OPZELURA label, nor do they recommend post-market requirements regarding hepatotoxicity risk. See the consult reviews dated August 13 and 27, 2025, in DAARTS for more detail.*

***Reviewer Recommendations regarding labeling of AESIs specific to JAKis**: After an assessment of incidences of serious infections, cytopenias, and abnormal liver enzymes in the subjects of Study 305, this reviewer has the following recommendations for the PI for Opzelura (ruxolitinib) 1.5% cream:*

- *For patients with mild to moderate AD ages 2 to <12 years, frequent and/or continuous application of ruxolitinib 1.5% cream may result in systemic absorption and the potential for adverse reactions known to occur with JAKis. To decrease the risk of high levels of ruxolitinib plasma concentration, the current limitations of use (for patients with mild to moderate AD ages 12 years and older) are limitation of use to <20% and no more than 60 gm in one week or 100gm in 2 weeks. To further minimize this risk in AD patients 2 to <12 yrs, the following additions are recommended:*
    - *Do not apply occlusive dressings over areas where Opzelura has been applied.*
    - *Do not use more than 60gm in 2 weeks.*
- *The current boxed warnings and Section 5. Warnings and Precautions detail the potential adverse reactions possible with the use of Opzelura. Assessment of TEAEs in Study 305, including serious infections, cytopenias, and abnormal liver enzymes, did not demonstrate any new or increased safety signals in AD patients 2 to <12 years beyond what is described in the current label.*
- *Regarding the potential risk for cytopenias, the current guidance in the PI recommends that prescribers "perform CBC monitoring as clinically indicated." The overall incidence rate of cytopenias (including neutropenias) in Study 305 were low (5.2-7.7%), less than the incidence rate in subjects applying vehicle (9.2%), were not sustained despite drug continuation, and did not result in clinically significant manifestations. Therefore, the current guidance on the PI is recommended as adequate to inform risk.*
- *I agree with the DNH consultant's recommendation that the following statement be added to Section 14 that "participants with cytopenias at screening defined as hemoglobin < 10 g/dL, absolute neutrophil count (ANC) < 1000/µL, and platelet count < 100,000/ µL were excluded from the trials… [and] that the impact on blood counts of ruxolitinib 1.5% cream in this population has not been studied."*

### 8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Not applicable.

### 8.2.7. Safety Analyses by Demographic Subgroups

Treatment-emergent AEs were analyzed by age group (2 to < 7 years and 7 to < 12 years), sex, and race (White and Black or African American). There were no patterns suggestive of meaningful differences in the safety profile of ruxolitinib cream for any subgroups evaluated. The primary limitation of safety evaluation by demographic subgroup are the small number of subjects per subgroup.

***Age***

**Disposition**

As previously discussed in Section 8.2.4, during the VC period of Study 305, there was an imbalance in the rates of discontinuation by treatment arm, with the highest rate of discontinuation occurring in the 2-6 year age group, especially in the vehicle arm (30.3%) due to lack of efficacy, lost to follow-up, and withdrawal by subject/guardian. For the treatment arms, the most common reasons for discontinuation were due to lost to follow-up and withdrawal by subject/guardian. See Table 41.

**Table 43. Subject Disposition by Age Group, Study 305, VC Period**

| | **Ruxolitinib cream, 1.5% N=130 2-6 yrs n=66 7-11 yrs n=64** | **Ruxolitinib cream, 0.75% N=134 2-6 yrs n=68 7-11 yrs n=66** | **Vehicle cream N=65 2-6 yrs n=33 7-11 yrs n=32** | **Total N=329 2-6 yrs n= 167 7-11 yrs n = 162** |
|---|---|---|---|---|
| **Study Status** | | | | |
| **Completed study** | **117 (90)** | **122 (91)** | **49 (75.4)** | **288 (87.5)** |
| 2-6 years | 60 (90.9) | 60 (88.2) | 23 (69.7) | 143 (85.6) |
| 7-11 years | 57 (89.1) | 62 (93.9) | 26 (81.3) | 145 (89.5) |
| **Discontinued study** | **13 (10)** | **12 (9)** | **16 (24.6)** | **41 (12.5)** |
| 2-6 years | 6 (9.1) | 8 (11.8) | 10 (30.3) | 24 (14.4) |
| 7-11 years | 7 (10.9) | 4 (6.1) | 6 (18.8) | 17 (10.5) |
| **Reasons for Discontinuation** | | | | |
| **Adverse event** | **1 (0.8)** | **1 (0.7)** | **1 (1.5)** | **3 (0.9)** |
| 2-6 years | 0 (0) | 1 (1.5) | 0 (0) | 1 (0.6) |
| 7-11 years | 1 (1.6) | 0 (0) | 1 (3.1) | 2 (1.2) |
| **Lack of efficacy** | **1 (0.8)** | **1 (0.7)** | **7 (10.8)** | **9 (2.7)** |
| 2-6 years | 0 (0) | 0 (0) | 5 (15.2) | 5 (3) |
| 7-11 years | 1 (1.6) | 1 (1.5) | 2 (6.3) | 4 (2.5) |
| **Lost to follow-up** | **5 (3.8)** | **5 (3.7)** | **2 (3.1)** | **12 (3.6)** |
| 2-6 years | 2 (3) | 4 (5.9) | 1 (3) | 7 (4.2) |
| 7-11 years | 3 (4.7) | 1 (1.5) | 1 (3.1) | 5 (3.1) |
| **Withdrawal by subject/guardian** | **5 (3.8)** | **3 (2.2)** | **5 (7.7)** | **13 (4)** |
| 2-6 years | 3 (4.5) | 1 (1.5) | 3 (9.1) | 7 (4.2) |
| 7-11 years | 2 (3.1) | 2 (3) | 2 (6.3) | 6 (3.7) |

