CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

215309Orig1s001

Name: Opzelura (ruxolitinib) cream.

Sponsor: Incyte Corporation

Approval Date: August 18, 2022

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA215309Orig1s001

CONTENTS

Reviews / Information Included in this Review

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
Labeling Review(s)	
REMS	
Officer/Employee List	
Multidiscipline Review(s) **• Summary Review** **• Office Director** **• Cross Discipline Team Leader** **• Clinical** **• Non-Clinical** **• Statistical** **• Clinical Pharmacology** **• Clinical Microbiology/Virology**	**X**
Product Quality Review(s)	
Other Review(s)	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative & Correspondence Documents	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA215309Orig1s001

APPROVAL LETTER

NDA 215309/S-001

SUPPLEMENT APPROVAL

Incyte Corporation
Attention: Fiona Lee, MS
Associate Director, Global Regulatory Affairs
1801 Augustine Cut-Off
Wilmington, DE 19803

Dear Fiona Lee:

Please refer to your supplemental new drug application (sNDA) dated October 17, 2021, received October 18, 2021, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Opzelura (ruxolitinib) cream.

We acknowledge receipt of your major amendment dated March 9, 2022, which extended the goal date by three months.

This Prior Approval supplemental new drug application provides for a new indication - the topical treatment of nonsegmental vitiligo in adult and pediatric patients 12 years of age and older.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to less than 2 years because necessary studies are impossible or highly impracticable. This is because the prevalence of nonsegmental vitiligo appears to be very low in patients less than 2 years of age.

We are deferring submission of your pediatric study for ages 2 to less than 12 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required by section 505B(a) of the FDCA is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the FDCA. This required study is listed below.

4304-1 Conduct a randomized, double-blind, vehicle-controlled 24-week trial of ruxolitinib 1.5% cream followed by a 28-week long-term safety extension period. The trial should enroll 150 pediatric subjects ≥ 2 years to < 12 years of age with nonsegmental vitiligo covering up to 10% body surface area (BSA) and minimum depigmentation involvement of at least 0.5% BSA on the face and at least 3% BSA on non-facial areas.

Draft Protocol Submission: 10/2022
Final Protocol Submission: 10/2023
Trial Completion*: 09/2026
Final Report Submission: 03/2027

* Completion of trial including the extension period, not completion of the primary endpoint data collection at Week 24

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit the protocol(s) to your IND 077101, with a cross-reference letter to this NDA. Reports of this required pediatric postmarketing study must be submitted as an NDA or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from this study. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

We note that you have fulfilled the pediatric study requirement for ages 12 to 17 years for this application.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[4]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Matthew White, Senior Regulatory Project Manager, at 301-796-4997.

Sincerely,

{See appended electronic signature page}

Shari L. Targum, MD, MPH, FACP, FACC
Deputy Director
Division of Dermatology and Dentistry
Office of Immunology and Inflammation
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide

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

/s/

SHARI L TARGUM
07/18/2022 04:48:44 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA215309Orig1s001

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use OPZELURA cream safely and effectively. See full prescribing information for OPZELURA cream.

OPZELURA™ (ruxolitinib) cream, for topical use
Initial U.S. Approval: 2011

WARNING: SERIOUS INFECTIONS, MORTALITY, MALIGNANCY, MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE), AND THROMBOSIS

See full prescribing information for complete boxed warning.

- **Serious infections leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral, and other opportunistic infections, have occurred in patients receiving Janus kinase inhibitors for inflammatory conditions. (5.1)**
- **Higher rate of all-cause mortality, including sudden cardiovascular death have been observed in patients treated with Janus kinase inhibitors for inflammatory conditions. (5.2)**
- **Lymphoma and other malignancies have been observed in patients treated with Janus kinase inhibitors for inflammatory conditions. (5.3)**
- **Higher rate of MACE (including cardiovascular death, myocardial infarction, and stroke) has been observed in patients treated with Janus kinase inhibitors for inflammatory conditions. (5.4)**
- **Thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis, some fatal, have occurred in patients treated with Janus kinase inhibitors for inflammatory conditions. (5.5)**

RECENT MAJOR CHANGES

Boxed Warning	07/2022
Indications and Usage (1.2, 1.3)	07/2022
Dosage and Administration (2.1, 2.3)	07/2022
Warnings and Precautions (5.2, 5.3, 5.4, 5.5)	07/2022

INDICATIONS AND USAGE

OPZELURA is a Janus kinase (JAK) inhibitor indicated for:

- the 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. (1.1)
- the topical treatment of nonsegmental vitiligo in adult and pediatric patients 12 years of age and older. (1.2)

Limitations of Use

Use of OPZELURA in combination with therapeutic biologics, other JAK inhibitors or potent immunosuppressants such as azathioprine or cyclosporine is not recommended. (1.3)

DOSAGE AND ADMINISTRATION

- Do not use more than one 60 gram tube per week or one 100 gram tube per 2 weeks. (2.1)
- For topical use only. (2.1)
- Not for intraocular, oral, or intravaginal use. (2.1)
- **Atopic Dermatitis**
  - Apply a thin layer twice daily to affected areas of up to 20% body surface area. (2.2)
- **Nonsegmental Vitiligo**
  - Apply a thin layer twice daily to affected areas of up to 10% body surface area. (2.3)

DOSAGE FORMS AND STRENGTHS

Cream: 1.5% ruxolitinib (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- *Serious Infections:* Serious bacterial, mycobacterial, fungal and viral infections have occurred. Regularly monitor patients for infection and manage it promptly. (5.1)
- *Non-melanoma Skin Cancers*. Basal cell and squamous cell carcinoma have occurred. Perform periodic skin examinations during treatment and following treatment as appropriate. (5.3)
- *Thrombosis.* Thromboembolic events have occurred. (5.5)
- *Thrombocytopenia, Anemia, and Neutropenia:* Thrombocytopenia, anemia, and neutropenia have occurred. Perform CBC monitoring as clinically indicated. (5.6)

ADVERSE REACTIONS

- In atopic dermatitis, the most common adverse reactions (incidence ≥ 1%) are nasopharyngitis, diarrhea, bronchitis, ear infection, eosinophil count increased, urticaria, folliculitis, tonsillitis, and rhinorrhea. (6)
- In nonsegmental vitiligo, the most common adverse reactions (incidence ≥ 1%) are application site acne, application site pruritus, nasopharyngitis, headache, urinary tract infection, application site erythema, and pyrexia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Incyte Corporation at 1-855-463-3463 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

USE IN SPECIFIC POPULATIONS

- Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 07/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFECTIONS, MORTALITY, MALIGNANCY, MAJOR ADVERSE CARDIOVASCULAR EVENTS, AND THROMBOSIS

SERIOUS INFECTIONS

Patients treated with oral Janus kinase inhibitors for inflammatory conditions are at risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.

Reported infections include:

- **Active tuberculosis, which may present with pulmonary or extrapulmonary disease.**
- **Invasive fungal infections, including cryptococcosis, and pneumocystosis.**
- **Bacterial, viral, including herpes zoster, and other infections due to opportunistic pathogens.**

Avoid use of OPZELURA in patients with an active, serious infection, including localized infections. If a serious infection develops, interrupt OPZELURA until the infection is controlled.

The risks and benefits of treatment with OPZELURA should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with OPZELURA *[see Warnings and Precautions (5.1)]*.

MORTALITY

In a large, randomized, postmarketing safety study in rheumatoid arthritis (RA) patients 50 years of age and older with at least one cardiovascular risk factor comparing an oral JAK inhibitor to tumor necrosis factor (TNF) blocker treatment, a higher rate of all-cause mortality, including sudden cardiovascular death, was observed with the JAK inhibitor *[see Warnings and Precautions (5.2)]*.

MALIGNANCIES

Malignancies were reported in patients treated with OPZELURA. Lymphoma and other malignancies have been observed in patients receiving JAK inhibitors used to treat inflammatory conditions. In RA patients treated with an oral JAK inhibitor, a higher rate of malignancies (excluding non-melanoma skin cancer (NMSC)) was observed when compared with TNF blockers. Patients who are current or past smokers are at additional increased risk *[see Warnings and Precautions (5.3)]*.

MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE)

In RA patients 50 years of age and older with at least one cardiovascular risk factor treated with an oral JAK inhibitor, a higher rate of major adverse cardiovascular events (MACE) (defined as cardiovascular death, myocardial infarction, and stroke), was observed when compared with TNF blockers. Patients who are current or past smokers are at additional increased risk. Discontinue OPZELURA in patients who have experienced a myocardial infarction or stroke *[see Warnings and Precautions (5.4)]*.

THROMBOSIS

Thromboembolic events were observed in trials with OPZELURA. Thrombosis, including pulmonary embolism (PE), deep venous thrombosis (DVT), and arterial thrombosis have been reported in patients receiving JAK inhibitors used to treat inflammatory conditions. Many of these adverse reactions were serious and some resulted in death. In RA patients 50 years of age and older with at least one cardiovascular risk factor treated with an oral JAK inhibitor, a higher rate of thrombosis was observed when compared with TNF blockers. Avoid OPZELURA in patients at risk. If symptoms of thrombosis occur, discontinue OPZELURA and treat appropriately *[see Warnings and Precautions (5.5)]*.

1 INDICATIONS AND USAGE

1.1 Atopic Dermatitis

OPZELURA is indicated for the 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.

1.2 Nonsegmental Vitiligo

OPZELURA is indicated for the topical treatment of nonsegmental vitiligo in adult and pediatric patients 12 years of age and older.

1.3 Limitations of Use

Use of OPZELURA in combination with therapeutic biologics, other JAK inhibitors, or potent immunosuppressants such as azathioprine or cyclosporine is not recommended.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

Do not use more than one 60 gram tube per week or one 100 gram tube per 2 weeks.

OPZELURA is for topical use only. OPZELURA is not for intraocular, oral, or intravaginal use.

2.2 Recommended Dosage for Atopic Dermatitis

Instruct patients to apply a thin layer of OPZELURA twice daily to affected areas of up to 20% body surface area.

Stop using when signs and symptoms (e.g., itch, rash, and redness) of atopic dermatitis resolve. If signs and symptoms do not improve within 8 weeks, patients should be re-examined by their healthcare provider *[see Clinical Studies (14.1)]*.

2.3 Recommended Dosage for Nonsegmental Vitiligo

Instruct patients to apply a thin layer of OPZELURA twice daily to affected areas of up to 10% body surface area.

Satisfactory patient response may require treatment with OPZELURA for more than 24 weeks. If the patient does not find the repigmentation meaningful by 24 weeks, the patient should be re-evaluated by the healthcare provider *[see Clinical Studies (14.2)]*.

3 DOSAGE FORMS AND STRENGTHS

Cream: 15 mg of ruxolitinib per gram (1.5%) of white to off-white cream.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infections

Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in patients receiving oral Janus kinase inhibitors.

Serious lower respiratory tract infections were reported in the clinical development program with topical ruxolitinib.

Avoid use of OPZELURA in patients with an active, serious infection, including localized infections. Consider the risks and benefits of treatment prior to initiating OPZELURA in patients:

- with chronic or recurrent infection
- with a history of a serious or an opportunistic infection
- who have been exposed to tuberculosis
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses; or
- with underlying conditions that may predispose them to infection.

Closely monitor patients for the development of signs and symptoms of infection during and after treatment with OPZELURA. Interrupt OPZELURA if a patient develops a serious infection, an opportunistic infection, or sepsis. Do not resume OPZELURA until the infection is controlled.

Tuberculosis

No cases of active tuberculosis (TB) were reported in clinical trials with OPZELURA. Cases of active TB were reported in clinical trials of oral Janus kinase inhibitors used to treat inflammatory conditions. Consider evaluating patients for latent and active TB infection prior to administration of OPZELURA.

During OPZELURA use, monitor patients for the development of signs and symptoms of TB.

Viral Reactivation

Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), were reported in clinical trials with Janus kinase inhibitors used to treat inflammatory conditions including OPZELURA. If a patient develops herpes zoster, consider interrupting OPZELURA treatment until the episode resolves.

Hepatitis B and C

The impact of Janus kinase inhibitors used to treat inflammatory conditions including OPZELURA on chronic viral hepatitis reactivation is unknown. Patients with a history of hepatitis B or C infection were excluded from clinical trials.

Hepatitis B viral load (HBV-DNA titer) increases, with or without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking oral ruxolitinib.

OPZELURA initiation is not recommended in patients with active hepatitis B or hepatitis C.

5.2 Mortality

In a large, randomized, postmarketing safety study of an oral JAK inhibitor in rheumatoid arthritis (RA) patients 50 years of age and older with at least one cardiovascular risk factor, a higher rate of all-cause mortality, including sudden cardiovascular death, was observed in patients treated with the JAK inhibitor compared with TNF blockers.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OPZELURA.

5.3 Malignancy and Lymphoproliferative Disorders

Malignancies, including lymphomas, were observed in clinical trials of oral JAK inhibitors used to treat inflammatory conditions. Patients who are current or past smokers are at additional increased risk.

Malignancies, including lymphomas, have occurred in patients receiving JAK inhibitors used to treat inflammatory conditions. In a large, randomized, postmarketing safety study of an oral JAK inhibitor in RA patients, a higher rate of malignancies (excluding non-melanoma skin cancer) was observed in patients treated with the JAK inhibitor compared to those treated with TNF blockers. A higher rate of lymphomas was observed in patients treated with the JAK inhibitor

compared to those treated with TNF blockers. A higher rate of lung cancers was observed in current or past smokers treated with the JAK inhibitor compared to those treated with TNF blockers. In this study, current or past smokers had an additional increased risk of overall malignancies.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OPZELURA, particularly in patients with a known malignancy (other than successfully treated non-melanoma skin cancers), patients who develop a malignancy when on treatment, and patients who are current or past smokers.

Non-melanoma Skin Cancers

Non-melanoma skin cancers including basal cell and squamous cell carcinoma have occurred in patients treated with OPZELURA. Perform periodic skin examinations during OPZELURA treatment and following treatment as appropriate. Exposure to sunlight and UV light should be limited by wearing protective clothing and using broad-spectrum sunscreen.

5.4 Major Adverse Cardiovascular Events (MACE)

In a large, randomized, postmarketing safety study of an oral JAK inhibitor in RA patients 50 years of age and older with at least one cardiovascular risk factor, a higher rate of major adverse cardiovascular events (MACE) defined as cardiovascular death, non-fatal myocardial infarction (MI), and non-fatal stroke was observed with the JAK inhibitor compared to those treated with TNF blockers. Patients who are current or past smokers are at additional increased risk.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OPZELURA, particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if they occur. Discontinue OPZELURA in patients that have experienced a myocardial infarction or stroke.

5.5 Thrombosis

Thromboembolic events were observed in clinical trials with OPZELURA.

Thrombosis, including deep vein thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis have been reported in patients receiving JAK inhibitors used to treat inflammatory conditions. Many of these adverse reactions were serious and some resulted in death.

In a large, randomized, postmarketing safety study of an oral JAK inhibitor in RA patients 50 years of age and older with at least one cardiovascular risk factor, higher rates of overall thrombosis, DVT, and PE were observed compared to those treated with TNF blockers.

Avoid OPZELURA in patients who may be at increased risk of thrombosis. If symptoms of thrombosis occur, discontinue OPZELURA and evaluate and treat patients appropriately.

5.6 Thrombocytopenia, Anemia, and Neutropenia

Thrombocytopenia, anemia, and neutropenia were reported in the clinical trials with OPZELURA. Consider the benefits and risks for individual patients who have a known history of these events prior to initiating therapy with OPZELURA. Perform CBC monitoring as

clinically indicated. If signs and/or symptoms of clinically significant thrombocytopenia, anemia, and neutropenia occur, patients should discontinue OPZELURA.

5.7 Lipid Elevations

Treatment with oral ruxolitinib has been associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Atopic Dermatitis

In two double-blind, vehicle-controlled clinical trials (TRuE-AD1 and TRuE-AD2), 499 adult and pediatric subjects 12 years of age and older with atopic dermatitis were treated with OPZELURA twice daily for 8 weeks. In the OPZELURA group, 62% of subjects were females, and 71% of subjects were White, 23% were Black, and 4% were Asian. The adverse reactions reported by ≥ 1% of OPZELURA treated subjects and at a greater incidence than in the vehicle arm are listed in Table 1.

Table 1: Adverse Reactions Occurring in ≥ 1% of Subjects Treated with OPZELURA for Atopic Dermatitis through Week 8 in TRuE-AD1 and TRuE-AD2

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

*TEAE – treatment emergent adverse events

Adverse reactions that occurred in TRuE-AD1 and TRuE-AD2 in < 1% of subjects in the OPZELURA group and none in the vehicle group were: neutropenia, allergic conjunctivitis, pyrexia, seasonal allergy, herpes zoster, otitis externa, Staphylococcal infection, and acneiform dermatitis.

Nonsegmental Vitiligo

In two double-blind, vehicle-controlled clinical trials (TRuE-V1 and TRuE-V2), 449 adult and pediatric subjects 12 years of age and older with nonsegmental vitiligo were treated with OPZELURA twice daily for 24 weeks. In the OPZELURA group, 55% of subjects were females, and 81% of subjects were White, 5% were Black, and 4% were Asian. The adverse reactions reported by OPZELURA treated subjects with an incidence of ≥ 1% and at least 1% greater incidence than in the vehicle arm in the 24-week double-blind period are listed in Table 2.

Table 2: Adverse Reactions Occurring in ≥ 1% of Subjects Treated with OPZELURA for Nonsegmental Vitiligo through Week 24 in TRuE-V1 and TRuE-V2

Adverse Reaction	**OPZELURA (N = 449) n (%)**	**Vehicle (N = 224) n (%)**
*Subjects with any TEAE**	*214 (48)*	*79 (35)*
Application site acne	26 (6)	2 (1)
Application site pruritus	23 (5)	6 (3)
Nasopharyngitis	19 (4)	5 (2)
Headache	17 (4)	6 (3)
Urinary tract infection	7 (2)	1 (< 1)
Application site erythema	7 (2)	1 (< 1)
Pyrexia	6 (1)	0

*TEAE – treatment emergent adverse events

Adverse reactions that occurred in TRuE-V1 and TRuE-V2 in ≥ 0.5% to < 1% of subjects in the OPZELURA group and none in the vehicle group were: application site dermatitis, hypertension, anxiety, application site discoloration, application site folliculitis, contusion, dermatitis contact, diarrhea, ear infection, gastritis, gastroenteritis, hordeolum, influenza-like illness, insomnia, nasal congestion, and vomiting.