| | | | | |
|---|---|---|---|---|
| **Physician decision** | **1 (0.8)** | **1 (0.7)** | 0 (0) | **2 (0.6)** |
| 2-6 years | 0 (0) | 1 (1.5) | 0 (0) | 1 (0.6) |
| 7-11 years | 1 (1.6) | 0 (0) | 0 (0) | 1 (0.6) |
| **Protocol specified withdrawal criterion** | 0 (0) | **1 (0.7)** | **1 (1.5)** | 2 (0.6) |
| 2-6 years | 0 (0) | 1 (1.5) | 1 (3) | 2 (1.2) |
| 7-11 years | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| **Protocol violation** | **1 (0.8)** | **0 (0)** | 0 (0) | 1 (0.3) |
| 2-6 years | 1 (1.5) | 0 (0) | 0 (0) | 1 (0.6) |
| 7-11 years | 0 (0) | 0 (0) | 0 (0) | 0 (0) |

**Source: Reviewer.**

### Drug interruptions/withdrawals

Overall, there were few drug interruptions and withdrawals during Study 305, and minimal differences in rates between age groups when comparing the active treatment arms to vehicle.

**Table 44. Drug Interruptions and Withdrawals by Age Group, Study 305, VC Period**

| | **Ruxolitinib cream, 1.5% N=130 2-6 yrs n=66 7-11 yrs n=64** | **Ruxolitinib cream, 0.75% N=134 2-6 yrs n=68 7-11 yrs n=66** | **Vehicle cream N=65 2-6 yrs n=33 7-11 yrs n=32** |
|---|---|---|---|
| **Drug interruption** | **1 (0.8)** | **4 (3)** | **4 (6.2)** |
| 2-6 years | 1 (0.8) | 4 (3) | 2 (3.1) |
| 7-11 years | 0 (0) | 0 (0) | 2 (3.1) |
| **Drug withdrawal** | **1 (0.8)** | **1 (0.7)** | **0 (0)** |
| 2-6 years | 0 (0) | 1 (0.7) | 0 (0) |
| 7-11 years | 1 (0.8) | 0 (0) | 0 (0) |

**Source: Reviewer.**

### TEAEs

When analyzing TEAEs by age group, there were minimal differences between the 1.5% and 0.75% strengths of ruxolitinib cream, and between ruxolitinib cream and vehicle.

**Table 45. TEAEs by Age Group, Study 305, VC Period**

| | **Ruxolitinib cream, 1.5% N=130 2-6 yrs n=66 7-11 yrs n=64** | **Ruxolitinib cream, 0.75% N=134 2-6 yrs n=68 7-11 yrs n=66** | **Vehicle cream N=65 2-6 yrs n=33 7-11 yrs n=32** |
|---|---|---|---|

| | | | |
|---|---|---|---|
| **Total TEAEs** | 76 | 61 | 22 |
| **Subjects, n (%)** | 45 (34.6) | 34 (25.4) | 16 (24.6) |
| Upper respiratory tract infection | 20 (15.4) | 12 (9) | 7 (10.8) |
| 2-6 years | 10 (15.2) | 6 (8.8) | 6 (18.2) |
| 7-11 years | 10 (15.6) | 6 (9.1) | 1 (3.1) |
| COVID-19 and other serious infection | 7 (5.4) | 5 (3.7) | 2 (3.1) |
| 2-6 years | 3 (4.5) | 3 (4.4) | 1 (3) |
| 7-11 years | 4 (6.3) | 2 (3) | 1 (3.1) |
| Application site pain | 6 (4.6) | 5 (3.7) | 0 (0) |
| 2-6 years | 4 (6.1) | 2 (2.9) | 0 (0) |
| 7-11 years | 2 (3.1) | 3 (4.5) | 0 (0) |
| White blood cell decreased | 3 (2.3) | 0 (0) | 1 (1.5) |
| 2-6 years | 1 (1.5) | 0 (0) | 0 (0) |
| 7-11 years | 2 (3.1) | 0 (0) | 1 (3.1) |
| Pyrexia | 3 (2.3) | 5 (3.7) | 0 (0) |
| 2-6 years | 2 (3) | 5 (7.4) | 0 (0) |
| 7-11 years | 1 (1.6) | 0 (0) | 0 (0) |

**Source: Reviewer.**

***Sex***

When analyzing TEAEs by sex, males applying ruxolitinib 0.75% or 1.5% cream experienced a greater incidence of upper and lower respiratory tract infections and application site pain. See Table 44.

**Table 46. TEAE by Sex, Study 305, VC period**

| | **Ruxolitinib cream, 1.5% N=130 Males n=61 Females n=73** | **Ruxolitinib cream, 0.75% N=134 Males n=63 Females n=67** | **Vehicle N=65 Males n=27 Females n=38** |
|---|---|---|---|
| **Total TEAEs** | 76 | 61 | 22 |
| **Subjects, n (%)** | 45 (34.6) | 34 (25.4) | 16 (24.6) |
| Upper respiratory tract infection | 20 (15.4) | 12 (9) | 7 (10.8) |
| Males | 11 (18) | 6 (9.5) | 3 (11.1) |
| Females | 9 (12.3) | 6 (9) | 4 (10.5) |
| COVID-19 and other serious infection | 7 (5.4) | 5 (3.7) | 2 (3.1) |
| Males | 4 (6.6) | 4 (6.3) | 0 (0) |
| Females | 2 (2.7) | 1 (1.5) | 2 (5.3) |
| Application site pain | 6 (4.6) | 5 (3.7) | 0 (0) |
| Males | 5 (8.2) | 4 (6.3) | 0 (0) |
| Females | 2 (2.7) | 1 (1.5) | 2 (5.3) |

| | | | |
|---|---|---|---|
| White blood cell decreased | 3 (2.3) | 0 (0) | 1 (1.5) |
| Males | 1 (1.6) | 0 (0) | 1 (3.7) |
| Females | 2 (2.7) | 0 (0) | 0 (0) |
| Pyrexia | 3 (2.3) | 5 (3.7) | 0 (0) |
| Males | 1 (1.6) | 2 (3.2) | 0 (0) |
| Females | 2 (2.7) | 3 (4.5) | 0 (0) |

**Source: Reviewer.**

***Race***

When analyzing TEAEs by race*, there were minimal differences between the 1.5% and 0.75% strengths of ruxolitinib cream, and between ruxolitinib cream and vehicle.