7 DRUG INTERACTIONS

Drug interaction studies with OPZELURA have not been conducted.

Ruxolitinib is known to be a substrate for cytochrome P450 3A4 (CYP3A4). Inhibitors of CYP3A4 may increase ruxolitinib systemic concentrations whereas inducers of CYP3A4 may decrease ruxolitinib systemic concentrations *[see Clinical Pharmacology (12.3)]*.

Strong Inhibitors of CYP3A4

Avoid concomitant use of OPZELURA with strong inhibitors of CYP3A4 as there is a potential to increase the systemic exposure of ruxolitinib and could increase the risk of OPZELURA adverse reactions *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy registry that monitors pregnancy outcomes in pregnant persons exposed to OPZELURA during pregnancy. Pregnant persons exposed to OPZELURA and healthcare providers should report OPZELURA exposure by calling 1-855-463-3463.

Risk Summary

Available data from pregnancies reported in clinical trials with OPZELURA are not sufficient to evaluate a drug-associated risk for major birth defects, miscarriage, or other adverse maternal or fetal outcomes. In animal reproduction studies, oral administration of ruxolitinib to pregnant rats and rabbits during the period of organogenesis resulted in adverse developmental outcomes at doses associated with maternal toxicity *(see Data)*.

The background risks of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies carry some risk of birth defects, loss, or other adverse outcomes. The background risk in the U.S. general population of major birth defects and miscarriage is 2-4% and 15-20%, respectively.

Data

Animal Data

Ruxolitinib was administered orally to pregnant rats or rabbits during the period of organogenesis, at doses of 15, 30, or 60 mg/kg/day in rats and 10, 30, or 60 mg/kg/day in rabbits. There were no treatment-related malformations at any dose. A decrease in fetal weight of approximately 9% was noted in rats at the highest and maternally toxic dose of 60 mg/kg/day. This dose resulted in systemic exposure approximately 22 times the clinical systemic exposure at the maximum recommended human dose (MRHD; the clinical systemic exposure from ruxolitinib cream, 1.5% applied twice daily to 25-40% atopic dermatitis-affected body surface area is used for calculation of multiples of human exposure). In rabbits, lower fetal weights of approximately 8% and increased late resorptions were noted at the highest and maternally toxic dose of 60 mg/kg/day. This dose resulted in systemic exposure approximately 70% the MRHD clinical systemic exposure.

In a pre-and post-natal development study in rats, pregnant animals were dosed with ruxolitinib from implantation through lactation at doses up to 30 mg/kg/day. There were no drug-related adverse effects on embryofetal survival, postnatal growth, development parameters or offspring reproductive function at the highest dose evaluated (3.1 times the MRHD clinical systemic exposure).

8.2 Lactation

Risk Summary

There are no data on the presence of ruxolitinib in human milk, the effects on the breastfed child, or the effects on milk production. Ruxolitinib was present in the milk of lactating rats *(see Data)*. When a drug is present in animal milk, it is likely that the drug will be present in human milk.

Because of the serious adverse findings in adults, including risks of serious infections, thrombocytopenia, anemia, and neutropenia, advise women not to breastfeed during treatment with OPZELURA and for approximately four weeks after the last dose (approximately 5-6 elimination half-lives).

Data

Lactating rats were administered a single dose of [14C]-labeled ruxolitinib (30 mg/kg) on postnatal Day 10, after which plasma and milk samples were collected for up to 24 hours. The AUC for total radioactivity in milk was approximately 13 times the maternal plasma AUC. Additional analysis showed the presence of ruxolitinib and several of its metabolites in milk, all at levels higher than those in maternal plasma.

8.4 Pediatric Use

Atopic Dermatitis

The safety and effectiveness of OPZELURA for the topical treatment of mild-to-moderate atopic dermatitis have been established in pediatric patients aged 12 to 17 years of age. Use of OPZELURA in this age group is supported by evidence from TRuE-AD1 and TRuE-AD2, which included 92 pediatric subjects aged 12 to 17 years with mild-to-moderate atopic dermatitis *[see Clinical Pharmacology (12.3) and Clinical Studies (14.1)]*. No clinically meaningful differences in safety or effectiveness were observed between adult and pediatric subjects.

The safety and effectiveness of OPZELURA in pediatric patients younger than 12 years of age with atopic dermatitis have not been established.

Nonsegmental Vitiligo

The safety and effectiveness of OPZELURA for the topical treatment of nonsegmental vitiligo have been established in pediatric patients aged 12 to 17 years of age. Use of OPZELURA in this age group is supported by evidence from TRuE-V1 and TRuE-V2, which included 55 pediatric subjects aged 12 to 17 years with nonsegmental vitiligo *[see Clinical Studies (14.2)]*. No clinically meaningful differences in safety or effectiveness were observed between adult and pediatric subjects.

The safety and effectiveness of OPZELURA in pediatric patients younger than 12 years of age with nonsegmental vitiligo have not been established.

Juvenile Animal Toxicity Data

Oral administration of ruxolitinib to juvenile rats resulted in effects on growth and bone measures. When administered starting at postnatal day 7 (the equivalent of a human newborn) at doses of 1.5 to 75 mg/kg/day, evidence of fractures occurred at doses ≥ 30 mg/kg/day, and effects on body weight and other bone measures [e.g., bone mineral content, peripheral quantitative computed tomography, and x-ray analysis] occurred at doses ≥ 5 mg/kg/day. When administered starting at postnatal day 21 (the equivalent of a human 2-3 years of age) at doses of 5 to 60 mg/kg/day, effects on body weight and bone occurred at doses ≥ 15 mg/kg/day, which were considered adverse at 60 mg/kg/day. Males were more severely affected than females in all age groups, and effects were generally more severe when administration was initiated earlier in the postnatal period. These findings were observed at systemic exposures that are at least 40% the MRHD clinical systemic exposure.

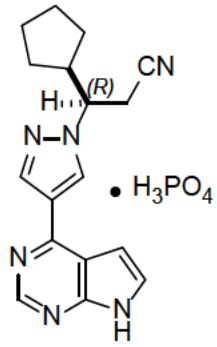
8.5 Geriatric Use

Of the 1249 total subjects with atopic dermatitis in clinical trials with OPZELURA, 115 (9%) were 65 years of age and older *[see Clinical Studies (14.1)]*. No clinically meaningful differences in safety or effectiveness were observed between subjects less than 65 years and subjects 65 years and older.

Of the 831 total subjects enrolled with nonsegmental vitiligo in clinical trials with OPZELURA, 65 (8%) were 65 years of age and older *[see Clinical Studies (14.2)]*. Clinical trials of OPZELURA in subjects with nonsegmental vitiligo did not include sufficient numbers of subjects 65 years of age and older to determine whether they respond differently from younger adult subjects.

11 DESCRIPTION

Ruxolitinib phosphate is a Janus kinase inhibitor with the chemical name (*R*)-3-(4-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)-3-cyclopentylpropanenitrile phosphate and a molecular weight of 404.36 g/mol. Ruxolitinib phosphate has the following structural formula:



Ruxolitinib phosphate is a white to off-white to light yellow to light pink powder.

OPZELURA (ruxolitinib) cream is a white to off-white oil-in-water, solubilized emulsion cream for topical use.

Each gram of OPZELURA contains 15 mg of ruxolitinib (equivalent to 19.8 mg of ruxolitinib phosphate) in a cream containing cetyl alcohol, dimethicone 350, edetate disodium, glyceryl stearate SE, light mineral oil, medium chain triglycerides, methylparaben, phenoxyethanol, polyethylene glycol 200, polysorbate 20, propylene glycol, propylparaben, stearyl alcohol, purified water, white petrolatum, and xanthan gum.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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 is not currently known.

12.2 Pharmacodynamics

Cardiac Electrophysiology

Under the conditions of clinical use, OPZELURA is not expected to prolong the QT interval.

12.3 Pharmacokinetics

The pharmacokinetics of ruxolitinib were evaluated in a study involving 20 adult subjects and 21 pediatric subjects 13 years and older with atopic dermatitis with a mean ± SD BSA involvement of 37.5 ± 16.1% (range 25% to 90%). Subjects applied approximately 1.5 mg/cm^2 of OPZELURA (dose range was approximately 1.2 grams to 37.6 grams per application) twice daily for 28 days.

Absorption

Plasma concentrations of ruxolitinib were quantifiable in all subjects. In adult subjects, the mean ± SD maximum plasma concentration (C_{max}) and area under the concentration time curve from 0 to 12 hours post dose (AUC_{0-12}) for ruxolitinib on Day 1 were 449 ± 883 nM and 3215 ± 6184 h*nM, respectively.

There is no evidence of ruxolitinib accumulation after daily application of OPZELURA for 28 days in subjects with atopic dermatitis.

Distribution

Plasma protein binding is approximately 97%.

Elimination

The mean terminal half-life of ruxolitinib following topical application of OPZELURA was estimated in 9 subjects and is approximately 116 hours.

Metabolism

Ruxolitinib is primarily metabolized by CYP3A4 and to a lesser extent by CYP2C9 in vitro.

Excretion

Ruxolitinib and its metabolites are primarily excreted by urine (74%) and feces (22%). Less than 1% is excreted as unchanged drug.

Specific Populations

Pediatric Patients

In adolescent subjects with atopic dermatitis (13 – 17 years of age), the mean ± SD C_{max} and AUC_{0-12} for ruxolitinib on Day 1 were 110 ± 255 nM and 801 ± 2019 h*nM, respectively.

Drug Interactions

Clinical Studies

Drug interaction studies with OPZELURA have not been conducted.

Strong CYP3A4 inhibitors

The C_{max} and AUC of ruxolitinib increased 33% and 91%, respectively, with administration of 10 mg single dose orally following ketoconazole 200 mg twice daily for four days, compared to receiving the oral ruxolitinib dose alone in healthy subjects.

Mild or moderate CYP3A4 inhibitors

There was an 8% and 27% increase in the C_{max} and AUC of ruxolitinib, respectively, with the administration of 10 mg single dose orally following erythromycin, a moderate CYP3A4 inhibitor, at 500 mg twice daily for 4 days, compared to receiving the oral ruxolitinib dose alone in healthy subjects. There are no clinical studies conducted with mild CYP3A4 inhibitor.

CYP3A4 inducers

The C_{max} and AUC of ruxolitinib decreased 32% and 61%, respectively, with the oral administration of 50 mg single dose of ruxolitinib following rifampin 600 mg once daily for 10 days, compared to receiving the oral ruxolitinib dose alone in healthy subjects.

In Vitro Studies

Cytochrome P450 (CYP) Enzymes: Ruxolitinib is not expected to inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and CYP3A4 or induce CYP1A2, 2B6 and 3A4 following topical application.

Transporter Systems: Ruxolitinib is not expected to inhibit P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1, or OAT3 transporter systems following topical application. Ruxolitinib is not a substrate for the P-gp transporter.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Ruxolitinib was not carcinogenic when administered orally in the 6-month Tg.rasH2 transgenic mouse model. In a 2-year oral rat carcinogenicity study, no drug-related tumors were observed at oral doses of ruxolitinib up to 60 mg/kg/day (3.5 times the MRHD clinical systemic exposure). In a 2-year dermal mouse carcinogenicity study, no drug-related tumors were observed at topical doses of ruxolitinib cream up to 1.5% applied at 100 µl/day (2.8 times the MRHD clinical systemic exposure).

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

In a fertility study, ruxolitinib was administered orally to male rats prior to and throughout mating and to female rats prior to mating and up to the implantation day (gestation day 7). Ruxolitinib had no effect on fertility or reproductive function in male or female rats at doses up to 60 mg/kg/day (22 times the MRHD clinical systemic exposure). However, in female rats,

doses of greater than or equal to 30 mg/kg/day (3.5 times the MRHD clinical systemic exposure) resulted in increased post-implantation loss.

14 CLINICAL STUDIES

14.1 Atopic Dermatitis

Two double-blind, randomized, vehicle-controlled trials of identical design (TRuE-AD1 and TRuE-AD2, NCT03745638 and NCT03745651, respectively) enrolled a total of 1249 adult and pediatric subjects aged 12 and older. A total of 20% of subjects were 12 to 17 years of age and 9% were 65 years or older. Females constituted 62% of subjects, 70% of subjects were White, 23% were Black, and 4% were Asian. Subjects had affected body surface area (BSA) of 3 to 20%, and an Investigator's Global Assessment (IGA) score of 2 (mild) to 3 (moderate) on a severity scale of 0 to 4. At baseline, subjects had a mean affected BSA of 9.8% and 39% had affected areas on the face, 25% of subjects had an IGA score of 2 and 75% had a score of 3. The baseline Itch Numerical Rating Scale (Itch NRS), defined as the 7-day average of the worst level of itch intensity in the last 24 hours, was 5 on a scale of 0 to 10.

In both trials, subjects were randomized 2:2:1 to treatment with OPZELURA, ruxolitinib cream, 0.75%, or vehicle cream twice daily (BID) for 8 weeks. The primary efficacy endpoint was the proportion of subjects at week 8 achieving IGA treatment success (IGA-TS) defined as a score of 0 (clear) or 1 (almost clear) with ≥ 2 grade improvement from baseline. Efficacy was also assessed using a ≥ 4-point improvement in Itch NRS.

Efficacy results for OPZELURA from the two trials are summarized in Table 3.

Table 3: Efficacy Results at Week 8 in Subjects with Atopic Dermatitis (TRuE-AD1 and TRuE-AD2)

	TRuE-AD1			TRuE-AD2		
	OPZELURA (N = 253)	**Vehicle (N = 126)**	**Treatment Difference and 95% Confidence Interval**	**OPZELURA (N = 228)**	**Vehicle (N = 118)**	**Treatment Difference and 95% Confidence Interval**
IGA-TS[a]	53.8% (136/253)	15.1% (19/126)	38.9% (30.3%, 47.4%)	51.3% (117/228)	7.6% (9/118)	44.1% (36.2%, 52.0%)
Itch NRS (≥ 4 point reduction) (n/N)[b]	52.2% (84/161)	15.4% (12/78)	36.7% (25.5%, 48.0%)	50.7% (74/146)	16.3% (13/80)	35.8% (24.4%, 47.2%)

[a] Defined as an IGA score of 0 or 1 with a ≥ 2-grade improvement from baseline
[b] N = subjects with a baseline Itch NRS score ≥ 4.

14.2 Nonsegmental Vitiligo

Two double-blind, randomized, vehicle-controlled trials of identical design (TRuE-V1 and TRuE-V2, NCT04052425 and NCT04057573, respectively) enrolled a total of 674 adult and pediatric subjects aged 12 years and older (11% of subjects were 12 to 17 years of age and 7% were 65 years or older). Females constituted 53% of subjects, 82% of subjects were White, 5% were Black, and 4% were Asian. Fitzpatrick skin types included I (2%), II (30%), III (40%), IV

(19%), V (7%), or VI (2%). Subjects had depigmented areas affecting ≥ 0.5% facial body surface area (F-BSA), ≥ 3% non-facial BSA, and total body vitiligo area (facial and non-facial, including hands, feet, upper and lower extremities, and trunk body areas) of up to 10% BSA. At baseline, subjects had a mean affected F-BSA of 1% and a mean affected total BSA of 7.4%. Phototherapy was not permitted during the trial. The mean time since diagnosis of nonsegmental vitiligo was 14.8 years prior to subjects enrolling in the trials.

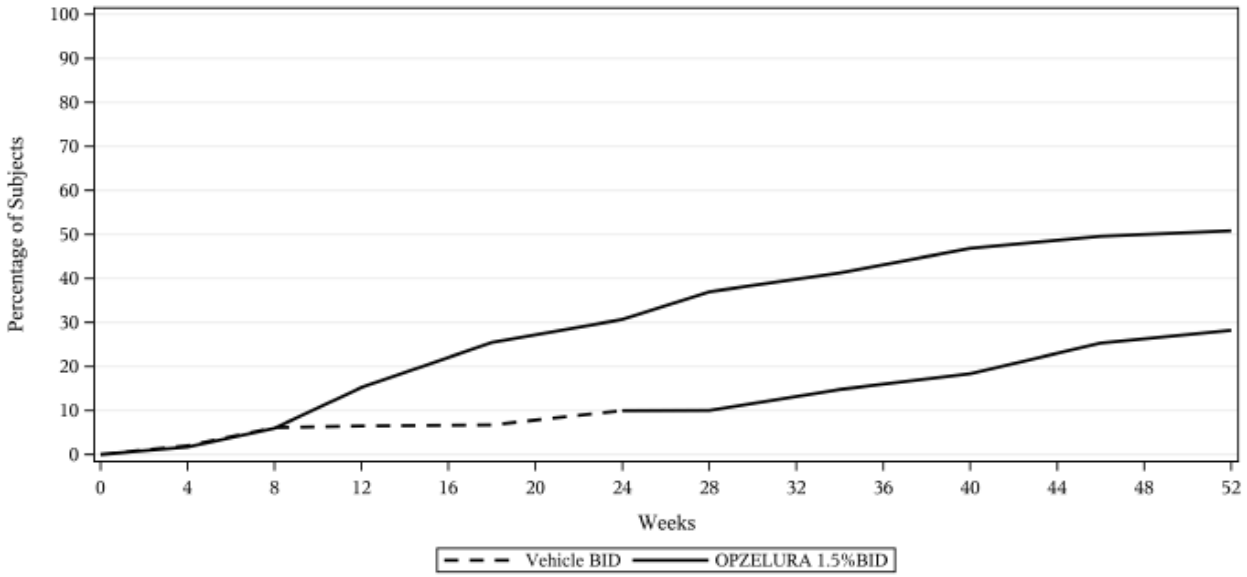
In both trials, subjects were randomized 2:1 to treatment with OPZELURA or vehicle cream twice daily (BID) for 24 weeks followed by an additional 28 weeks of treatment with OPZELURA BID for all subjects. Lesions on the face were assessed with the facial Vitiligo Area Scoring Index (F-VASI) and lesions on the total body (including the face) were assessed with the total body Vitiligo Area Scoring Index (T-VASI). The primary efficacy endpoint was the proportion of subjects achieving at least 75% improvement in F-VASI (F-VASI75) at Week 24. The proportion of participants achieving at least 90% improvement in F-VASI (F-VASI90) was also evaluated.