**Table 47. TEAEs by Race, Study 305, VC Period***

| | **Ruxolitinib cream, 1.5% N=130 Whites n=68 Blacks/AA n=42** | **Ruxolitinib cream, 0.75% N=134 Whites n=75 Blacks/AA n=45** | **Vehicle N=65 Whites n=37 Blacks n=19** |
|---|---|---|---|
| **Total TEAEs** | 76 | 61 | 22 |
| **Subjects, n (%)** | 45 (34.6) | 34 (25.4) | 16 (24.6) |
| Upper respiratory tract infection | 20 (15.4) | 12 (9) | 7 (10.8) |
| White | 11 (16.2) | 7 (9.3) | 3 (8.1) |
| Black or African American | 4 (9.5) | 3 (6.7) | 3 (15.8) |
| COVID-19 and other serious infx | 7 (5.4) | 5 (3.7) | 2 (3.1) |
| White | 3 (4.4) | 4 (5.3) | 2 (5.4) |
| Black or African American | 3 (7.1) | 1 (2.2) | 0 (0) |
| Application site pain | 6 (4.6) | 5 (3.7) | 0 (0) |
| White | 5 (7.4) | 4 (5.3) | 0 (0) |
| Black or African American | 0 (0) | 1 (2.2) | 0 (0) |
| White blood cell decreased | 3 (2.3) | 0 (0) | 1 (1.5) |
| White | 1 (1.5) | 0 (0) | 0 (0) |
| Black or African American | 1 (2.4) | 0 (0) | 0 (0) |
| Pyrexia | 3 (2.3) | 5 (3.7) | 0 (0) |
| White | 3 (4.4) | 3 (4) | 0 (0) |
| Black or African American | 0 (0) | 2 (4.4) | 0 (0) |

**Source: Reviewer.**
*Not all races were analyzed due to small number of subjects in non-White and non-Black or African American categories.

***Reviewer Comment:*** *There were minimal differences in TEAEs amongst age groups, sex, or race in Study 305.*

### 8.2.8. Specific Safety Studies/Clinical Trials

**INCB 18424-109 – Maximal Usage Study (MUsT)**

As previously discussed, INCB 18424-109 (Study 109) was a phase 2, maximal usage trial (MUsT), as supportive safety information. There were 3 phases to Study 109: a 4-week MUsT phase, a 4-week treatment extension phase, and a 44-week LTS period (52 weeks total). The demographics of the study population were described in Section 8.2.2. Twenty-nine pediatric subjects ages 2 to 12 with moderate-to-severe atopic dermatitis, defined as IGA ≥3 and ≥35% of the BSA (excluding the scalp), were enrolled into the 4-week MUsT phase. Of the 29 subjects, 17 (58.6%) of the subjects were ages 2 to <7 and 12 (41.4%) were ages 7 to <12. Twenty-six subjects continued into the treatment extension phase, and 22 continued into the LTS phase. All subjects were treated with ruxolitinib cream, 1.5%.

**Deaths and SAEs**

There were no deaths or SAEs in Study 109.

**Discontinuations**

During the 4-week MUsT phase, 28 subjects (96.6%) completed the and 1 subject (3.4%) discontinued due to parent/guardian withdrawal. Of the 28 subjects who completed the first phase, 26 continued into the 4-week treatment extension phase. One subject (3.8%) discontinued due to parent/guardian withdrawal and 25 (96.2%) completed the second phase. Of these 25, 22 continued into the LTS phase. Of these 22, 14 (63.6%) completed the study, while 8 (36.4%) discontinued the study. There were no discontinuations due to adverse events.

**Table 48. Discontinuations During LTS Period, Study 109**

| | **Ruxolitinib 1.5% N=22** |
|---|---|
| **Study Status** | |
| Completed study | 14 (63.6) |
| Discontinued study | 8 (36.4) |
| **Reasons for Discontinuation** | |
| Adverse event | 0 (0) |
| Lack of efficacy | 2 (9.1) |
| Lost to follow-up | 2 (9.1) |
| Withdrawal by subject/guardian | 4 (18.2) |
| Physician decision | 0 (0) |
| Protocol specified withdrawal criterion | 0 (0) |
| Protocol violation | 0 (0) |
| Non-compliance with study drug | 0 (0) |
| Other | 0 (0) |

**Source: Reviewer.**

**TEAEs**

During the initial 8 weeks of treatment (MUsT and TE periods), the overall number of TEAEs were low. During the LTS phase, the number/incidence rates of AEs increased, particularly in the 2-6 yo age group. The majority of the TEAEs were infections.