Efficacy results for OPZELURA at Week 24 from the two trials are summarized in Table 4. The percentage of subjects who achieved F-VASI75 and T-VASI75 (at least 75% improvement in T-VASI) over the 52-week treatment period in both trials are shown in Figure 1 and Figure 2.

Table 4: Efficacy Results at Week 24 in Subjects with Nonsegmental Vitiligo (TRuE-V1 and TRuE-V2)

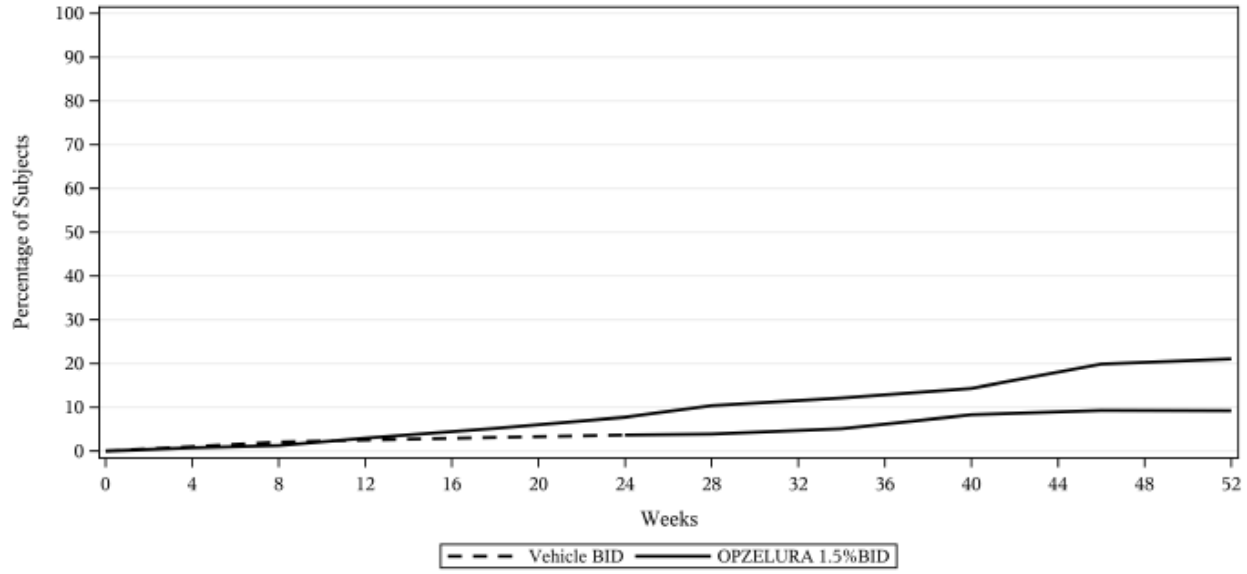
	TRuE-V1			**TRuE-V2**		
	OPZELURA (N = 221)	**Vehicle** (N = 109)	**Treatment Difference and 95% Confidence Interval**	**OPZELURA** (N = 229)	**Vehicle** (N = 115)	**Treatment Difference and 95% Confidence Interval**
F-VASI75	29.9%	7.5%	22.5% (14.2%, 30.8%)	29.9%	12.9%	16.9% (7.8%, 26.0%)
F-VASI90	15.5%	2.2%	13.3% (7.5%, 19.1%)	15.4%	1.9%	13.5% (7.7%, 19.3%)

Figure 1: Percentage of Subjects with Nonsegmental Vitiligo Achieving F-VASI75 During the 52-Week Treatment Period (TRuE-V1 and TRuE-V2 Combined)



Note: Subjects on the vehicle arm received vehicle for 24 weeks followed by OPZELURA for 28 weeks.

Figure 2: Percentage of Subjects with Nonsegmental Vitiligo Achieving T-VASI75 During the 52-Week Treatment Period (TRuE-V1 and TRuE-V2 Combined)



Note: Subjects on the vehicle arm received vehicle for 24 weeks followed by OPZELURA for 28 weeks.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

OPZELURA is a white to off-white cream containing 1.5% ruxolitinib and is supplied in 60 g and 100 g tubes.

60 g tube: NDC 50881-007-05

100 g tube: NDC 50881-007-07

Storage and Handling

Store OPZELURA at 20ºC to 25ºC (68ºF to 77ºF); excursions permitted from 15ºC to 30ºC (59ºF to 86ºF) *[see USP Controlled Room Temperature]*.

17 PATIENT COUNSELING INFORMATION

Advise the patient or caregivers to read the FDA-approved patient labeling (Medication Guide).

Infections

Inform patients that they may be at increased risk for developing infections, including serious infections, when taking Janus kinase inhibitors. Instruct patients to tell their healthcare provider if they develop any signs or symptoms of an infection *[see Warnings and Precautions (5.1)]*.

Advise patients that Janus kinase inhibitors increase the risk of herpes zoster, and some cases can be serious *[see Warnings and Precautions (5.1)]*.

Malignancies and Lymphoproliferative Disorders

Inform patients that Janus kinase inhibitors may increase the risk for developing lymphomas and other malignancies including skin cancer *[see Warnings and Precautions (5.3)]*.

Instruct patients to inform their health care provider if they have ever had any type of cancer. Inform patients that periodic skin examinations should be performed while using OPZELURA. Advise patients that exposure to sunlight, and UV light should be limited by wearing protective clothing and using a broad-spectrum sunscreen *[see Warnings and Precautions (5.3)]*.

Major Adverse Cardiovascular Events

Advise patients that events of major adverse cardiovascular events (MACE) including non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death, have been reported in clinical studies with Janus kinase inhibitors used to treat inflammatory conditions. Instruct all patients, especially current or past smokers or patients with other cardiovascular risk factors, to be alert for the development of signs and symptoms of cardiovascular events *[see Warnings and Precautions (5.4)]*.

Thrombosis

Advise patients that events of DVT and PE have been reported in clinical studies with Janus kinase inhibitors used to treat inflammatory conditions. Instruct patients to tell their healthcare provider if they develop any signs or symptoms of a DVT or PE *[see Warnings and Precautions (5.5)]*.

Thrombocytopenia, Anemia, and Neutropenia

Advise patients of the risk of thrombocytopenia, anemia, and neutropenia with OPZELURA. Instruct patients to tell their healthcare provider if they develop any signs or symptoms of thrombocytopenia, anemia, or neutropenia *[see Warnings and Precautions (5.6)]*.

Administration Instructions

Advise patients or caregivers that OPZELURA is for topical use only *[see Dosage and Administration (2.1)]*.

Advise patients to limit treatment to one 60 gram tube per week or one 100 gram tube per 2 weeks *[see Dosage and Administration (2.1)]*.

Pregnancy

Inform patients to report their pregnancy to Incyte Corporation at 1-855-463-3463 *[see Use in Specific Populations (8.1)]*.

Lactation

Advise a patient not to breastfeed during treatment with OPZELURA and for about four weeks after the last dose *[see Use in Specific Populations (8.2)]*.

Manufactured for:
Incyte Corporation
1801 Augustine Cut-off
Wilmington, DE 19803

MEDICATION GUIDE

OPZELURA™ (OP-zuh-LUR-ah)

(ruxolitinib) cream

Important: OPZELURA is for use on the skin only. Do not use OPZELURA in your eyes, mouth, or vagina.

What is the most important information I should know about OPZELURA?

OPZELURA may cause serious side effects, including:

- **Serious Infections.** OPZELURA contains ruxolitinib. Ruxolitinib belongs to a class of medicines called Janus kinase (JAK) inhibitors. JAK inhibitors are medicines that affect your immune system. JAK inhibitors can lower the ability of your immune system to fight infections. Some people have had serious infections while taking JAK inhibitors by mouth, including tuberculosis (TB), and infections caused by bacteria, fungi, or viruses that can spread throughout the body. Some people have been hospitalized or died from these infections. Some people have had serious infections of their lungs while using OPZELURA.
  - Your healthcare provider should watch you closely for signs and symptoms of TB during treatment with OPZELURA.

  OPZELURA should not be used in people with an active, serious infection, including localized infections. You should not start using OPZELURA if you have any kind of infection unless your healthcare provider tells you it is okay. You may be at a higher risk of developing shingles (herpes zoster) while using OPZELURA.

  Before starting OPZELURA, tell your healthcare provider if you:
  - are being treated for an infection
  - have had an infection that does not go away or that keeps coming back
  - have diabetes, chronic lung disease, HIV, or a weak immune system
  - have TB or have been in close contact with someone with TB
  - have had shingles (herpes zoster)
  - have or have had hepatitis B or C
  - live in an area, or have lived in an area, or have traveled to certain parts of the country (such as the Ohio and Mississippi River valleys and the Southwest) where there is an increased chance for getting certain kinds of fungal infections. These infections may happen or become more severe if you use OPZELURA. Ask your healthcare provider if you do not know if you have lived in an area where these infections are common.
  - think you have an infection or have symptoms of an infection such as:
    - fever, sweating, or chills
    - muscle aches
    - cough or shortness of breath
    - blood in your phlegm
    - weight loss
    - warm, red, or painful skin or sores on your body
    - diarrhea or stomach pain
    - burning when you urinate or urinating more often than usual
    - feeling very tired

  After starting OPZELURA, call your healthcare provider right away if you have any symptoms of an infection.

  OPZELURA can make you more likely to get infections or make worse any infections that you have. If you get a serious infection, your healthcare provider may stop your treatment with OPZELURA until your infection is controlled.
- **Increased risk of death due to any reason (all causes).** Increased risk of death has happened in people 50 years of age and older who have at least 1 heart disease (cardiovascular) risk factor and are taking a medicine in the class of medicines called JAK inhibitors by mouth.
- **Cancer and immune system problems.** OPZELURA may increase your risk of certain cancers by changing the way your immune system works.
  - Lymphoma and other cancers have happened in people taking a medicine in the class of medicines called JAK inhibitors by mouth.
  - People taking JAK inhibitors by mouth have a higher risk of certain cancers including lymphoma and lung cancer, especially if they are a current or past smoker.
  - Some people have had skin cancers while using OPZELURA. Your healthcare provider will regularly check your skin during your treatment with OPZELURA. Limit the amount of time you spend in the sunlight. Wear protective clothing when you are in the sun and use a broad-spectrum sunscreen.
  - Tell your healthcare provider if you have ever had any type of cancer.

- **Increased risk of major cardiovascular events.** Increased risk of major cardiovascular events such as heart attack, stroke, or death have happened in people 50 years of age and older who have at least 1 heart disease (cardiovascular) risk factor and taking a medicine in the class of medicines called JAK inhibitors by mouth, especially in current or past smokers.

  Get emergency help right away if you have any symptoms of a heart attack or stroke while using OPZELURA, including:
  - discomfort in the center of your chest that lasts for more than a few minutes, or that goes away and comes back
  - severe tightness, pain, pressure, or heaviness in your chest, throat, neck, or jaw
  - pain or discomfort in your arms, back, neck, jaw, or stomach
  - shortness of breath with or without chest discomfort
  - breaking out in a cold sweat
  - nausea or vomiting
  - feeling lightheaded
  - weakness in one part or on one side of your body
  - slurred speech
- **Blood clots.** Blood clots in the veins of your legs (deep vein thrombosis, DVT) or lungs (pulmonary embolism, PE) can happen in some people taking OPZELURA. This may be life-threatening. Blood clots in the vein of the legs (deep vein thrombosis, DVT) and lungs (pulmonary embolism, PE) have happened more often in people who are 50 years of age and older and with at least 1 heart disease (cardiovascular) risk factor taking a medicine in the class of medicines called JAK inhibitors by mouth.
  - Tell your healthcare provider if you have had blood clots in the veins of your legs or lungs in the past.
  - Tell your healthcare provider right away if you have any signs and symptoms of blood clots during treatment with OPZELURA, including:
    - swelling, pain, or tenderness in one or both legs
    - sudden, unexplained chest or upper back pain
    - shortness of breath or difficulty breathing

See **"What are the possible side effects of OPZELURA?"** for more information about side effects.

What is OPZELURA?

OPZELURA is a prescription medicine used on the skin (topical) for:

- short-term and non-continuous chronic treatment of mild to moderate eczema (atopic dermatitis) in non-immunocompromised adults and children 12 years of age and older whose disease:
  - is not well controlled with topical prescription therapies or
  - when those therapies are not recommended.
- the treatment of a type of vitiligo called nonsegmental vitiligo in adults and children 12 years of age and older.

The use of OPZELURA along with therapeutic biologics, other JAK inhibitors, or strong immunosuppressants such as azathioprine or cyclosporine is not recommended.

It is not known if OPZELURA is safe and effective in children less than 12 years of age with atopic dermatitis or nonsegmental vitiligo.

Before using OPZELURA, tell your healthcare provider about all of your medical conditions, including if you:

- See **"What is the most important information I should know about OPZELURA?"**
- have an infection
- are a current or past smoker
- have had a heart attack, other heart problems, or a stroke
- have or have had low white or red blood cell counts
- have high levels of fat in your blood (high cholesterol or triglycerides)
- are pregnant or plan to become pregnant. It is not known if OPZELURA will harm your unborn baby.
  - **Pregnancy Exposure Registry.** There is a pregnancy exposure registry for individuals who use OPZELURA during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. If you become exposed to OPZELURA during pregnancy, you and your healthcare provider should report exposure to Incyte Corporation at 1-855-463-3463.

- are breastfeeding or plan to breastfeed. It is not known if OPZELURA passes into your breast milk. Do not breastfeed during treatment with OPZELURA and for about 4 weeks after the last dose.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I use OPZELURA?

- OPZELURA is for use on the skin only. Do not use OPZELURA in your eyes, mouth, or vagina.
- Use OPZELURA exactly as your healthcare provider tells you.
- Apply a thin layer of OPZELURA 2 times a day to affected areas. **Do not** use more than one 60 gram tube each week or more than one 100 gram tube every 2 weeks. Ask your healthcare provider if you have questions about applying OPZELURA.
- If you are using OPZELURA for atopic dermatitis, stop using OPZELURA when your signs and symptoms of atopic dermatitis, such as itching, rash, and redness go away, or as directed by your healthcare provider. Tell your healthcare provider if your symptoms do not improve within 8 weeks of treatment.
- If you are using OPZELURA for nonsegmental vitiligo, tell your healthcare provider if your treated skin does not improve within 24 weeks of treatment.
- Wash your hands after applying OPZELURA, unless hands are being treated. If someone else applies OPZELURA, they should wash their hands after applying OPZELURA.

What are the possible side effects of OPZELURA?

OPZELURA may cause serious side effects, including:

- See **"What is the most important information I should know about OPZELURA?"**
- **Low blood cell counts.** OPZELURA may cause low platelet counts (thrombocytopenia), low red blood cell counts (anemia), and low white blood cell counts (neutropenia). If needed, your healthcare provider will do a blood test to check your blood cell counts during your treatment with OPZELURA and may stop your treatment if signs or symptoms of low blood cell counts happen. Tell your healthcare provider right away if you develop or have worsening of any of these symptoms:
  - unusual bleeding
  - bruising
  - tiredness
  - shortness of breath
  - fever
- **Cholesterol increases.** Cholesterol increase has happened in people when ruxolitinib is taken by mouth. Tell your healthcare provider if you have high levels of fat in your blood (high cholesterol or triglycerides).

The most common side effects of OPZELURA in people treated for atopic dermatitis include:

- common cold (nasopharyngitis)
- diarrhea
- bronchitis
- ear infection
- increase in a type of white blood cell (eosinophil) count
- hives
- inflamed hair pores (folliculitis)
- swelling of the tonsils (tonsillitis)
- runny nose (rhinorrhea)

The most common side effects of OPZELURA in people treated for nonsegmental vitiligo include:

- acne at the application site
- itching at the application site
- common cold (nasopharyngitis)
- headache
- urinary tract infection
- redness at the application site
- fever

These are not all of the possible side effects of OPZELURA.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to Incyte Corporation at 1-855-463-3463.

How should I store OPZELURA?

- Store OPZELURA at room temperature between 68°F to 77°F (20°C to 25°C).

Keep OPZELURA and all medicines out of the reach of children.

General information about the safe and effective use of OPZELURA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use OPZELURA for a condition for which it is not prescribed. Do not give OPZELURA to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or healthcare provider for information about OPZELURA that is written for healthcare professionals.

What are the ingredients in OPZELURA?

Active ingredient: ruxolitinib phosphate

Inactive ingredients: cetyl alcohol, dimethicone 350, edetate disodium, glyceryl stearate SE, light mineral oil, medium chain triglycerides, methylparaben, phenoxyethanol, polyethylene glycol 200, polysorbate 20, propylene glycol, propylparaben, stearyl alcohol, purified water, white petrolatum, and xanthan gum.