**Table 49. TEAEs in Study 109, by Period and Age**

| | MUsT Period N=29 2-6 yrs, n=17 7-11 yrs, n=12 | TE Period N=26 2-6 yrs, n=15 7-11 yrs, n=11 | LTS Period N=22 2-6 yrs, n=13 7-11 yrs, n=9 |
|---|---|---|---|
| Total TEAEs, n | 5 | 2 | 22 |
| 2-6 yrs | 2 | 2 | 18 |
| 7-11 yrs | 3 | 0 | 4 |
| Subjects | 4 (13.8) | 2 (7.7) | 6 (27.3) |
| 2-6 yrs | 2 (11.8) | 2 (13.3) | 4 (30.8) |
| 7-11 yrs | 2 (16.7) | 0 (0) | 2 (22.2) |
| URI[a] | 1 (3.4) | 0 (0) | 3 (13.6) |
| 2-6 yrs | 1 (5.9) | 0 (0) | 2 (15.4) |
| 7-11 yrs | 0 (0) | 0 (0) | 1 (11.1) |
| COVID-19[b] | 0 (0) | 1 (3.8) | 3 (13.6) |
| 2-6 yrs | 0 (0) | 1 (6.7) | 3 (23.1) |
| 7-11 yrs | 0 (0) | 0 (0) | 0 (0) |
| Ear infection[c] | 0 (0) | 0 (0) | 2 (9.1) |
| 2-6 yrs | 0 (0) | 0 (0) | 2 (15.4) |
| 7-11 yrs | 0 (0) | 0 (0) | 0 (0) |
| Folliculitis[d] | 1 (3.4) | 1 (3.8) | 0 (0) |
| 2-6 yrs | 0 (0) | 1 (6.7) | 0 (0) |
| 7-11 yrs | 1 (8.3) | 0 (0) | 0 (0) |
| Gastroenteritis | 0 (0) | 0 (0) | 2 (9.1) |
| 2-6 yrs | 0 (0) | 0 (0) | 2 (15.4) |
| 7-11 yrs | 0 (0) | 0 (0) | 0 (0) |

**Source: Reviewer.**

[a] Upper respiratory infection (URI) includes Upper respiratory infection and pharyngitis streptococcal.

[b] COVID-19 includes COVID-19, bronchitis, and influenza.

[c] Ear infection includes Ear infection and otitis media.

[d] Folliculitis includes Folliculitis and application site folliculitis.

*Reviewer Comment: Although the incident rates of TEAEs increased in the LTS period, they were not the cause for discontinuation from Study 109.*

### 8.2.9. Additional Safety Explorations

**Human Carcinogenicity or Tumor Development**

Not applicable.

**Human Reproduction and Pregnancy**

Not applicable.

**Pediatrics and Assessment of Effects on Growth**

Because oral administration of ruxolitinib to juvenile rats in non-clinical studies showed effects on growth and bone measures, the effect of topical ruxolitinib cream, 1.5% on bone growth was assessed in the pediatric development plan, specifically in the maximal usage study (Study 109) and the phase 3 study (Study 305). The Divisions of Pediatric and Maternal Health (DPMH) and General Endocrinology (DGE) were consulted for advice during the development phase, prior to the initiation of Studies 109 and 305, to assist in clinically assessing growth in future studies. In Study 109, bone biomarker data, serum markers of bone formation (P1NP and bone specific alkaline phosphatase [BSAP]) and resorption (collagen type 1 C-telopeptide [CTX]) showed "large variability and no obvious trends over time". However, biomarker data was only collected for 4-8 weeks and no growth data was collected. DPMH and DGE concluded that "growth measurements are the most important clinically relevant assessments to rule out significant bone toxicity." Therefore, in Study 109 (LTS extension) and Study 305, growth (height/weight) data from baseline to Week 52 was collected in addition to the bone biomarkers, which was reviewed by the DGE clinical reviewer. After reviewing the bone biomarker and growth (height/weight) data for 84 pediatric subjects, the reviewer concluded that "there is no evidence of an adverse effect of Opzelura (ruxolitinib) 1.5% cream on bone growth in children over 52 weeks of treatment" and "no evidence of an adverse effect of Opzelura (ruxolitinib) 1.5% cream on biomarkers of bone formation or resorption in children over 4-8 weeks of treatment" (while noting that changes in biomarkers of bone formation have not been validated as surrogates for growth assessment). See the DGE consult review dated April 23, 2025, in DAARTS for more detail.

***Reviewer Comment:*** *While long-term studies are not powered for safety, this reviewer agrees with the DGE reviewer that based on the assessments conducted in Study 305, it is unlikely that longer-term, intermittent application of topical ruxolitinib affects bone growth in pediatric subjects ages 2 to <12 years of age.*

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

Not applicable.

### 8.2.10. Safety in the Postmarket Setting

**Safety Concerns Identified Through Postmarket Experience/Expectations on Safety in the Postmarket Setting**

Analysis of postmarket safety data did not identify any new safety signals. There are no safety concerns that are expected to change the benefit/risk assessment or lead to increased risk for Opzelura

(ruxolitinib) cream, 1.5% in the postmarket setting. However, additional safety data is required to characterize the safety profile of ruxolitinib cream, 1.5% in pediatric patients ages 3 to <24 months. A PMR covering the assessment in this age group was issued with the original NDA approval of mild to moderate atopic dermatitis in patients 12 and older dated September 21, 2021. See Section 13.

### 8.2.11. Integrated Assessment of Safety

The safety database included 329 subjects ages 2 to <12 years of age with mild to moderate atopic dermatitis from Study 305, including 130 treated with ruxolitinib 1.5% cream and 134 treated with ruxolitinib 0.75% cream twice daily for 8 weeks. In addition, Study 305 included an open-label, long-term safety (LTS) study of 282 subjects (138 assigned to ruxolitinib 1.5% cream and 144 to ruxolitinib 0.75% cream) who rolled over from the phase 3 vehicle-controlled period for up to an additional 44 weeks. The safety analysis of Study 305 was adequate to characterize the safety profile of ruxolitinib cream, 1.5% and 0.75%, for the treatment of mild to moderate AD in subjects ages 2 to <12 years of age.

There were no deaths and no serious adverse events (SAE) related to ruxolitinib cream, 1.5% and 0.75%, during the vehicle-controlled phases of Studies 109 and 305. During the VC phase, 10% of the subjects in the ruxolitinib 1.5% arm and 9% of the ruxolitinib 0.75% arm discontinued treatment, only 1 (0.7%) in the ruxolitinib 0.75% arm who discontinued due to application site pain. A primary cause (~50%) for withdrawal by parent/guardian was due to blood draws.

In Study 305, 45 subjects (34.6%) in the ruxolitinib 1.5% cream group, 34 subjects (25.4%) in the ruxolitinib 0.75% group, and 16 subjects (24.6%) in the vehicle group experienced at least one AE. The adverse reactions reported through Week 8 in ≥1% of subjects treated with ruxolitinib 1.5% and 0.75% cream (and ≥1% difference between subjects receiving ruxolitinib cream and vehicle) were upper respiratory tract infection (15.4% in the ruxolitinib 1.5% group, 9% in the ruxolitinib 0.75% group, and 10.8% in the vehicle group), COVID-19 (4.6%, 3.7%, and 3.1%, respectively), application site pain (4.6%, 3.7%, 1.5%), pyrexia (2.3%, 4.5%, 0%), and white blood cell decreased (1.5%, 0%, 0%). AEs seen in the 2-11 years AD population that were not seen in the 12 years and older studies included COVID-19, pyrexia, and application site reactions. Although TEAEs in general were fewer in the lower strength ruxolitinib 0.75% cream, these differences did not carry through when assessed by age group (2-6 years and 7-11 years). With the exception of pyrexia, incidence rates of the most common TEAEs were similar between the age groups.

Consults with the Division of Non-Malignant Hematology (DNH) and the Drug Induced Liver Injury (DILI) team were sought to evaluate the hematologic abnormalities and hepatic enzyme elevations, respectively, in Study 305. In the case of hematologic abnormalities, the DNH reviewer's opinion was that the clinical data did not raise any new concerns for clinically significant neutropenia or lymphopenia compared to the previously-studied 12 years and older AD population. In addition, the clinical data did not demonstrate a significant difference in cytopenias observed between [the] two age groups (2-6 years and 7-11 years) or strengths (1.5% and 0.75%). The DNH reviewer stated that the recommendations and precautions in the current PI were adequate to mitigate any risk, although the DNH reviewer recommended an additional statement in Section 14 to note the trial exclusion of

subjects with Grade 3 and 4 cytopenias at baseline. Similarly, the DILI team did not find any signal for hepatic enzyme elevations that were of clinical significance. The DILI team recommended no additional language regarding hepatotoxicity in the PI and further stated that no post-market requirements regarding hepatotoxicity risk were recommended.

The available data from Study 305 demonstrated that both strengths of ruxolitinib, 1.5% and 0.75%, were safe in the treatment of pediatric patients ages 2 to <12 years with mild to moderate atopic dermatitis. This reviewer recommends no additional postmarketing risk management assessments for this age group.

## 8.3.Statistical Issues

For the primary endpoint of IGA-TS at Week 8, the key statistical issue was that 5 investigators did not use the protocol-specified IGA instrument at baseline. Three of the investigators used an alternate 5-point scale with slightly different wording to describe the categories, and two of the investigators used a 6-point scale. All scales included the category descriptors of clear, almost clear, mild, moderate, and severe. If the subjects enrolled at these sites are removed from the analyses, the point estimates remain nearly the same and the statistical significance was retained for each dose relative to vehicle. Thus, this protocol violation did not impact the overall conclusions and it is reasonable to include the subjects from these 5 sites in the presentation of results. IGA-TS response rates were consistent across age groups and other demographic subgroups.

The study failed to demonstrate statistical significance for the key secondary endpoint of Itch NRS response (at least a 4-point improvement from baseline) at Week 8, among subjects 6 years of age and older with a baseline Itch NRS score of at least 4. The applicant has not provided evidence that the Itch NRS instrument is fit for purpose in this age group. Note that two other recent approvals of topical products for the treatment of atopic dermatitis only evaluated itch/pruritus in subjects 12 years of age and older (VTAMA (tapinarof) cream and ZORYVE (roflumilast) cream 0.15%).

## 8.4.Conclusions and Recommendations

Study INCB 18424-305 demonstrated the efficacy of ruxolitinib cream 1.5% and 0.75% in non-immunocompromised subjects 2 to less than 12 years of age with mild to moderate atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. The primary endpoint of IGA-TS at Week 8, defined as a score of clear or almost clear on the IGA with at least a 2-grade reduction from baseline, was statistically significant relative to vehicle for both ruxolitinib 1.5% and ruxolitinib 0.75%, with appropriate control for multiplicity. The IGA-TS response rates at Week 8 were 56.6% for ruxolitinib 1.5%, 36.8% for ruxolitinib 0.75%, and 10.8% for vehicle. IGA-TS response rates were consistent across age groups and other demographic

subgroups and the findings were robust to the handling of missing data. An effect on itching was not demonstrated in this study for subjects aged 6 to less than 12 years.

There was a higher incidence of respiratory infections in this pediatric population compared to the 12 years and older population with mild to moderate atopic dermatitis; however, this might be expected as pediatric patients in the general population are more prone to respiratory infections than adolescents and adults as their immune system develop and mature. Notably, there were few discontinuations due to adverse events, and the dose of ruxolitinib cream was not changed during the course of the majority of these AEs.