Manufactured for: Incyte Corporation, 1801 Augustine Cut-off, Wilmington, DE 19803

U.S. Patent Nos. 7598257; 8415362; 8722693; 8822481; 9079912; 9974790; 10610530; 10639310; 10758543; 10869870; 11219624

For more information go to www.Opzelura.com or call 1-855-463-3463

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 07/2022

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA215309Orig1s001

MULTIDISCIPLINE REVIEW(s)

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	Efficacy Supplement - New Indication (SE1)
Application Number(s)	NDA 215309/S-001
Priority or Standard	Priority
Submit Date(s)	18 October 2021
Received Date(s)	18 October 2021
PDUFA Goal Date	18 July 2022
Division/Office	DDD/OII
Review Completion Date	18 July 2022
Established/Proper Name	Ruxolitinib
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 twice daily to affected areas of up to 10% body surface area
Applicant Proposed Indication(s)/Population(s)	OPZELURA is indicated for the topical treatment of vitiligo in patients 12 years of age and older
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	56727007 / Vitiligo (disorder)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	The topical treatment of nonsegmental vitiligo in adult and pediatric patients 12 years of age and older
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	56727007 / Vitiligo (disorder)
Recommended Dosing Regimen	Apply a thin layer of OPZELURA twice daily to affected areas of up to 10% body surface area

Table of Contents

Table of Tables

Table of Figures

Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Matthew White
Office of Clinical Pharmacology/Pharmacometrics Reviewer	Da Zhang, PhD
Office of Clinical Pharmacology Team Leader	Chinmay Shukla, PhD
Division of Pharmacometrics Team Leader	Youwei Bi, PhD
Clinical Reviewer	Brenda Carr, MD
Clinical Team Leader	Hon-Sum Ko, MD
Statistical Reviewer	Kathleen Fritsch, PhD
Statistical Analyst	Wei Tan, MA
Statistical Team Leader	Mohamed Alosh, PhD
Cross-Disciplinary Team Leader	Hon-Sum Ko, PhD
Deputy Division Director	Shari L. Targum, MD, MPH

Additional Reviewers of Application

Deputy Director for Safety	Tatiana Oussova, MD, MPH
OPQ	Joel S. Hathaway, PhD/David Lewis, PhD
DMPP	Jessica Chung, PharmD, MS/Ruth Mayrosh, PharmD/Sharon Mills, BSN, RN, CCRP
OPDP	Laurie Buonaccorsi, PharmD/Matthew Falter, PharmD
OSE/DMEPA	Madhuri Patel, PharmD/Sevan Kolejian, PharmD, MBA, BCPPS
OSE SRPM	Tri Bui-Nguyen, PhD
OB/DBIII/PFSS	Weimeng Wang, MA, MEd (primary), Lili Garrard, PhD (secondary)
DCOA	Mira Patel, PhD (primary), Selena Daniels, PharmD, PhD (secondary)
OSI	Phil Phuc Nguyen, MD/ Karen Bleich, MD/Kassa Ayalew, MD, MPH

DBIII=Division of Biometrics III
DMEPA=Division of Medication Error Prevention and Analysis
DMPP= Division of Medical Policy Programs
DCOA= Division of Clinical Outcome Assessment
OB=Office of Biostatistics
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
PFSS=Patient-Focused Statistical Support
SRPM = Safety Regulatory Project Manager

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Da Zhang, PhD	OCP/DPM	Section:6, 15.3	**Select one:** _X__ Authored ___ Approved
	Signature: See DARRTS signature page			
Clinical Pharmacology Team Leader	Chinmay Shukla, PhD	OCP/DIIP	Section:6, 15.3	**Select one:** ___ Authored _X__ Approved
	Signature: See DARRTS signature page			
Pharmacometrics Team Leader	Youwei Bi, PhD	OCP/DPM	Section: 6, 15.3	**Select one:** ___ Authored _X_ Approved
	Signature: See DARRTS signature page			
Patient-Focused Statistical Support Reviewer	Weimeng Wang, MA, MEd	OB/DBIII	Sections: 15.4.1	**Select one:** _X_ Authored ___ Approved
	Signature: See DARRTS signature page			
Patient-Focused Statistical Support Team Leader	Lili Garrard, PhD	OB/DBIII	Sections: 15.4.1	**Select one:** ___ Authored _X_ Approved
	Signature: See DARRTS signature page			
Statistical Analyst	Wei Tan, MA	OB/DAI	Sections: 1.2, 8.1, 8.3	**Select one:** _X_ Authored ___ Approved
	Signature: See DARRTS signature page			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Biostatistics Reviewer	Kathleen Fritsch, PhD	OB/DBIII	Sections: 1.2, 8.1, 8.3	**Select one:** _X_ Authored ___ Approved
	Signature: See DARRTS signature page			
Statistical Team Leader/ Deputy Division Director	Mohamed Alosh, PhD	OB/DBIII	Sections:1.2, 8.1, 8.3	**Select one:** ___ Authored _X_ Approved
	Signature: See DARRTS signature page			
Division of Clinical Outcome Assessment Team Leader	Selena Daniels, PharmD, PhD	ODES/DCOA	Sections: 8.1.3, 15.4, 15.5	**Select one:** _X_ Authored ___ Approved
	Signature: See DARRTS signature page			
Division of Clinical Outcome Assessment Division Director	David Reasner, PhD	ODES/DCOA	Sections: 8.1.3, 15.4, 15.5	**Select one:** ___ Authored _X_ Approved
	Signature: See DARRTS signature page			
Clinical Reviewer	Brenda Carr, MD	OII/DDD	Sections: 2, 3, 7, 8,2, 8.4, 9, 10, 11, 12, 13, 15.1, 15.2	**Select one:** ___ Authored _x_ Approved
	Signature: See DARRTS signature page			
Clinical Team Leader	Hon-Sum Ko, MD	OII/DDD	Sections: 1	**Select one:** _x__ Authored _x__ Approved
	Signature: See DARRTS signature page			
Deputy Division Director (Clinical)	Shari L. Targum, MD, MPH	OII/DDD	Sections: 14	**Select one:** ___ Authored _X_ Approved
	Signature: See DARRTS signature page			

Glossary

AD	atopic dermatitis
AE	adverse event
ALT	alanine transaminase
AR	adverse reaction
ASR	application site reaction
AST	aspartate aminotransferase
BCC	basal cell carcinoma
BID	twice daily
BSA	body surface area
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CK	creatine kinase
CLINRO	clinician-reported outcome
CMC	chemistry, manufacturing, and controls
COA	clinical outcome assessment
CRF	case report form
CSR	clinical study report
Css	(plasma) concentration at steady state
CTCAE	Common Terminology Criteria for Adverse Events
DCOA	Division of Clinical Outcome Assessment
DDD	Division of Dermatology and Dentistry
ECG	electrocardiogram
eCDF	Empirical Cumulative Distribution Function
ED	emergency department
EOP2	End of Phase 2
F-PaGIC-V	Facial Patient Global Impression of Change-Vitiligo
F-PhGVA	Facial Physician's Global Vitiligo Assessment Scale
F-VASI	Vitiligo Area Scoring Index of the face
FDA	Food and Drug Administration
GGT	gamma-glutamyl transferase
ICH	International Conference on Harmonisation
IND	Investigational New Drug
iPSP	initial Pediatric Study Plan
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
LAD	left anterior descending
MACE	major adverse cardiovascular event
MedDRA	Medical Dictionary for Regulatory Activities

mITT	Modified intent to treat
NB-UVB	Narrowband ultraviolet B
NDA	New Drug Application
NMSC	nonmelanoma skin cancer
OCS	Office of Computational Science
OII	Office of Immunology and Inflammation
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PDF	Probability Density Function
PFSS	Patient-Focused Statistical Support
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PREA	Pediatric Research Equity Act
PRO	patient-reported outcome
PUVA	psoralen + ultraviolet A
PT	preferred term
QD	once daily
QoL	quality of life
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SCC	squamous cell carcinoma
sNDA	supplemental New Drug Application
SOC	system organ class
T-PaGIC-V	Total Body Patient Global Impression of Change-Vitiligo
T-PhGVA	Total Body Physician Global Vitiligo Assessment
T-VASI	Vitiligo Area Scoring Index of total body
TCI	topical calcineurin inhibitors
TCS	topical corticosteroid
TEAE	treatment emergent adverse event
VASI	Vitiligo Area Scoring Index
VNS	Vitiligo Noticeability Scale

1 Executive Summary

1.1. Product Introduction

The Applicant of this supplemental new drug application (sNDA), Incyte Corporation, requests approval of the product, OPZELURA (ruxolitinib) Cream, 1.5%, for the topical treatment of vitiligo in adult and pediatric patients 12 years of age and older. OPZELURA has been approved on September 21, 2021 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." [1]

OPZELURA contains the active ingredient, ruxolitinib (15 mg, in 19.8 mg of ruxolitinib phosphate) in a cream base with excipients including cetyl alcohol, dimethicone 350, edetate disodium, glyceryl stearate SE, light mineral oil, medium chain triglycerides, methylparaben, phenoxyethanol, polyethylene glycol 200, polysorbate 20, propylene glycol, propylparaben, stearyl alcohol, purified water, white petrolatum, and xanthan gum.

OPZELURA's active ingredient, ruxolitinib, was first approved in the U.S. on November 16, 2011 in the form of oral tablets with the proprietary name JAKAFI under NDA 202192 for the treatment of myelofibrosis. JAKAFI's current indications include myelofibrosis, polycythemia vera, acute and chronic graft-versus-host diseases.

Ruxolitinib inhibits Janus kinase (JAK) 1 and JAK2, enzymes mediating the signaling of cytokines and growth factors important for hematopoiesis and immune function. However, the relevance of inhibition of specific JAK enzymes to the therapeutic effectiveness of OPZELURA is not known. For use in vitiligo, the Applicant stipulates that based on studies showing that melanocytes from patients with vitiligo are more vulnerable to stress, and that stressed melanocytes may release inflammatory signals activating innate immunity, then the oxidative stress, cell damage, and cytokines secreted from innate immune cells trigger CXCL10 release by skin cells. This recruits $CD8^+$ T cells to the site for activation and production of interferon-gamma (IFNγ) and other inflammatory mediators to target and destroy melanocytes. JAK inhibition with ruxolitinib may be a strategy for treating vitiligo by interfering IFNγ signaling which utilizes the JAK-STAT pathway. Also, targeting the local immune response with a topical ruxolitinib product can be a directed therapy to minimize systemic adverse effects.[2]

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant provided substantial evidence of effectiveness from two adequate and well-controlled phase 3 trials of ruxolitinib cream, 1.5% twice daily in the treatment of nonsegmental vitiligo in adult and pediatric patients 12 years of age and older (Studies 306 and

307), with approximately 11% of subjects being 12 to 17 years of age. The dose for these studies had been chosen based on a phase 2 trial on 157 adults 18 to 75 years of age which included arms for 4 dose strengths of ruxolitinib cream (0.15% QD, 0.5% QD, 1.5% QD, or 1.5% BID) and vehicle cream BID in a 24-week, double-blind, vehicle-controlled treatment period for evaluation of efficacy (Study 211).

The two phase 3 studies enrolled 673 subjects with nonsegmental vitiligo covering up to 10% body surface area (BSA) and minimum depigmentation involvement of at least 0.5% BSA on the face and at least 3% BSA on nonfacial areas, and followed the subjects for 52 weeks. In the first 24 weeks, subjects were randomized 2:1 to ruxolitinib or vehicle. From Weeks 24 to 52, all subjects were treated with ruxolitinib. Efficacy was assessed by the investigator using the Vitiligo Area Scoring Index on the face (F-VASI) and total body (T-VASI) scales. The VASI has two components: percent body surface area (BSA) of vitiligo involvement for each vitiligo site and the "degree of depigmentation" for each vitiligo site, estimated to the nearest of the following percentages: 0%, 10%, 25%, 50%, 75%, 90%, or 100%. The VASI is then derived by multiplying the percent BSA involvement with vitiligo by the percentage of affected skin for each site and summing all values together.[*]

The primary endpoint, defined as at least a 75% reduction in F-VASI (F-VASI 75) from baseline to Week 24, was statistically significant in both studies. The results for F-VASI 75 at Week 24 were consistent across subgroups and plausible assumptions for missing data handling.

- Study 306: 29.9% vs. 7.5% (ruxolitinib vs. vehicle; p<0.0001)
- Study 307: 29.9% vs. 12.9% (ruxolitinib vs. vehicle; p=0.0021)

The results for the key secondary endpoints were also statistically significant in both studies under the multiplicity control scheme. The key secondary endpoints included at least a 50% reduction in F-VASI from baseline to Week 24 (F-VASI 50), at least a 90% reduction in F-VASI from baseline to Week 24 (F-VASI 90), at least a 50% reduction in T-VASI from baseline to Week 24 (T-VASI 50), response on the patient-reported Vitiligo Noticeability Scale at Week 24, and percent change in facial BSA from baseline to Week 24.

While the primary endpoint and the majority of key secondary endpoints evaluated vitiligo on the face, one of the key secondary endpoints evaluated vitiligo on the total body (T-VASI 50 at Week 24). This key secondary endpoint was statistically significant. Although there are concerns that a 50% improvement on T-VASI may not be clinically meaningful, quantitative anchor-based analyses and exit interview data from the phase 3 trials lend support to its being clinically meaningful. In addition, the findings from exploratory analyses of data over the 52-week extension period demonstrated that the proportion of subjects treated with ruxolitinib with at

[*] "Degree of depigmentation" was an ***estimation of the area of depigmentation*** within the lesion being assessed ***instead of the severity of pigment loss*** (see Figures 37 and 38). As such, both components of VASI are area-based, i.e., (%BSA of lesion or region) x (estimated %area affected by depigmentation within the lesion or region) and would ***not*** address the degree of pigment loss.

least 75% improvement of vitiligo on the total body (T-VASI 75) continued to increase through Week 52. Even though subjects on the control arm were treated with 24 weeks of vehicle followed by 28 weeks of ruxolitinib rather than continuous vehicle treatment, treatment effects for T-VASI 75 at Week 52 of 9.6% (20.3% vs. 10.8%, p=0.0675) in Study 306 and 10.8% (20.7% vs. 9.9%, p=0.0240) in Study 307 were observed. The observed effects would likely be larger if the studies had been designed with a 52-week vehicle-controlled period. Together these analyses indicate that ruxolitinib treatment has a clinically meaningful effect on total body vitiligo over the 52-week treatment period.

Thus, the totality of evidence from the two Phase 3 trials supports the efficacy of ruxolitinib cream, 1.5%, in the treatment of nonsegmental vitiligo in adult and pediatric patients 12 years of age and older.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Vitiligo is a chronic, acquired disorder of depigmentation. It may be psychosocially devastating and profoundly impact quality of life (QOL), especially in pediatric patients during their emotional development.

Vitiligo can be segmental or nonsegmental. It embraces a complex process believed to involve the Janus kinase (JAK) pathway to destroy melanocytes. Signaling disruption by JAK inhibitors such as ruxolitinib may have therapeutic potential.

Effectiveness

The Applicant provided evidence of effectiveness from two adequate and well-controlled trials of ruxolitinib cream, 1.5%, BID in the treatment of nonsegmental vitiligo in patients 12 years of age and older (Studies 306, 307). In the first 24 weeks, subjects were randomized 2:1 to ruxolitinib or vehicle. From Weeks 24 to 52, all were treated with ruxolitinib. Efficacy was assessed using the Vitiligo Area Scoring Index on the face (F-VASI) and total body (T-VASI). VASI has two components: percent body surface area (BSA) of vitiligo involvement for each vitiligo site and "degree of depigmentation" for the site, which is estimated to be 0%, 10%, 25%, 50%, 75%, 90%, or 100%. VASI is obtained by multiplying these components for each site and summing all values together.[†]

The primary endpoint, at least a 75% reduction in F-VASI (F-VASI 75) from baseline to Week 24, was statistically significant in both studies. F-VASI 75 at Week 24 were consistent across subgroups and plausible assumptions for missing data handling.

- Study 306: 29.9% vs. 7.5% (ruxolitinib vs. vehicle; p<0.0001)
- Study 307: 29.9% vs. 12.9% (ruxolitinib vs. vehicle; p=0.0021)

Results for key secondary endpoints were also statistically significant in both studies under the multiplicity control scheme. They include improvements from baseline to Week 24 for:

- at least 50% reduction in F-VASI (F-VASI 50),

[†] "Degree of depigmentation" was an ***estimation of the area of depigmentation*** within the lesion being assessed ***instead of the severity of pigment loss*** (see Figures 37 and 38). As such, both components of VASI are area-based, i.e., (%BSA of lesion or region) x (estimated %area affected by depigmentation within the lesion or region) and would ***not*** address the degree of pigment loss.

- at least 90% reduction in F-VASI (F-VASI 90),
- at least 50% reduction in T-VASI (T-VASI 50),
- percent change in facial BSA,
- response on Vitiligo Noticeability Scale (patient-reported).

Although T-VASI 50 at Week 24 was statistically significant, there were concerns that a 50% improvement may not be clinically meaningful. However, quantitative anchor-based analyses and exit interview data from the phase 3 trials have lent support to its clinical meaningfulness. Also, findings from exploratory analyses demonstrated that the proportion of subjects treated with ruxolitinib who showed 75% or greater improvement (T-VASI 75) continued to increase through Week 52. Although subjects on the control arm were treated with 24 weeks of vehicle followed by 28 weeks of ruxolitinib rather than continuous vehicle treatment, the observed treatment effects for T-VASI 75 at Week 52 were:

- Study 306 - 9.6% (20.3% vs. 10.8%, p=0.0675)
- Study 307 - 10.8% (20.7% vs. 9.9%, p=0.0240).

The observed effects would likely be larger if the studies had been designed with a 52-week vehicle-controlled period. Together, these analyses indicate that ruxolitinib treatment has a clinically meaningful effect on total body vitiligo over the 52-week treatment period.

Thus, the totality of evidence from the two Phase 3 trials supports the efficacy of ruxolitinib cream, 1.5%, in the treatment of nonsegmental vitiligo in adult and pediatric patients 12 years of age and older.

Safety

The Applicant conducted the primary safety analysis on Pool 1, which consisted of data of 673 subjects through the double-blind, vehicle-controlled 24-week period in the phase 3 trials (306 and 307): 449 (67%) in the ruxolitinib 1.5% group and 224 (33%) in the vehicle group. A total of 55 subjects were 12 to <18 years of age and received treatment with ruxolitinib 1.5% cream.

Of 767 subjects in the dtabase who applied ruxolitinib 1.5% cream BID, 589 had exposure to this dosing regimen for ≥24 weeks, 220 for ≥52 weeks, and 51 for ≥104 weeks. These numbers exceed the minimum recommended for the 6-month and one-year timepoints in the International Council for Harmonisation (ICH) E1A guideline. The average use of ruxolitinib cream, 1.5%, in the phase 3 studies was 31 gm/week with application up to 10% of BSA for vitiligo lesions. As labeling will provide a dosing limit of 60 gm/week or 100 gm/2 weeks, a sufficient safety margin for its use is anticipated.

Overall, 79 subjects (35.5%) in the vehicle group and 214 subjects (47.7%) in the ruxolitinib group experienced a treatment-emergent adverse

event (TEAE). No deaths occurred in the development program. The overall incidence of serious adverse events (SAEs) was low: 1 subject (0.4%) in the vehicle group; 8 subjects (1.8%) in the ruxolitinib group. There were only single reports of all SAEs, i.e., no one type of SAE was reported in more than one subject. Investigators assessed all of the SAEs as not reasonably caused by ruxolitinib cream. There were other factors that might predispose the subject to some of the SAEs. The pattern and occurrence of SAEs upon longer exposure raised no new safety concerns.

TEAEs were most frequently reported in the Infections and Infestations system organ class (SOC), with 98 subjects (21.8%) in the ruxolitinib arm and 37 (16.5%) in the vehicle arm, and nasopharyngitis being the most commonly reported TEAE in this SOC: vehicle with 5 subjects (2.2%), and ruxolitinib with 19 (4.2%). Application site reactions (ASRs) were reported in 13 subjects (5.8%) in the vehicle group and 67 (14.9%) in the ruxolitinib group. Application site acne was the most commonly reported ASR in the ruxolitinib group: vehicle with 2 subjects (0.9%) and ruxolitinib with 26 (5.8%). The signal for application site acne was not observed in the clinical program for AD. An assessment of adverse events of interest (relating to oral ruxolitinib or systemic JAK inhibitors for other indications) raised no new safety concerns. The applicant has reported no TEAEs of MACE[‡].

In phase 3 studies, 11% of subjects were 12 to <18 years of age. The safety profile in adolescents was similar to that in adults. Their safety is also supported by data in the AD trials. Additionally, ruxolitinib 1.5% cream will have safety labeling similar to that of other oral JAK inhibitors to ensure prescriber awareness.

In conclusion, safety of ruxolitinib cream, 1.5%, in the treatment of vitiligo has been demonstrated in its development program.

[‡] MACE: major adverse cardiovascular events - there were no agree-upon criteria of MACE and the Applicant has a list in Appendix B to the Clinical Summary of Safety for Adverse Event of Interest for Oral JAK Inhibitors which includes MACE, but some of the events, according to the list, would not be considered MACE unless death occurred. In the safety database, there are reports of arterial and venous thromboembolic events including coronary artery occlusion, thrombosis in lower leg, transient ischemic attack, etc. (Module 2 Section 2.7, Clinical Summary of Safety Section 2.1.8.2.6.1). Despite being reported, these events were not likely related to the use of ruxolitinib.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Vitiligo is a chronic, acquired disorder of depigmentation that results from a selective destruction of melanocytes. The two major phenotypes are nonsegmental (NSV) and segmental (SV) vitiligo. NSV is the more common form and is generally progressive, with lesions increasing in size and number over time. SV tends to rapidly progress, and then spontaneously stabilize. SV also tends to be more resistant to treatment. • The pathogenesis of vitiligo is not fully understood. A complex process wherein stressed melanocytes release inflammatory mediators that activate the innate immune system may be operative. This recruits activated CD8+ T cells that secrete inflammatory mediators, including interferon-gamma (IFNγ) which utilizes the Janus kinase (JAK) pathway for pathogenesis. Thus, JAK inhibition might have potential for treatment of vitiligo, and on this basis the Applicant developed ruxolitinib cream for its treatment.	The Applicant limited enrollment in their phase 3 studies to subjects with NSV, and the label should reflect that this was the population studied. Therefore, the indication statement should specify that ruxolitinib 1.5% cream is indicated for "the topical treatment of nonsegmental vitiligo in adult and pediatric patients 12 years of age and older with nonsegmental vitiligo." Safety and efficacy of the product have not been established for treatment of SV. Although the safety of ruxolitinib 1.5% cream for SV would not be expected to differ from that for NSV, the treatment response could, as the biological behaviors of NSV and SV differ.
Current Treatment Options	• Current pharmacologic treatments are off-label uses. Topical treatment (corticosteroids and calcineurin inhibitors) is considered first-line therapy, and may be used as monotherapy for small areas or when other therapies are unavailable. Topical calcineurin inhibitors (tacrolimus and pimecrolimus) may be selected as initial treatment for areas that are particularly vulnerable to local adverse reactions related to TCS atrophy e.g., face, intertriginous areas. • Phototherapy is indicated for more widespread disease, i.e., > 5 to 10% BSA or for rapidly spreading disease. When under 10% BSA involvement, phototherapy may be considered for disseminated disease if topical therapy is impractical, and may be considered for more limited disease if topical therapy has been ineffective.	There is a clear unmet medical need, as there are no approved pharmacologic therapies for repigmentation of any form of vitiligo. Approval of ruxolitinib 1.5% cream would represent the first safe and effective pharmacologic treatment for a repigmentation of vitiligo indication.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	The Applicant has provided substantial evidence of effectiveness from two adequate and well-controlled phase 3 trials of ruxolitinib cream, 1.5%, twice daily in the treatment of NSV in adult and pediatric patients 12 years of age and older. The primary endpoint, defined as at least a 75% reduction in F-VASI (F-VASI 75) from baseline to Week 24, was statistically significant in both studies. The results for F-VASI 75 at Week 24 were consistent across subgroups and plausible assumptions for missing data handling. • Study 306: 29.9% vs. 7.5% (ruxolitinib vs. vehicle; p<0.0001) • Study 307: 29.9% vs. 12.9% (ruxolitinib vs. vehicle; p=0.0021) The results for the key secondary endpoints were also statistically significant in both studies under the multiplicity control scheme. The key secondary endpoints included at least a 50% reduction in F-VASI from baseline to Week 24 (F-VASI 50), at least a 90% reduction in F-VASI from baseline to Week 24 (F-VASI 90), at least a 50% reduction in T-VASI from baseline to Week 24 (T-VASI 50), response on the patient-reported Vitiligo Noticeability Scale at Week 24, and percent change in facial BSA from baseline to Week 24. On exploratory analysis, reduction in T-VASI has been shown to consistently increase across studies through Week 52 of ruxolitinib treatment, and when compared to the control arm treated with 24 weeks of vehicle followed by 28 weeks of ruxolitinib rather than continuous vehicle treatment, the observed treatment effects for T-VASI 75 at Week 52 were: • Study 306 - 9.6% (20.3% vs. 10.8%, p=0.0675) • Study 307 - 10.8% (20.7% vs. 9.9%, p=0.0240). The observed effects would likely be larger if the studies had been designed	The data submitted from the two adequate and well-controlled trials meet the evidentiary standard for providing substantial evidence of effectiveness. The Applicant has established that ruxolitinib 1.5% cream is effective for treatment of NSV of the face and total body areas in patients 12 years and older under the conditions of use evaluated in the clinical trials.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	with a 52-week vehicle-controlled period. Together, these analyses indicate that ruxolitinib treatment has a clinically meaningful effect on total body vitiligo over the 52-week treatment period.	
Risk and Risk Management	• Local skin reactions are a possibility with topical products. Application site acne was the most common TEAE in ruxolitinib-treated subjects in the vitiligo studies and seems likely to present in the postmarket setting. • With sufficient systemic exposure, the safety profile could be similar to that of oral ruxolitinib or other JAK inhibitors indicated for treatment of inflammatory conditions, and the approved label for ruxolitinib cream includes extensive discussion of safety in the context of systemic exposure in the Warnings and Precautions section (as well as a Boxed Warning). The likelihood of this degree of systemic exposure is unclear.	Prescription labeling, patient labeling and routine pharmacovigilance activities are considered adequate to manage the risks of ruxolitinib 1.5% cream.

1.4. Patient Experience Data

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

☒	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	☒	Clinical outcome assessment (COA) data, such as		7.1, 15.4, 15.5
		☒	Patient reported outcome (PRO)	7.1, 15.4, 15.5
		□	Observer reported outcome (ObsRO)	
		☒	Clinician reported outcome (ClinRO)	7.1, 15.4, 15.5
		□	Performance outcome (PerfO)	
	☒	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		7.1
	□	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		2.1
	☒	Patient-focused drug development or other stakeholder meeting summary reports		2.1
	□	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

Introduction

Vitiligo is a chronic, acquired disorder of depigmentation that results from a selective destruction of melanocytes.[3,4,5] Classic lesions are stark or milky white, sharply-demarcated, nonscaly macules on the skin and/or mucous membranes. Hairs in affected areas may also be depigmented (leukotrichia). Lesions are generally asymptomatic, but may occasionally be pruritic.[5] It may be psychosocially devastating[6], significantly impacting self-esteem and self perception[5] and profoundly impacting the overall quality of life (QOL).[7] Affected individuals may frequently experience feelings of worry, anger, shame, and depression.[8] Some patients may limit their social outings because of the risk of sunburn or limit activities that may involve exposure of skin. [7] Children and adolescents experience the disease during their emotional development and, for adolescents, this coincides with the period of development of identity. The disease may impact friendships, schoolwork, and patients may be subjected to bullying.[9]

Epidemiology

Vitiligo is estimated to affect 0.5% to 2% of the population worldwide[10] and occurs in males and females with equal frequency.[4] The rates of occurrence do not differ by skin type or race.[5] Onset is before the age of 20 years in approximately 50% of individuals.[3,11] However, it can present at any age.[3,4] Vitiligo may cluster in families, with up to 30% of patients having an affected family member.[12]

Etiology and Pathogenesis

The pathogenesis is not entirely understood, and several mechanisms have been proposed, including genetic susceptibility, autoimmunity (involving cytotoxic T cells),[3,13,14] and oxidative/cellular stress.[11,12] Melanocytes from patients with vitiligo are more vulnerable to oxidative stress compared to melanocytes from those without the disease.[3] This vulnerability may relate to a genetic inability to adequately handle stresses related to normal cellular functions (e.g., melanogenesis) or certain environmental exposures (e.g., injury or chemicals). [3] The "neural hypothesis" posits that the nervous system may play some role in the pathogenesis,[13] and this theory has been suggested as underlying the band-like presentation of segmental vitiligo. Under the neural hypothesis, nerve endings near melanocytes may secrete a neurochemical medicator that is cytotoxic to melanocytes.[15] However, the prevailing theory on causation is autoimmunity, principally because of the autoimmune comorbidities, as further discussed below.[3,4,6] First-degree relatives of patients with vitiligo also have a higher prevalence of many of the same autoimmune diseases, which suggests a general genetic predisposition to

autoimmunity.[17] However, no one mechanism may be causative, and, the "convergence theory" or "integrated theory" proposes that several mechanisms may work in concert to effect melanocyte destruction.[3,13]

Melanocytes are not limited to the skin and may also be found in the eye (uveal tract, retinal pigment epithelium) and ear (membranous labyrinth of the inner ear).[4,17] Additionally, vitiligo pathogenic processes are not specific to melanocytes in the skin; there may be systemic destruction of melanocytes.[4] Affected melanocytes may result in clinical dysfunction of the corresponding organs,[17] and there is a known association between vitiligo and uveitis.[4] Approximately 12.5-18.9% of patients with vitiligo have been reported to have sensorineural hearing loss,[18] mainly involving the high frequency and making it subclinical for most.[19] Bilateral cochlear dysfunction is reported as being common in patients with nonsegmental and segmental vitiligo.[18]

Clinical Features

The 2 major phenotypes are nonsegmental and segmental. These may have different pathophysiological bases[3] and may be considered distinct entities because of the many clinical differences.[20] Rarely, however, a patient may present with both types, a presentation termed "mixed vitiligo."[21]

Nonsegmental vitiligo is most common, representing nearly 85 to 90% of all cases.[11] It generally presents as bilateral, symmetrical lesions. While unpredictable in its course,[3,5] it is generally progressive, with lesions increasing in size and number.[17] The course may be marked by long periods of quiescence, then periods of extension of lesions.[22] Some patients experience an "acceleration phase" of rapid progression in a span of weeks to months.[3] Additionally, patients may display the Koebner phenomenon, wherein new lesions develop at sites of, and in the pattern of, trauma.[17] Spontaneous repigmentation has been reported, but this is thought to be uncommon.[22,23] There are several subtypes, including:

- focal (small, stable macules in random distribution),[13]
- acrofacial (typically limited to head/face, hands, feet),[5,17]
- mucosal (involves oral and/or genital mucosae in isolation or in the setting of more extensive disease),[4,13]
- generalized (widespread, bilaterally distributed macules or patches),[13] and
- universal (or universalis) is near complete depigmentation, involving 80-90% of body surface area.[5,13]

Segmental vitiligo classically presents unilaterally, often in a linear or band pattern.[3] Lesions typically show rapid progression during the initial 6 months to 2 years then spontaneously stabilize.[13,17] However, it is generally not dermatomally oriented, and to describe it as having a "dermatomal distribution" may be inaccurate.[25] Rarely, lesions may spread after years of quiescence.[3] It is reported to occur in 10% to 15% of patients with vitiligo.[26] Approximately 87% of cases occur before the age of 30 years and before the age of 10 years in approximately 41%.[3]

Leukotrichia is a frequent association and develops rapidly.[17] Segmental vitiligo tends to be more resistant to treatment,[13,17] relative to other vitiligo variants. This may relate to the leukotrichia, which limits the potential for repigmentation due to the absence of melanocyte reservoirs in the hair follicles which source the repigmentation.[17] However, in the early stages, segmental vitiligo may potentially respond to the medical therapies and narrowband UVB treatment discussed in Section 2.2.[3]

Comment: *In their phase 3 studies, the Applicant required that subjects have pigmented hairs on the face, but this requirement was not in place for other sites. It is not clear whether this may have (negatively) impacted outcomes for non-facial sites.*

"Vitiligo" is generally used to refer to all forms of vitiligo. However, "vitiligo" has been proposed as an umbrella term to represent all forms of nonsegmental vitiligo.[3,13] In their clinical trials, the Applicant limited enrollment to subjects with nonsegmental vitiligo. In discussion of the clinical development program for ruxolitinib cream, "vitiligo" in this review refers to nonsegmental vitiligo, the Applicant's study population. However, the label should specify the population studied, subjects with nonsegmental vitiligo, as this was the population for whom efficacy and safety were established.

Diagnosis

Irrespective of subtype, vitiligo is usually clinically diagnosed.[13,17] The diagnosis may be aided by examination under Wood's lamp,[11,17]a hand-held device that emits ultraviolet A (UVA).[22] Wood's lamp examination may aid in the diagnosis by enhancing the starkness of the depigmentation, as lesions emit a blue-white fluorescence.[13] Wood's lamp examination may also reveal areas that are not clinically apparent.[22] Dermoscopy may facilitate differentiation of vitiligo from other disorders of depigmentation and may be helpful in assessing disease activity.[13]

Histology

Melanocytes are absent (or nearly so) in vitiligo lesions.[17] In the central region of a lesion, there is a total absence of melanin and melanocytes in the epidermis.[13]In early lesions, an interface dermatitis of CD8+ cytotoxic lymphocytes may be observed, with penetration into the epidermis near the melanocytes.[17] Perivascular and perifollicular lymphocytic infiltrates may be noted at the advancing border of the lesions.[13,17] The absence of melanocytes in a lesion can be assessed noninvasively by in vivo confocal microscopy.[13]

Disease Associations

Vitiligo can be associated with numerous other autoimmune diseases. Thyroid disease (Hashimoto thyroiditis, Graves disease)[12] is the most common association.[12,17] Other

associations include type 1 diabetes mellitus, pernicious anemia, Addision's disease and alopecia areata.[12,16] Additional associations include rheumatoid arthritis, and systemic lupus erythematous.[16]

The Voice of the Patient Report for the Patient-Focused Drug Development Meeting on Vitiligo

The U.S. Food and Drug Administration (FDA) held a public meeting on 03/08/2021 to hear perspectives on vitiligo from patients, caregivers, and other patient representatives. The FDA sought their perspectives on the most relevant symptoms of vitiligo and on current treatment approaches. A Voice of the Patient[24] report was issued in 12/2021 and summarized the input from meeting participants. The report presents key themes from the meeting as including:

- Participants described depigmentation and skin sensitivity as the most burdensome aspects of their vitiligo. Vitiligo is more than a cosmetic condition; it has debilitating physical and emotional impacts.
- Vitiligo has a severe emotional impact on daily life. The disease has caused anxiety, depression, suicidal ideation, a loss of identity and decreased self-confidence. The disease impacts the relationships, working, attending school, and participation in social events.
- Participants described their experiences with therapies, dietary modifications, and corrective cosmetics. They emphasized the need for a long-lasting treatment option that could offer permanent repigmentation. They identified the need for cost- and time-effective treatment options that could be conveniently administered at home.

Additional perspectives included:

- Some described the fear associated with the unpredictability of the disease course.
- The tedious and time-consuming nature of current therapies is a primary reason for discontinuing treatment. Additionally, the cost of treatment is a key concern.
- Some expressed a willingness to accept side effects of a treatment with promising results.
- "Most" participants expressed that their face was the most important area when considering treatment.

Comment: *Many of the expressed sentiments appear to be consistent with information in the literature.*

2.2. Analysis of Current Treatment Options

Treatment of vitiligo has been described as "one of the most difficult dermatological challenges."[13] There are no approved pharmacologic therapies for repigmentation of vitiligo.

The only approved therapy with an indication for vitiligo patients is Benoquin® (monobenzone) Cream, 20% (NDA 008173; approved 11/10/1952). It is not an agent for repigmentation, but is indicated for "final *depigmentation* in extensive vitiligo," and is to be "applied topically to *permanently depigment* normal skin surrounding vitiliginous lesions in patients with disseminated (greater than 50 percent of body surface area) idiopathic vitiligo."[25] Per the most recent annual report (submitted 01/07/2022), "Benoquin (monobenzone) Cream Structured Product Labeling (SPL) is no longer available since the product is not currently manufactured or distributed and has been de-listed."