In the current PI (for 12 years and older), there are several warnings and precautions, including a boxed warning, to highlight the potential adverse events of the JAK inhibitor class of drugs. In addition, there are limitations of use to include the limitation of application to no more than 20% BSA and no more than 60 grams per week. To further mitigate the risk of systemic absorption and potential adverse events in the 2 to <12-year population, the following additions to the PI are recommended in Section 2.1:

- Do not use OPZELURA with occlusive dressings.
- Do not use more than one 60 gram tube of OPZELURA per 2 weeks.

The DNH reviewer also recommended the addition of the following statement which is recommended by this reviewer to be added under Section 6.1 (Clinical Trials Experience): "Subjects with cytopenias at screening defined as hemoglobin < 10 g/dL, absolute neutrophil count (ANC) < 1000/µL, and platelet count < 100,000/ µL were excluded from the trials. The impact on blood counts of ruxolitinib 1.5% cream in this population has not been studied." Otherwise, the current PI is adequate to inform the risks of ruxolitinib cream, 1.5% in the pediatric and adult patients 2 years and old with mild to moderate atopic dermatitis. No additional safety requirements or monitoring beyond the current recommendations in the PI is recommended.

The Applicant requested approval for the currently-marketed ruxolitinib 1.5% strength only. While both strengths of ruxolitinib were demonstrated to be both safe and effective for their intended use in this population, the difference in efficacy based on the primary efficacy endpoint of the IGA-TS response rates at Week 8 (56.6% for ruxolitinib 1.5% cream vs 36.6% for ruxolitinib 0.75% cream) in Study 305, with acceptable safety profiles supports approval of the 1.5% strength.

Based on the efficacy and safety results as described above, the review team recommends that ruxolitinib cream, 1.5% be approved for the indication of the topical short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised adult and pediatric patients 2 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

# 9 Advisory Committee Meeting and Other External Consultations

Not applicable.

# 10 Pediatrics

See Sections 3 (Regulatory History) and 13 (Postmarketing Requirements) for the regulatory history and previously-issued PMR for the assessment of pediatric patients 3 to <24-months with mild to moderate atopic dermatitis.

With the completion of INCB 18424-109 and INCB 18424-305, PMRs 4147-1 and 4147-2 are recommended to be considered fulfilled.

# 11 Labeling Recommendations

## 11.1. Prescription Drug Labeling

The Applicant submitted proposed prescribing information (PI), patient package insert (PPI), instructions for use, and carton/container labels for ruxolitinib 1.5% cream. The review team provided recommendations regarding PI, which are provided throughout this review.

The Office of Prescription Drug Promotion (OPDP) reviewed and provided comments regarding the proposed PI, PPI, and carton/container labeling and label. Refer to the OPDP review by Motherson L. Saint Juste, Regulatory Review Officer, dated April 30, 2025. These comments are reflected in the final labeling. Table 48 provides the location in this review of the discussion of each section of the product labeling.

**Table 50. Locations of Discussion of Significant High-Level Labeling Changes**

| Section | Location of Reviewer Comments on Proposed Labeling |
|---|---|
| 1 Indications and Usage | Sections 1.1, 1.2, 6, 8.2 |
| 6 Adverse Reactions | Section 8.2 |
| 8 Use in Specific Populations | Section 8.1, 8.2 |
| 12 Clinical Pharmacology | Section 6 |
| 14 Clinical Studies | Sections 6, 8 |

# 12 Risk Evaluation and Mitigation Strategies (REMS)

Based on the favorable safety profile of this product, risk mitigation measures beyond prescription labeling, patient labeling, and routine pharmacovigilance are not recommended at this time.

# 13 Postmarketing Requirements and Commitment

With the original approval of OPZELURA (ruxolitinib) cream, 1.5% on September 21, 2021, for the indication of short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in nonimmunocompromised patients 12 years of age and older, the submission of pediatric studies for ages 3 to <24 months was deferred, and the following PMR was issued:

4147-3 Conduct an open-label safety study in 100 subjects ages ≥ 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.

Draft Protocol Submission: 10/2026
Final Protocol Submission: 02/2027
Study Completion: 08/2029
Final Report Submission: 01/2030

No additional PMRs/PMCs are recommended.

# 14 Division Director (DHOT) Comments

APPEARS THIS WAY ON ORIGINAL

## 15 Division Director (OCP) Comments

APPEARS THIS WAY ON ORIGINAL

## 16 Division Director (OB) Comments

APPEARS THIS WAY ON ORIGINAL

## 17 Division Director (Clinical) Comments

APPEARS THIS WAY ON ORIGINAL

## 18 Deputy Division Director for safety (Signatory) Comments

I agree with the review team conclusion recommending an approval of Opzelura (ruxolitinib) cream, 1.5% for the treatment of pediatric patients 2 years to less than 12 years of age with atopic dermatitis (AD).
The applicant provided sufficient evidence of efficacy and safety in this population. The product is already approved for ages 12 years and above.
Opzelura (ruxolitinib) cream, 1.5% is to be applied twice daily to affected areas not to exceed 20 % of the total body area in the amount not to exceed 60 grams per 2 weeks in patients 2 years to 12 years of age with AD.
Opzelura (ruxolitinib) cream, 0.75% was also evaluated in a clinical trial together with 1.5% strength and demonstrated sufficient evidence of efficacy and safety however, the applicant does not seek approval of this strength and does not intend to market it.

# 19 Appendices

## 19.1. References

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## 19.2. Financial Disclosure

In compliance with 21 CFR Part 54, the Applicant provided Certification/Disclosure Forms from clinical investigators and sub-investigators who participated in covered clinical studies for ruxolitinib 1.5% and 0.75% cream. Prior to trial initiation, the investigators certified the absence of certain financial interests or arrangements or disclosed, as required, those financial interests or arrangements as delineated in 21 CFR 54.4 (a)(3) (i-iv).