Important factors to consider in determining a treatment approach include the disease subtype, extent of affected body surface area (BSA), and the disease's impact on the QOL.[13,23] Other factors to consider include skin phototype[13] and the patient's assessment of the risk-benefit calculus.[23] Repigmentation presents in a perifollicular pattern or begins from the lesional edges.[13] Most treatments are time intensive,[13] and responses are typically slow to present.[12]

Topical

Topical treatment (corticosteroids and calcineurin inhibitors) is considered first-line therapy[3,13,23] and may be used as monotherapy for small areas or when other therapies are unavailable.[23] Topical treatment should be discontinued if signs of repigmentation are not apparent after 3 to 4 months of treatment.[26]

Factors to consider in selection of the potency of the topical corticosteroid (TCS) include the location(s) of the lesions to be treated and the age of the patient.[23] TCS are used in various regimens, which may include directed interruptions of use.[3,15,23] Labels for TCS describe numerous potential local and systemic adverse reactions. Listed local potential adverse reactions include atrophy, striae, telangiectasias, burning, itching, and irritation. Hypothalamic pituitary- adrenal (HPA) axis suppression is a potential systemic adverse reaction that is described in product labels. Discontinuous use (e.g., use every other week) may decrease the risk of treatment-related adverse effects.[3,23]

Topical calcineurin inhibitors (TCI), tacrolimus and pimecrolimus, may be selected as initial treatment for areas that are particularly vulnerable to local adverse reactions related to TCS atrophy e.g., face, intertriginous areas.[27] They may be particularly effective for treatment of vitiligo on the face.[12] TCI may also be used on an alternate schedule with TCS i.e., on those days when the TCS are not being used.[23] The labels for TCI include a Boxed Warning that advises that the safety of their long-term use has not been established and that advises against continuous

long-term use.[28,29] Additionally, the Boxed Warning advises that use should be limited to areas affected by atopic dermatitis (AD), the indicated population.[28,29] The Boxed Warning describes that rare cases of malignancy (e.g., skin and lymphoma) have been reported in patients treated with topical calcineurin inhibitors; a causal relationship has not been established.[28,29] Both labels include Warnings and/or Precautions regarding bacterial and viral skin infections and avoidance of sunlight, even when product is not on the skin. [28,29]

When optimal repigmentation has been achieved, TCS or TCI can be tapered and discontinued.[27] If used for maintenance, these products can be used intermittently e.g., twice weekly.[27] TCS and TCI may be used in combination with phototherapy, if the response to phototherapy alone has not been satisfactory.[11,23]

Vitamin D analogs such as calcipotriene have been used for treatment of vitiligo, mostly with other treatments, usually phototherapy.[23] Calcipotriene is ineffective as monotherapy, and such use is not recommended.[12,22]

Systemic

Systemic corticosteroids may be administered to stabilize rapidly progressive disease[23,27] i.e., lesions that are progressing over weeks to months.[27] For disease stabilization, systemic corticosteroids may be dosed by different regimens and administered by different routes (oral or intramuscular).[27] A minipulse regimen may be considered for disease stabilization.[13,15] Minipusle therapy is the discontinuous use of suprapharmacologic doses of oral corticosteroids, usually administered with other treatments.[23]

There are limited data regarding the use of other systemic immunosuppressants and biologics for treatment of vitiligo.[23]

Phototherapy

Phototherapy is indicated for widespread disease, i.e., > 5 to 10% BSA or for disease that is rapidly spreading.[23] For disseminated disease of less than 10% BSA involvement, phototherapy may also be considered, as topical therapy may be impractical with this presentation.[15] Additionally, phototherapy may be considered for more limited disease (< 10%) when topical therapy has been ineffective.[27] Treatment courses span over several months.

The 3 types of phototherapy that are used for treatment of vitiligo are discussed below.

- Narrowband (NB-UVB)

NB-UVB involves use of ultraviolet lamps with peak emission at 311 nm.[11,30] Because of its good safety profile, including the lack of systemic toxicity, NB-UVB may be considered first-line treatment in children and adults with widespread disease.[11,13,27] It is administered 2 or 3 times

weekly. Treatment may be discontinued in the absence of any repigmentation after 3 months of treatment[3,31] or with a poor response (< 25%) after 6 months of treatment.[30] Approximately 9 months of treatment is typically necessary for maximal repigmentation.[11,12] However, it may take 12 to 24 months of continuous treatment to achieve maximal repigmentation.[31] The best results are obtained on the face, then the trunk and limbs.[11] The average treatment period is 9 to 12 months, and if patients are continuing to repigment, treatment may be continued up to 24 months or 200 sessions before tapering treatment.[27] However, there is no consensus on the ideal duration of treatment.[30] If maintenance therapy is needed, sessions may be administered intermittently e.g., a session every other week. However, some authors do not recommend maintenance irradiation.[31] TCS or TCI may be used intermittently with NB-UVB.[27]

- Targeted Phototherapy

Monochromatic excimer light (lasers or lamps with emission at 308 nm) is used for targeted UVB therapy for localized or limited disease.[3,13] This targeted approach lowers the cumulative UVB dose and avoids treatment exposure to unaffected areas.[12,13] It may be as effective as NB-UVB and may work more rapidly.[12] However, it may not stabilize disease, as treatment is directed only at affected sites.[23]

- Psoralen plus UVA

Psoralen, a photosensitizing agent, plus UVA light (320-400 nm) constitutes a photochemotherapy known by the acronym "PUVA." It was the first phototherapy treatment for vitiligo. However, it is used less often now due to an increased risk of skin cancer, compliance issues (e.g., requires post-treatment eye protection against phototoxicity), and side effects (e.g., GI distress).[23] Treatment should be continued for at least 6 months before a determination of unresponsiveness is made, and continuous treatment of 12 to 24 months may be required for maximal repigmentation.[31] Current practices generally favor NB-UVB, which is considered first-line therapy for widespread, progressive disease because it is more effective than PUVA and has a relative better safety profile.[23,27]

Surgical Therapies

Broadly, surgical procedures involve the transplantation of melanocytes from pigmented areas to vitiliginous areas.[27,31] Surgical approaches may be considerations for patients with stable segmental vitiligo or patients with nonsegmental vitiligo that has been unresponsive to other therapies and has been stable for at least 1 year and who have no history of the Koebner phenomenon.[3,31] Disease may be considered to be stable if there have been no new or expanding lesions over a 6 month to 2 year period.[23]

Tissue grafts involve the transplanting of solid tissue from a donor site to a recipient site in a 1:1 ratio[23] and include the following procedures:

- With the punch technique, grafts are obtained from pigmented areas by minipunch biopsy (1 to 1.5 mm),[23] and the graft is inserted into a wound of corresponding size created by punches at the recipient site.[4] It is the simplest and least expensive surgical method.[4,31]

- Suction blister epidermal grafting[23] or blister grafting[4] involves creation of a blister at a donor site of unaffected skin.[4,23] The blister roof from the clinically normal, pigmented site is then grafted onto an abraded surface at the recipient, vitiliginous site.[23]

- Cellular grafts involve the creation of a cellular suspension containing keratinocytes and melanocytes from a skin graft.[4,23,31] These suspensions are either cultured or noncultered.[3,23] Unlike the tissue graft techniques, cellular grafts may allow for treatment of larger areas. However, processing procedures are more complex[13,23] and more expensive than tissue grafts.[23]

Camouflage

Camouflage techniques can be very effective for covering affected areas. Highly-pigmented creams are waterproof and applied daily.[11,23] Self-tanning products are also waterproof and provide coverage that may last for several days.[23,31] The most commonly used self-tanning agent is dihydroxyacetone, a brown dye.[11,12] Some patients may have tattoos placed on vitiliginous areas.[23] However, risks of this approach include poor matching of pigment to native skin color, infection, and progression of the lesion beyond the tattooed area. [23] Also, oxidation of tattoo pigment may result in additional dyschromia.[27]

Sunscreen

Because of the vulnerability of the affected areas, patients should avoid the sun during peak hours and use broad-spectrum sunscreen daily [depending on the area(s) of involvement].[22,26]

Differences in Treatment Responses

There is regional anatomic variation in the likelihood of a response that does not relate to the treatment modality.[12] Generally, the best treatment outcomes are reported for the face.[3] Regarding the likelihood of a response, the prognosis for the face has been deemed “excellent,” the hands and feet may respond in 10 to 20% of patients, and the response of truncal lesions is “intermediate” (to the face and hands and feet).[12] Similarly, Taieb et al. described that the best treatment responses are seen on the face, then the trunk and limbs.[11] Acral lesions are notoriously difficult to treat.[27] Typically, patients are assessed for signs of a treatment response 3 to 6 months after treatment initiation.[27] Indications of a response may be seen 8 to 12 weeks after treatment has begun, characteristically presenting as perifollicular repigimentation.[15] Nicolaidou found that 34.4% of patients achieved cosmetically acceptable results on the face after a mean time of 6 +/- 3.3 months of UVB treatment, while this was true for lesions on the

body of 7.4% of patients after a mean treatment time of 9.2 +/- 3 months of treatment.[32] Yones et al. allowed approximately 4 months of phototherapy before making a determination of absence of improvement.[33]

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

On 09/21/2021, ruxolitinib cream, 1.5% was approved 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. It is currently marketed for this indication under the tradename "Opzelura."

Ruxolitinib is also currently marketed in tablet dosage forms for oral administration under the tradename Jakafi®. Jakafi® was approved on 11/16/2011 under NDA 202192, and Incyte is the owner of that NDA. Jakafi® is approved for the following indications:

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

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant discussed the development program with the Agency at milestone meetings, as discussed below.

<u>End-of-Phase 2 Meeting (05/01/2019)</u>

Comments/Discussion included the following:

- Lesions on the face may be more treatment responsive and may drive outcomes for total body endpoints, e.g., T-VASI, since total body endpoints may consider the disease in toto.

- The sponsor inquired about the acceptability of pursuing an indication of vitiligo of the face. The Agency responded that this would be acceptable.

- The minimum extent of BSA involvement should be sufficiently large to allow a meaningful assessment of efficacy.

- The requirement for pigmented hair within the vitiligo lesion on the face, but not for other sites, could favor positive outcomes for the face.

- The patient assessment(s) may be as important as the objective assessment. The Agency encouraged the Sponsor to engage patients and patient advocacy groups to obtain their perspectives on the extent of repigmentation that would be clinically meaningful.

- The available (limited) literature suggests reliability and validity of the VASI. However, limitations of studies in the literature included small sample size and assessment of only one type of validity[§]. Therefore, the Division recommended that the Applicant use their phase 2 data to support the reliability, validity, and score interpretability of the VASI. The Division noted that the VASI uses a calculated total score, (arithmetic sum of the product of degree of depigmentation and percentage of affected skin for each vitiligo involvement site), which may make scores difficult to interpret and describe clinical benefit (i.e., translate into meaningful labeling). Meaningful interpretability of scores in this instrument will be important (e.g., what does a score represent and how will it be translated for labeling), as well as what constitutes a meaningful improvement in scores.

- Repigmentation outcomes for site-specific endpoints e.g., (b) (4) may not be adequate for establishing efficacy for vitiligo in the broader sense, as site-specific responses may not be generalizable to other affected sites.

- The phase 3 trials can be designed to establish efficacy for the total body with the option to establish efficacy for the face only. (b) (4)

[§] The literature cited by Applicant (Hamzavi I, Jain H, McLean D, Shapiro J, Zeng H, Lui H. Arch Dermatol 2004;140:677-683) for VASI validation used photographic assessment and is different from that in the Incyte studies with direct visual assessment. Importantly, the study included assessment of hand, upper extremities (excluding hands), trunk, feet and lower extremities (excluding feet) but not head and neck or face and thus does not support VASI evaluation of face. In addition, the phase 3 trials implemented use of VASI as the Applicant deferred addressing the COA recommendations for validation. The phase 3 VASI results were part of the data used for validation after completion of pivotal studies.

(b) (4). In this case, the Agency would expect total body involvement to be recorded at baseline, treatment should include all involved areas and total body response should be evaluated as well. Minimum enrollment criteria on an acceptable vitiligo disease severity scale should be prespecified in the protocol for the indication (b) (4)) that the Applicant would be seeking.

- (b) (4)

- After assessment of the validity and reliability of the scale, the Applicant may investigate the appropriate threshold level on the VASI score and how it correlates with a meaningful change of the investigator and patient scales (e.g., anchor based analyses), as well as patient input from their exit interview study. The Agency recommended that the Applicant submit the discussion guide and interview transcripts for the exit interview study and publications that support the patient experience of vitiligo.

- A 30-day posttreatment follow-up period was not of sufficient duration to adequately assess the durability of effect (repigmentation). The Agency requested that the Applicant propose a longer posttreatment follow-up duration, to permit meaningful assessment of durability of repigmentation. Also, the Applicant was requested to address how they would assess maintenance treatment (which may differ from treatment that induced the response).

<u>Pre-sNDA (07/28/2021)</u>

Comments/Discussion (information reiterated from the EOP2 is not repeated below):

- The topline data appeared sufficient to support an sNDA for the indication of vitiligo of the face in patients 12 years of age and older. Support for a broader indication would be a review issue. The Agency noted that the primary endpoint in both phase 3 trials was the F-VASI75 at Week 24.

The Applicant indicated that they planned to seek the broad indication of vitiligo based on the reported statistically significant findings for the T-VASI50. The Agency noted that the study was designed, including power, for F-VASI75 and the indication is generally guided by the primary endpoint for the clinical trials. T-VASI50 was a secondary endpoint, and the 50% improvement from baseline may not be the appropriate threshold level for evaluating efficacy. As the clinical trials were completed, discussion about an indication that differed from the primary endpoint would be a review issue, and analysis of other threshold levels would be post-hoc.

The Agency expressed concerns about the limited amount of long-term safety data that the Applicant planned to provide, including the amount of data in adolescents, at the time of sNDA submission, in light of the safety issues reported in association with JAK inhibitors. The Agency did not specify any numbers for the safety database. During meeting discussion, the Agency noted that the number of adolescents appeared to be too small to make a reasonable safety evaluation for this age group. Additional safety data for adolescents would be helpful.

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

4.1. Office of Scientific Investigations (OSI)

From the Clinical Inspection Summary

OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS:
Incyte Corporation has submitted data from two phase-3 studies to the Agency in support of a supplemental New Drug Application (NDA 215309-S1) for ruxolitinib cream as a topical treatment for vitiligo in patients 12 years of age and older. Three clinical investigators (Drs. Feser, Rayhan, and Rkein) were selected for surveillance clinical inspections.

Based on these inspections, studies INCB18424-306 and INCB18424-307 appear to have been adequately conducted, and the study data generated by the inspected entities appear acceptable in support of the indication in this sNDA.

RESULTS (by Site)

1. **Christina Feser, D.O.**
   1035 N. Highland Ave., Murfreesboro, TN 37130,
   USA Study: INCB18424-306
   Site Number: 603
   Dates of Inspection: 2/9/2022-2/15/2022

   This inspection was conducted on-site. At the time of the inspection, 25 subjects were screened, 20 enrolled and 10 subjects finished the study. Primary efficacy data: Baseline and week 24's facial BSA and facial lesion's depigmentation scores for the 20 enrolled subjects were reviewed against source data, with no discrepancies. There was no evidence of under- reporting of protocol deviations. The inspection revealed no deficiencies with maintenance of the blind.

   A concomitant, restricted medication for one participant was recorded, but not included in the individual patient- level data line listings submitted to the Agency. The medication was given over a 2 week period.

Subject/(Arm)	Concomitant Medication not reported	Dates	Notes
(b) (6) / (ruxolitinib 1.5%)	Prednisone, "1 tab", PO Daily	02/14/2020-02/28/2020	Given for AE: sinusitis reported on 2/14/2020-2/28/2020; deemed unlikely related to IP

Reviewer comment: The protocol considers less than 7 days' use of oral corticosteroid for nondermatologic reasons as a restricted medication and procedure, but makes no determination of oral corticosteroid use for longer than 7 days for nondermatologic reasons as either prohibited or restricted. Regardless, the medication should have been included in reporting to FDA.

Except the finding described above, the inspection revealed adequate adherence to the regulations and the investigational plan. Data from this site appear acceptable in support of is NDA.

2. David Rayhan M.D.
17742 Beach Blvd, Ste 245, Huntington Beach, CA 92647, United States
Study: INCB18424-306
Site Number: 610
Dates of Inspection: 1/3/2022-1/5/2022

This inspection was conducted on-site. At the time of the inspection, 28 subjects were screened and 17 enrolled into the study. There were no issues with the informed consent process. Data for all 28 subjects were reviewed. Primary efficacy data: baseline and week 24's facial BSA and facial lesion's depigmentation scores were verified for all enrolled subjects. There was no evidence of under-reporting of adverse events or under-reported protocol deviations. The inspection revealed no deficiencies with maintenance of the blind.

Overall, the inspection revealed adequate adherence to the regulations and the investigational plan. Data from this site appear acceptable in support of this NDA.

3. Ali Rkein M.D.
1688 E. Boston St., Gilbert, AZ 85295, United States
Study: INCB18424-307
Site Number: 711
Dates of Inspection: 3/7/2022-3/10/2022

This inspection was conducted on-site. At the time of the inspection, 28 subjects were screened and 17 enrolled into the study, with 9 subjects completing the study. 22

subjects' consents were reviewed, and primary efficacy data--baseline and week 24's facial BSA and facial lesion's depigmentation scores ---for 7 subjects were verified against source data. All primary efficacy endpoints were verifiable. There was no evidence of under-reporting of adverse events or under-reported protocol deviations. The inspection revealed no deficiencies with maintenance of the blind. There were no issues with the informed consent process, or IP administration.

Overall, the inspection revealed adequate adherence to the regulations and the investigational plan. Data from this site appear acceptable in support of this NDA.

4.2. Product Quality

Executive Summary:
This Efficacy supplement was submitted to NDA 215309 for Opzelura® (ruxolitinib) Cream, 1.5%, to provide for a new indication: the topical treatment of vitiligo in patients 12 years of age and older.