The covered clinical studies as defined in 21 CFR 54.2 (e) were INCB 18424-109 and INCB 18424-305, which provided the primary data to establish effectiveness and safety of this product. Refer to Section 5 of this review for the trial designs. The Applicant provided the following disclosures for significant payments of other sorts from the Applicant of the covered studies [21 CFR 54.4 (a)(3) (ii), 54.2 (f)]:

**Covered Clinical Study (Name and/or Number): INCB 18424-109**

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes ☒ | No ☐ (Request list from Applicant) |
| Total number of investigators identified: 39 | | |
| 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)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____<br>Significant payments of other sorts: _____<br>Proprietary interest in the product tested held by investigator: _____<br>Significant equity interest held by investigator in S<br>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) |

**Covered Clinical Study (Name and/or Number): INCB 18424-305**

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes ☒ | No ☐ (Request list from Applicant) |
| Total number of investigators identified: 166 | | |
| 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)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____<br>Significant payments of other sorts: _____<br>Proprietary interest in the product tested held by investigator: _____<br>Significant equity interest held by investigator in S<br>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) |

## 19.3. Nonclinical Pharmacology/Toxicology

[Insert carci data as needed. Limit to 2 pages]

## 19.4. OCP Appendices (Bioanalytical Method Validation Summary supporting OCP recommendations)

A summary of bioanalytical methods and assay validation of ruxolitinib cream clinical studies in pediatric participants with AD to support the extension of proposed indication for AD in pediatric participants 2 to < 12 years of age using an Turbo Ion Spray LC/MS/MS are presented in Table 51. The proposed method was successfully validated for the determination of ruxolitinib (INCB018424) in human plasma over a concentration range of 1.00 to 1000 nM using 50 µL of plasma.

**Table 51. Summary of Acceptance Criteria and Validation Parameters of the Bioanalytical Method for the Determination of Ruxolitinib Concentrations in Human Plasma (DMB-07.111)**

| Parameter | Acceptance Criteria[a] | Experimental Results |
|---|---|---|
| Calibration curve | 2/3 of standards within ± 15% of nominal concentration (minimum of 5 acceptable standard) | All of standards within ± 15% of nominal concentration |
| Intraday accuracy | Mean concentration 85%-115% of nominal (80%-120% at LLOQ) | Overall range 90.9%-108% |
| Interday accuracy | Mean concentration 85%-115% of nominal (80%-120% at LLOQ) | Overall range 96.3%-100% |
| Intraday precision | At each concentration, %CV ≤ 15% (≤ 20% at LLOQ) | Overall range 1.8%-6.0% |
| Interday precision | At each concentration, %CV ≤ 15% (≤ 20% at LLOQ) | Overall range 4.7%-7.1% |
| Sensitivity | Mean concentration 80%-120% of nominal, with %CV ≤ 20% | Mean conc. range 98.1%-106% %CV range 2.9%-4.6% |
| Selectivity | 6 lots of matrix | |
| Blank matrix | No interference > 20% of LLOQ | No interference observed. Criteria met. |
| Selectivity at LLOQ | %CV of 6 lots spiked at LLOQ ≤ 20%with mean concentration 80%-120% of nominal | %CV 2.9% with mean concentration 94.6% of nominal |
| Matrix effect | None, minimal impact on assay performance | Mean matrix effect 0.96 indicating minimal matrix effect |
| Extraction efficiency | None, should be consistent, precise, and reproducible | Mean extraction efficiency ranged from 87.2% to 92.7% for INCB018424 |
| Chromatographic carryover | Peak area of blank ≤ 20% of mean LLOQ peak area | No carryover detected. Criteria met. |
| Stability | | |
| Stock solution | < 10% decrease in response over the duration evaluated | −0.7% difference from fresh solution after 82 days |
| Room temperature | Mean results within 15% of freshly prepared samples | Mean results ranged from −5.0% to 1.0% difference of original results |
| Freeze/thaw | Following 3 cycles, mean results within 15% of freshly prepared samples | Mean results ranged from −0.6% to −1.4% difference of original results |
| Long-term frozen plasma | Mean results of reassayed samples within 15% of original results | Long-term frozen plasma stability established for 372 days |
| Reinjection reproducibility | Mean results of reinjected samples within 15% of original results | Mean results ranged from 96.4% to 101%. |
| Dilution of samples | Mean concentration 85%-115% of nominal with %CV < 15% | Mean concentration 4685 nM mean accuracy 93.7% with %CV 2.4% |

| Parameter | Acceptance Criteria[a] | Experimental Results |
|---|---|---|
| Calibration curve | 2/3 of standards within ± 15% of nominal concentration (within ± 20% at LLOQ; minimum of 5 acceptable standards) | All acceptable standards within ± 15% of nominal concentration (within ± 20% at LLOQ) |
| Intraday accuracy (for 1801 Augustine Cut-Off site validation) | Mean concentration within ± 15% of nominal (within ± 20% at LLOQ) | Overall range: −5.7% to 3.0% bias |
| Interday accuracy (for 1801 Augustine Cut-Off site validation) | Mean concentration within ± 15% of nominal (within ± 20% at LLOQ) | Overall range: −1.7% to 2.0% bias |
| Intraday precision (for 1801 Augustine Cut-Off site validation) | At each concentration, %CV ≤ 15% (≤ 20% at LLOQ) | Overall range: 0.7% to 11.7% CV |
| Interday precision (for 1801 Augustine Cut-Off site validation) | At each concentration, %CV ≤ 15% (≤ 20% at LLOQ) | Overall range: 1.1% to 8.0% CV |
| Intraday accuracy (for 1.32 to 1320 nm range) | Mean concentration within ± 15% of nominal | Overall range: −3.8% to 2.3% bias |
| Interday accuracy (for 1.32 to 1320 nm range) | Mean concentration within ± 15% of nominal | Overall range: −2.8% to −0.3% bias |
| Intraday precision (for 1.32 to 1320 nM range) | At each concentration, %CV ≤ 15% | Overall range: 0.8% to 1.5% CV |
| Interday precision (for 1.32 to 1320 nm range) | At each concentration, %CV ≤ 15% | Overall range: 1.5% to 2.1% CV |
| Sensitivity (for 1.32 to 1320 nM range) | Peak area of zero sample ≤ 20% of LLOQ peak area | Criteria met |
| Intraday accuracy Sciex API 4000 MS | Mean concentration within ± 15% of nominal (within ± 20% at LLOQ) | Overall range: −0.7% to 3.0% bias |
| Intraday precision Sciex API 4000 MS | At each concentration, %CV ≤ 15% (≤ 20% at LLOQ) | Overall range: 1.2% to 3.5% CV |
| Intraday accuracy Sciex 6500 MS platform | Mean concentration within ± 15% of nominal (within ± 20% at LLOQ) | Overall range: −1.0%to 8.3% bias |
| Intraday precision Sciex 6500 MS platform | At each concentration, %CV ≤ 15% (≤ 20% at LLOQ) | Overall range: 1.9% to 4.2% CV |
| Intraday accuracy Sciex 6500 MS platform with change to 100 nM IS | Mean concentration within ± 15% of nominal (within ± 20% at LLOQ) | Overall range: 4.0% to 11.0% bias |
| Intraday precision Sciex 6500 MS platform with change to 100 nM IS | At each concentration, %CV ≤ 15% (≤ 20% at LLOQ) | Overall range: 3.5% to 4.4% CV |

| Parameter | Acceptance Criteria[a] | Experimental Results |
|---|---|---|
| Selectivity on Sciex 6500 MS platform with change to 100 nM IS | 6 lots of matrix | |
| Blank matrix | No interference > 20% of LLOQ | No interference observed. Criteria met. |
| Selectivity at LLOQ | %CV of 6 lots spiked at LLOQ ≤ 20% with mean concentration within ± 20% of nominal | %CV 2.3% with mean concentration 8.0% bias from nominal on a more sensitive instrument |
| Matrix effect | None, minimal impact on assay performance | INCB018424: 97.9% to 99.3% from 6 lots per concentration<br>INCB028452 (IS): 99.5% to 99.6% from 6 lots per concentration<br>IS-normalized matrix factor: 0.984 to 0.997 |
| Extraction efficiency | None, should be consistent, precise, and reproducible | INCB018424: 88.3% to 91.9% from 6 replicates per concentration<br>INCB028452 (IS): 93.5% to 98.0% from 6 replicates per concentration |
| Chromatographic carryover (for 1.32 to 1320 nM range) | Peak area of blank ≤ 20% of mean LLOQ peak area | No carryover detected for analyte or IS. Criteria met. |
| Batch size | Run must be acceptable | 293 injections |
| Stability | | |
| Stock solutions | < 10% change in response over the duration evaluated | INCB018424: 0.6% difference from fresh solution after 934 days at 4°C, nominal<br>INCB028452 (IS): −0.2% difference from fresh solution after 1319 days at 4°C, nominal |
| Working solution | < 10% change in response over the duration evaluated | −1.6% difference from fresh 132 nM solution after 100 hours at ambient temperature |
| Room temperature in plasma | Mean results within 15% of freshly prepared samples | Based on 3 samples per concentration (assayed in duplicate): Mean results ranged from −0.9% to −0.8% difference from nominal, after 31 hours |
| Long-term frozen plasma | Mean results of reassayed samples within 15% of original results | Long term frozen plasma stability established for 672 days at −70°C, nominal |
| Reinjection reproducibility | Mean results of reinjected samples within 15% of nominal | Mean results ranged from −2.8% to −0.5% difference from nominal after 73 hours at 15°C, nominal |
| Processed sample stability | Mean results of reinjected samples within 15% of nominal | Mean results ranged from 0.0% to 4.0% difference from nominal after 98 hours at 15°C, nominal |

| Parameter | Acceptance Criteria[a] | Experimental Results |
|---|---|---|
| Interference tests | | |
| Hemolyzed plasma | Mean results within 15% of nominal | No effect observed |
| Lipemic plasma | Mean results within 15% of nominal | No effect observed |
| Renal-impaired patient(s) plasma | Mean results within 15% of nominal | No effect observed |
| Hepatic-impaired patient(s) plasma | Mean results within 15% of nominal | No effect observed |
| Donor(s) of Japanese origin plasma | Mean results within 15% of nominal | No effect observed |
| Concomitant medicines | Mean results within 15% of nominal | Regorafenib at 10,000 nM to INCB018424 at 3 nM: No effect observed<br>INCB050465 at 5000 nM to INCB018424 at 1 nM: No effect observed<br>INCB039110 at 1000 nM to INCB018424 at 1 nM: No effect observed |

| Parameter | Experimental Results |
|---|---|
| Stability | |
| Processed sample stability | 122 hours stored at 15°C |
| Matrix freeze-thaw stability | 5 cycles, from −70°C to ambient temperature |
| Long-term frozen plasma | 908 days at −70°C, nominal |
| Long-term frozen plasma | 1560 days at −70°C, nominal |
| Interference tests | |
| Concomitant medicines - steroids | Prednisone at 0.5 µg/mL to INCB018424 at 1 nM: No effect observed<br>Prednisolone at 3.32 µg/mL to INCB018424 at 1 nM: No effect observed<br>Methylprednisolone at 1.3 µg/mL to INCB018424 at 1 nM: No effect observed |

**Source: Applicant, Study DMB-07.111.4, INCB018424**

## 19.5. Additional Clinical Outcome Assessment Analyses

Not applicable.

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