No changes were proposed to the CMC-related sections of the labeling (Sections 3 Dosage Forms and Strengths, 11 Description, 16 How Supplied/Storage and Handling) or to the carton and container labels.[**]

The Applicant has requested a Categorical Exclusion from the requirement for preparation of an Environmental Assessment for the proposed change, which would result in increased usage of the active moiety upon approval. The claim included an estimate of total annual usage of the active ingredient from all products, and a calculation of the Estimated Introduction Concentration (EIC) therefrom; the estimate falls well below the 1ppb action limit. The Categorical Exclusion request is therefore granted.

Conclusions & Recommendations:
This supplement is recommended for approval.

Comments/Deficiencies to be Conveyed to Applicant:
None. Approval is recommended.

[**] There were no changes when the sNDA was submitted, but approval of a manufacturing supplement in April 2022 added a 100-gram tube of OPZELURA for marketing. Thus, labeling for the current supplement (S001) will be adjusted to include the additional information about the 100-gram tube, including dosing limit with the 100-gram tube (100 gm per 2 weeks) in the Dosage and Administration section of labeling and in the Medication Guide.

5 Nonclinical Pharmacology/Toxicology

In this efficacy supplement the applicant provided additional in vitro pharmacology information to support the development of OPZELURA Cream for the vitiligo indication. The applicant also proposed minor labeling changes. 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 dated 02/18/2022 for detailed information.

6 Clinical Pharmacology

6.1. Executive Summary

Ruxolitinib is a Janus kinase (JAK) inhibitor with selectivity for JAK1 and JAK2 isoforms. Intracellular JAK signaling is known to be associated with STAT (signal transducers and activators of transcription) signaling of cytokine receptors and modulation of gene expression. Inflammatory cytokines such as IL-4, -13, and -22 involved in the pathogenesis of atopic dermatitis are thought to be linked to the JAK/STAT pathway activation.

In 2021, ruxolitinib 1.5% cream (OPZELURA®) was approved for the topical treatment of short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis (AD) in non-immunocompromised patients 12 years of age and older whose disease is not adequately controlled with other topical prescription therapies or when those therapies are not advisable. The approved dosing regimen for AD is application of a thin layer of ruxolitinib 1.5% cream twice daily to affected areas of up to 20% body surface area. Do not use more than 60 grams per week or100 grams per 2 weeks.

Under this supplemental NDA (sNDA), the Applicant has submitted data and study reports to support topical ruxolitinib cream, 1.5%, to treat subjects with vitiligo in patients 12 years of age and older. The proposed dosing regimen for the treatment of vitiligo is the application of a thin layer of ruxolitinib 1.5% cream twice daily to affected areas of up to 10% body surface area. To support this indication, the Applicant conducted a phase 2 dose-ranging study (INCB 18424-211) and two pivotal Phase 3 studies (INCB 18424-306 and INCB 18424-307) to evaluate the efficacy and safety of ruxolitinib cream, 1.5%, in patients 12 years and older with up to 10% BSA involved with vitiligo. Trough level PK assessment of ruxolitinib in Phase 3 trials indicated that plasma ruxolitinib Css generally increases with age, %BSA treated and application rate and decreases with total BSA. The Applicant proposed to limit the BSA to 10% in the proposed label which is reasonable as they have not studied higher % BSA in the Phase 3 trials.

Recommendation

The office of Clinical Pharmacology/Division of Inflammation and Immune Pharmacology finds NDA 215309 S-001 acceptable.

PMC/PMR recommendation

None.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Pharmacokinetics of ruxolitinib in phase 3 trials

Studies INCB 18424-306 (306) and INCB 18424-307 (307) were two identical, double-blind, vehicle-controlled, randomized studies in subjects with nonsegmental vitiligo with ≥ 0.5% F-BSA, ≥ 0.5 F-VASI, ≥ 3% BSA on nonfacial areas, and ≥ 3 T-VASI and with total body involved vitiligo area (facial and nonfacial) not exceed 10% BSA.

During the double-blind, vehicle-controlled period, participants applied ruxolitinib 1.5% cream BID or vehicle BID for 24 weeks. After completion of the Week 24 assessments, participants were offered the opportunity to continue in the treatment extension period. Participants initially randomized to vehicle were crossed over to active drug, and participants treated with ruxolitinib cream received an additional 28 weeks of treatment with ruxolitinib 1.5% cream BID.

Trough plasma ruxolitinib concentrations for the pooled Phase 3 population were similar at Weeks 4, 24, and 40 after treatment with ruxolitinib 1.5% cream BID, which indicates steady state was reached at or before Week 4. Application of ruxolitinib 1.5% cream BID resulted in mean (geometric mean, GCV%) Css (average of trough concentrations per participant) of 57 nM (27.4 nM, 282%). Similar Css were observed for participants from Europe and North America, for participants with Fitzpatrick scale Types I or II and Types III, IV, V, or VI, and/or the combination of geographic region and Fitzpatrick scale types. The Css for the age groups of 18 to < 65 years (n = 347) and ≥ 65 years (n = 28) are comparable, although relatively lower Css was observed for the age group of 12 to < 18 years (n = 54). The mean (geometric mean) topical bioavailability for ruxolitinib cream in participants with vitiligo in this study was 9.72% (5.78%). The extent of variability in estimated bioavailability was high: > 200% GCV overall.

Summary of safety in phase 3 trials (based on interim data with cutoff date 03/18/2021)

In both trials (306 and 307), there were no fatal TEAEs and no events that appeared to be related to long-term treatment with ruxolitinib cream. Ruxolitinib cream was generally well-tolerated in participants with vitiligo. In the primary analysis of the 24-week, vehicle-controlled, double-blind (DB) period; application site acne was the most common TEAE among participants who applied ruxolitinib 1.5% cream BID and was reported in more participants treated with ruxolitinib cream than vehicle cream (5.8% in the ruxolitinib cream BID treatment group vs 0.9% in the vehicle cream BID treatment group). Other common TEAEs in participants in the ruxolitinib 1.5% cream BID treatment group (> 2%) included application site pruritus, nasopharyngitis, headache, COVID-19, upper respiratory tract infection, and sinusitis; of these events, application site acne, application site pruritus, and nasopharyngitis were reported more frequently for the ruxolitinib 1.5% cream BID treatment group compared with the vehicle cream treatment group (≥ 2.0% difference in incidence). The frequency of Grade 3 or higher TEAEs, serious TEAEs, and TEAEs leading to study drug interruption or discontinuation was low for all pooled populations. For additional details see Section 8 of this review.

Metabolism of ruxolitinib

In vitro studies suggest that CYP3A4 is the major enzyme responsible for metabolism of ruxolitinib. Ruxolitinib is the predominant entity in humans, representing approximately 60% of the drug-related material in circulation following oral administration. Two major and active metabolites were identified in the plasma of healthy participants, representing 25% and 11% of the parent AUC. These 2 metabolites have one-fifth and one-half of the pharmacological activity of ruxolitinib, respectively. The sum of all active metabolites contributes to 18% of the overall PD of ruxolitinib when administered orally.

The metabolism of ruxolitinib was examined in plasma from participants with psoriasis topically treated with ruxolitinib cream (0.5% QD, 1.0% QD, and 1.5% QD) for 12 weeks in study INCB 18424-203. Ruxolitinib was transdermally absorbed and underwent oxidative metabolism consistent with metabolic pathways elucidated following oral administration of ruxolitinib in humans. The parent molecule, ruxolitinib, was the predominant moiety detected in plasma. Five metabolites identified in plasma, all of them mono-oxygenated species, had also been found after oral dosing in humans and preclinical species and at levels of 10% to 25% of the parent compound on at least 1 day during treatment. Trace-level metabolites with expected abundances of less than 1% of parent ruxolitinib were also detected but were not reported. Based on the low plasma concentrations following topical administration, no significant pharmacological activity related to the metabolites is expected. Furthermore, the role of metabolites towards efficacy of a topically administered product is not very well understood at this time. In the original ruxolitinib cream approval, based on the evidence collected from study INCB 18424-203, the Applicant obtained agreement from the Agency on not conducting metabolite assessments in the maximum usage study (MUsT) in participants with AD.

Drug interaction of ruxolitinib

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

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

Dosing in subjects with renal or hepatic impairment

Since the %BSA treated in the approved labeling will be limited to not more than 10% and the systemic exposure in subjects that would use the product as per the approved labeling is expected to be lower than the lowest oral dose of 5 mg, no specific dosing recommendation is being proposed for subjects with renal or hepatic impairment.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed dosing regimen is to apply a thin layer of ruxolitinib cream 1.5% twice daily to affected areas via topical route to a body surface area of not more than 10%. Do not use more than 60 grams per week or 100 grams per 2 weeks.

Therapeutic Individualization
The Applicant has not proposed any therapeutic individualization. The available clinical pharmacology information does not warrant a need for therapeutic individualization.

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

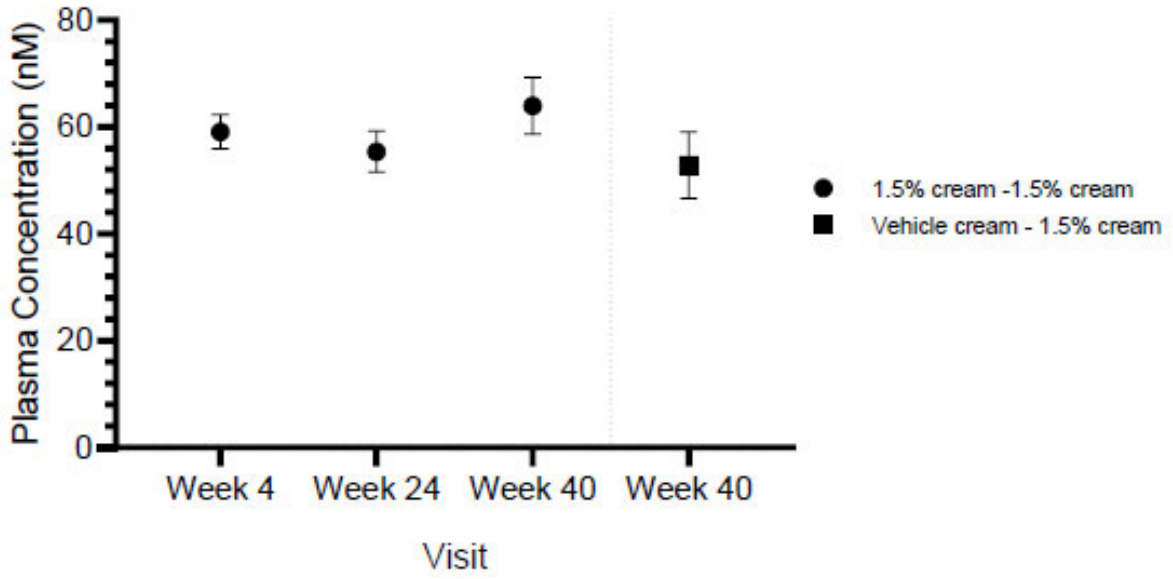
Phase 3 trials:

Studies INCB 18424-306 (306) and INCB 18424-307 (307) were two identical, double-blind, vehicle-controlled, randomized studies of subjects with nonsegmental vitiligo with ≥ 0.5% F-BSA, ≥ 0.5 F-VASI, ≥ 3% BSA on nonfacial areas, and ≥ 3 T-VASI and with total body involved vitiligo area (facial and nonfacial) not exceed 10% BSA. Participants were stratified by region (North America or Europe) and skin type (Fitzpatrick scale Type I or II vs Type III, IV, V, or VI). The PK population includes 429 participants (214 and 215 in Studies INCB 18424-306 and INCB 18424-307, respectively) in the double-blind, vehicle-controlled period and 290 participants (147 and 143 in Studies INCB 18424-306 and INCB 18424-307, respectively) in the treatment extension period.

During the double-blind, vehicle-controlled period, participants applied ruxolitinib 1.5% cream BID or vehicle BID for 24 weeks to depigmented areas only on the face and body up to 10% total BSA. Participants were instructed to continue treating depigmented areas identified for treatment at baseline even if the area began to improve or fully repigmented. After completion of the Week 24 assessments, participants were offered the opportunity to continue in the treatment extension period. Participants that were initially randomized into vehicle arm were crossed over into active drug arm, and participants treated with ruxolitinib cream received an additional 28 weeks of treatment with ruxolitinib 1.5% cream BID. To be eligible for the treatment extension, participants must have completed the baseline and Week 24 visit assessments, be compliant with study procedures, and not have any safety issues. During the treatment extension, participants continue to treat depigmented areas identified for treatment at baseline even if the area begins to improve or fully repigmented. Total treated areas (facial and nonfacial) should not exceed 10% BSA.

Trough plasma ruxolitinib concentrations for the pooled Phase 3 population were similar at Weeks 4, 24, and 40 after treatment with ruxolitinib 1.5% cream BID (**Figure 1**), which indicates steady state was reached at or before Week 4. Application of ruxolitinib 1.5% cream BID resulted in mean [geometric mean, geometric coefficient of variation (GCV%)] Css (average of trough concentrations per participant) of 56.9 nM (27.4 nM, 282%) (**Table 1**). Similar Css were observed for participants from Europe and North America, and for participants with Fitzpatrick scale Types I or II and Types III, IV, V, or VI, and/or the combination of geographic region and Fitzpatrick scale types (**Figure 2**). The Css for the age groups of 18 to < 65 years (n = 347) and ≥ 65 years (n = 28) were comparable, although relatively lower Css was observed for the age group of 12 to < 18 years (n = 54) (**Figure 2**). The mean (geometric mean) topical bioavailability for ruxolitinib cream in participants with vitiligo in this study was 9.72% (5.78%). The extent of variability in estimated bioavailability was high: > 200% GCV overall and > 100% GCV for all subgroups by geographic region, skin types, or age group.

Figure 1. Plasma Concentrations of Ruxolitinib (Mean ± SE) Following Topical Administration of Ruxolitinib 1.5% Cream BID in Phase 3 Studies



Source: Figure 2. 2.7.2 Summary of Clinical Pharmacology Studies (vitiligo)

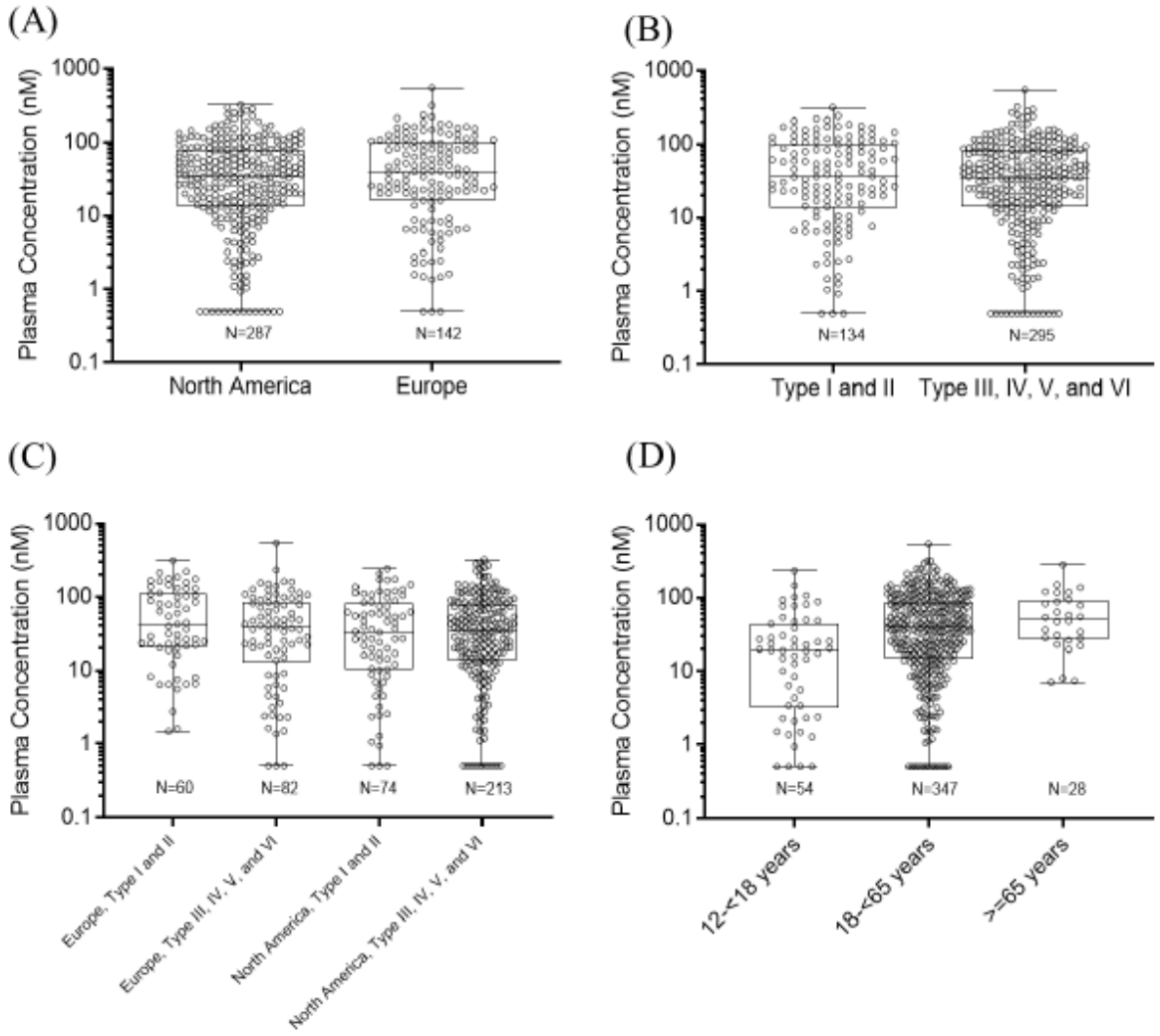
Table 1. Summary of Baseline Population Characteristics and Ruxolitinib Steady-State Pharmacokinetic Parameters by Geographic Region, Skin Type, and Age Group in Phase 3 Vitiligo Studies

Groups		N	BSA (m^2)	% BSA (%)	C_{ss} (nM)[a]	Bioavailability (%)
All participants		429	1.88 ± 0.253 (1.86, 13.6)	7.31 ± 2.02 (7.00, 31.2)	56.9 ± 62.6 (27.4, 282)	9.72 ± 8.14 (5.78, 205)
Region	Europe	142	1.82 ± 0.261 (1.8, 14.4)	7.28 ± 1.91 (7.01, 29)	63.2 ± 71.3 (30.9, 263)	10.8 ± 8.56 (6.97, 167)
	North America	287	1.91 ± 0.245 (1.89, 12.9)	7.32 ± 2.07 (6.99, 32.3)	53.8 ± 57.7 (25.8, 291)	9.20 ± 7.88 (5.27, 223)
Skin type	Type I or II	134	1.88 ± 0.254 (1.86, 13.6)	7.24 ± 2.11 (6.9, 32.9)	60.7 ± 61.8 (29.7, 268)	10.4 ± 7.42 (6.62, 200)
	Type III, IV, V, or VI	295	1.88 ± 0.254 (1.86, 13.6)	7.34 ± 1.98 (7.04, 30.5)	55.2 ± 63.0 (26.4, 288)	9.40 ± 8.43 (5.44, 207)
Age	12 to < 18 years	54	1.67 ± 0.266 (1.65, 15.7)	7.30 ± 2.20 (6.93, 34.9)	32.4 ± 43.1 (12.4, 371)	7.71 ± 7.99 (3.62, 304)
	18 to < 65 years	347	1.91 ± 0.242 (1.89, 12.6)	7.28 ± 1.98 (6.99, 30.4)	59.9 ± 64.7 (29.7, 268)	9.84 ± 8.12 (5.99, 195)
	≥ 65 years	28	1.92 ± 0.186 (1.91, 9.33)	7.62 ± 2.13 (7.26, 34.6)	66.6 ± 59.0 (46.2, 116)	12.2 ± 8.06 (9.21, 116)

[a] C_{ss} is the average concentration of Weeks 4 and 24 for individual participants.
Note: Values are presented in the format of mean ± STD (geometric mean, GCV%).

Source: Table 3. 2.7.2 Summary of Clinical Pharmacology Studies (vitiligo)

Figure 2. Comparison of Steady-State Ruxolitinib Plasma Concentration Following Topical Administration of Ruxolitinib 1.5% Cream Twice Daily in Phase 3 Studies by Geographic Region (A), Skin Type (B), Region and Skin Type (C), and Age (D) Group



Source: Figures 3. 2.7.2 Summary of Clinical Pharmacology Studies (vitiligo)

***In-vitro* metabolism and *in vitro* DDI studies:**

In the original oral ruxolitinib NDA, the Applicant conducted a total of 11 *in vitro* metabolism and drug interaction studies to assess the metabolism of ruxolitinib and drug interaction potential of ruxolitinib. No new studies were conducted for the topical dosage form of ruxolitinib. The results of the *in vitro* metabolism studies indicate that CYP3A4 is mainly responsible for ruxolitinib metabolism.

There were 8 oxidative metabolites identified *in vitro*, which are pharmacologically active, but their activity is 20% to 50% of the activity of the parent compound. Results from *in vivo* study with topical ruxolitinib cream 1.5% demonstrated that plasma metabolite concentrations following topical application were low relative to the parent. The systemic exposures of the metabolites were not assessed in MUsT and this was considered acceptable in the ruxolitinib cream original approval for AD indication (NDA 215309, approved 09/21/2021) and is also considered acceptable for vitiligo indication.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

No. For topical product, PK assessed under maximal use conditions in the original ruxolitinib cream approval (for AD) supports systemic safety rather than efficacy. No new maximal use study was conducted for vitiligo indication as the original maximal use study for the AD indication was considered as supportive.

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

Yes.

Clinical pharmacology considers the Applicant proposed ruxolitinib cream dosing regimen for vitiligo (see below) acceptable:

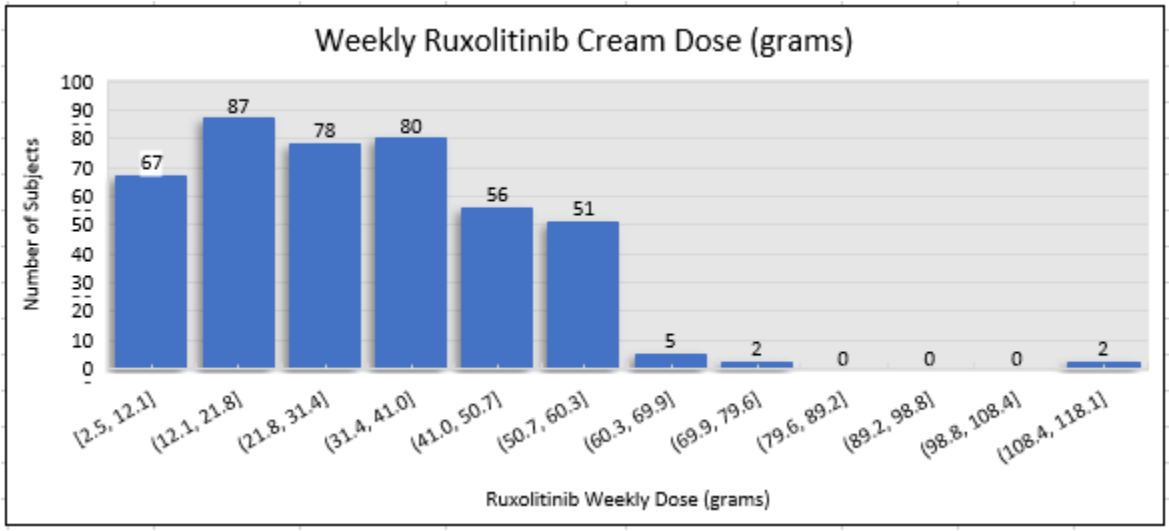
- Apply a thin layer of ruxolitinib cream 1.5% twice daily to affected areas via topical route to a body surface area of not more than 10%. Do not use more than 60 grams per week or 100 gm per 2 weeks.

Clinical pharmacology found the Applicant proposed dose reasonable due to the following reasons:

- The average daily ruxolitinib usage based on the pooled pivotal phase 3 studies (306 and 307) was estimated to be (b) (4) which was equivalent to a weekly average application of ruxolitinib cream at (b) (4).
- Considering the average %BSA treated in the pooled pivotal phase 3 studies assessed to be 7.31%, when a body surface area of 10% (the maximal allowed %BSA treated) being treated, the weekly average application of ruxolitinib cream would be (b) (4).

- As shown in the weekly ruxolitinib cream dose distribution observed in the pooled pivotal phase 3 studies, more than 97% of patients were treated with ruxolitinib cream lower than 60 grams per week (**Figure 3**).

Figure 3. Weekly Ruxolitinib Cream Application (grams)



Source: Reviewer's independent analysis

Hence, the Applicant proposed ruxolitinib cream total dose of no more than 60 grams per week or 100 grams per 2 weeks appears acceptable.

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

Plasma ruxolitinib Css generally increases with age, %BSA treated and application rate and decreases with total BSA (See Appendix. studies INCB18424-211, INCB18424-306, INCB18424-307 and pharmacometrics review). No specific dosing is being recommended for subjects with renal or hepatic impairment (See Section 6.2.1).

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

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

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 2. Listing of Clinical Trials*

Study Identifier (Type of Study)	Primary Objective(s) of the Study	Study Design and Type of Control	Test Product(s), Dosage Regimen, and Route of Administration	Number of Participants Enrolled	Healthy Participants or Diagnosis of Participants	Estimated Duration of Treatment	Study Status; Type of Report	Countries Involved
INCB 18424-211 (Efficacy, safety, dose-response); Week 52 and Week 104	Efficacy	Randomized, double-blind, vehicle-controlled, dose-ranging, multicenter, Phase 2 study	Ruxolitinib cream 0.15%, 0.5%, 1.5% QD, topical Ruxolitinib 1.5% cream BID, topical Vehicle cream, QD or BID topical	157 (VC Period 32: vehicle BID, 31: 0.15% QD, 31: 0.5% QD, 30: 1.5% QD, 33: 1.5% BID) (Continued DB Period 14: vehicle BID or 0.15% QD to 0.5% QD, 14: vehicle BID or 0.15% QD to 1.5% QD, 14: vehicle BID or 0.15% QD to 1.5% BID 11: 0.15% QD 30: 0.5% QD 26: 1.5% QD 30: 1.5% BID) (Open-Label Extension Period 122: 1.5% BID)	Adult participants with vitiligo	156 weeks total 24 weeks (VC period) 28 weeks (DB period) 104 weeks (open-label extension period)	VC and DB periods completed, Open-label extension ongoing; Interim (Week 52 and Week 104)a	US

Study Identifier (Type of Study)	Primary Objective(s) of the Study	Study Design and Type of Control	Test Product(s), Dosage Regimen, and Route of Administration	Number of Participants Enrolled	Healthy Participants or Diagnosis of Participants	Estimated Duration of Treatment	Study Status; Type of Report	Countries Involved
INCB 18424-306 *(Efficacy, safety) 5.3.5.1*	Efficacy	Randomized, double-blind, vehicle-controlled multicenter, Phase 3 study	Ruxolitinib 1.5% cream BID, topical Vehicle cream BID, topical	330 (DB period 221: 1.5% BID, 109: vehicle BID) (TE period 283: 1.5% BID	Adolescents and adults with non-segmental vitiligo with depigmented area including ≥ 0.5% BSA on the face, ≥ 0.5 F-VASI, ≥ 3% BSA on nonfacial areas, ≥ 3 T-VASI and total body vitiligo area (facial and nonfacial) not exceeding 10% BSA	52 weeks total 24 weeks (DB period) 28 weeks (TE period)	DB period completed, TE period ongoing; Interimb	Bulgaria, Canada, France, Germany, Italy, Poland, Spain, US
INCB 18424-307 *(Efficacy, safety)*	Efficacy	Randomized, double-blind, vehicle-controlled multicenter, Phase 3 study	Ruxolitinib 1.5% cream BID, topical Vehicle cream BID, topical	344 (DB period 228: 1.5% BID, 115: vehicle BID) (TE period 297: 1.5% BID	Adolescents and adults with nonsegmental vitiligo with depigmented area including ≥ 0.5% BSA on the face, ≥ 0.5 F-VASI, ≥ 3% BSA on nonfacial areas, ≥ 3 T-VASI and total body vitiligo area (facial and nonfacial) not exceeding 10% BSA	52 weeks total 24 weeks (DB period) 28 weeks (TE period)	DB period completed, TE period ongoing; Interimb	Bulgaria, Canada, France, Germany, Netherlands, Poland, Spain, US

Study Identifier (Type of Study)	Primary Objective(s) of the Study	Study Design and Type of Control	Test Product(s), Dosage Regimen, and Route of Administration	Number of Participants Enrolled	Healthy Participants or Diagnosis of Participants	Estimated Duration of Treatment	Study Status; Type of Report	Countries Involved
INCB 18424-308c (Efficacy, safety)	Efficacy	Phase 3, double-blind, vehicle-controlled, randomized withdrawal (Cohort A) and treatment extension (Cohorts A and B) study	Cohort A: ruxolitinib 1.5% cream BID or vehicle cream BID, topical Cohort B: ruxolitinib 1.5% cream BID	155 totald Cohort A: 47 Cohort B: 108	Adolescent and adult participants with nonsegmental vitiligo who successfully complete Studies INCB 18424-306 or -307 without safety concerns and with good compliance	52 weeks	Ongoing; NA	Canada, USe
0306090 (Noninterventional)	Patient-reported outcomesf	Individual phone interviews with patients	NA	23	Adolescents and adults with facial vitiligo	NA	Completed; Final	US

* Source: Section 5.2 of NDA 2153-0/S-001

a The interim Week 52 and Week 104 CSRs report results through the Week 52 visit and results through a data cutoff date of 12 MAR 2020 (when all participants had completed the Week 104 visit), respectively.

b The interim CSR reports results through a data cutoff date of 18 MAR 2021, when all participants had completed the Week 24 visit.

c Location of the study Protocol and SAE line listings. Data from the clinical database are not included in the submission.

d Number of participants enrolled as of 18 MAR 2021.

e Countries with sites that had enrolled participants as of the data cutoff date (18 MAR 2021).

f The objective of these qualitative interviews was to better understand patients' experiences with facial vitiligo and the outcomes most important to them and to support use of the F-VASI instrument in the Phase 3 clinical studies of vitiligo.

7.2. Review Strategy

The Applicant has included data from 3 studies conducted in subjects with vitiligo:

- 2 identical phase 3 studies in adolescents and adults: INCB 18424-306 and -307 (306 and 307, respectively).
- a phase 2 study in adults with vitiligo INCB 18424-211 (211).

Studies 306 and 307 evaluated treatment of up to 10% affected body surface area (BSA) (face and body), and consist of:

- a vehicle-controlled, double-blind period (Day 1 through Week 24), which evaluated ruxolitinib cream, 1.5% twice daily (BID) and vehicle and
- an open-label treatment extension period (Weeks 24 through 52), in which all subjects were treated with 1.5% BID.

At the time of data cut-off for the sNDA (03/18/2021), all subjects had either completed treatment through Week 24 in Studies 306 and 307 or discontinued treatment early. The extension treatment period was ongoing at the time of data cut-off for the supplement. The Applicant submitted data through Week 52 in response to an Information Request.

Study 211 was a phase 2 dose-ranging study in adults and evaluated up to 20% affected BSA and consists of 3 periods:

- a completed vehicle-controlled, double-blind period (Day 1 through Week 24), which evaluated the following treatment regimens:
  - ruxolitinib cream, 0.15%, 0.5%, and 1.5% once daily (QD)
  - ruxolitinib cream, 1.5% BID
  - Vehicle BID
- a double-blind extension period, which continued evaluation of the above regimens, with cross-over of vehicle subjects to one of the active arms (Weeks 24 through 52; completed), and
- an open-label extension period, in which all subjects received treatment with ruxolitinib 1.5% BID (Weeks 52 through 156; ongoing at data cut-off).

INCB 18424-308 (308) is the fourth study conducted in subjects with vitiligo and was also ongoing at data cut-off. Study 308 is a vehicle-controlled, double-blind, randomized withdrawal treatment extension study that enrolls subjects from the phase 3 studies (306 and 307) after 52 weeks of treatment and continues treatment through Week 104 (i.e., an additional treatment extension of 52 weeks). The Applicant did not include safety or exposure data from study 308, as data from the vehicle-controlled cohort remain blinded, and they considered “insufficient” data to be available from the open-label cohort to “meaningfully summarize.”

The names of all clinical studies begin with “INCB 18424-,” with specific studies being identified by the number that follows the hyphen. In this review, studies are referenced by the specific

identifying number. For example, the pivotal studies for vitiligo were “INCB 18424-306” and “INCB 18424-307” and are referenced in the review as “306” and “307.”
The Applicant also references studies 306 and 307 by an acronym based on the titles of the phase 3 studies: ***T***opical ***Ru***xolitinib ***E***valuation in ***V***itiligo Study **1** (TRuE-V1) is study 306 and TRuE-V2 is study 307. The phase 3 studies will be referenced by these titles in product labeling.

The review will focus on data from the phase 3 studies 306 and 307, as the Applicant is relying on these data for approval, and these data provide the primary safety and efficacy data. The dose chosen for the phase studies (1.5% cream twice daily) is based on data from Study 211.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Studies INCB 18424-306 and INCB 18424-307

Trial Design

Study INCB 18424-306 (Study 306) and Study INCB 18424-307 (Study 307) were identical randomized, double-blind, vehicle-controlled Phase 3 trials in subjects with nonsegmental vitiligo. The studies enrolled subjects 12 years of age and older with a clinical diagnosis of nonsegmental vitiligo. Vitiligo severity was assessed using the Face Vitiligo Area Scoring Index (F-VASI) and the Total Body Vitiligo Area Scoring Index (T-VASI). The VASI has two components: percent body surface area (BSA) of vitiligo involvement for each vitiligo site and the degree of depigmentation for each vitiligo site.[††] Based on protocol instruction, the “degree of depigmentation” is a scale estimated as follows:

- “The degree of depigmentation for each vitiligo involvement site is determined and estimated to the nearest of the following percentages: 0, 10%, 25%, 50%, 75%, 90%, or 100%. At 100% depigmentation, no pigment is present; at 90%, specks of pigment are present; at 75%, the depigmented area exceeds the pigmented area; at 50%, the depigmented and pigmented area are equal; at 25%, the pigmented area exceeds the depigmented area; at 10%, only specks of depigmentation are present.”

[††] As described in the protocol, “degree of depigmentation” was an ***estimation of the area of depigmentation*** within the lesion being assessed ***instead of the severity of pigment loss,*** using the ***discontinuous scale*** as stated above (also see Figures 37 and 38 in Appendix 15.5). As such, both components of VASI are area-based, i.e., (%BSA of lesion or region) x (estimated %area affected by depigmentation within the lesion or region) and would ***not*** address the degree of pigment loss. In addition, the definitions are imprecise; for instance, a 75% value can cover depigmentation within the assessed site from 51% to 89% because it only requires the size of the depigmented area to be in excess of the pigmented area’s.

At baseline, subjects were to have:[‡‡]

- ≥ 0.5% body surface area (BSA) on the face and a score ≥ 0.5 on the F-VASI
- ≥ 3% BSA on non-facial areas and a score ≥ 3 on the T-VASI at baseline
- total body vitiligo area ≤ 10% BSA

Each study was designed to enroll approximately 300 subjects randomized in a 2:1 ratio to ruxolitinib 1.5% cream BID or vehicle cream BID. Areas on the face and body identified for treatment at baseline were treated twice daily for 24 weeks, even if the area fully repigmented.

At Week 24, subjects who completed the Week 24 assessments with no safety concerns entered a 28-week open-label period where all subjects were treated with ruxolitinib 1.5% cream through Week 52.

Study Endpoints

The primary efficacy endpoint is F-VASI 75 at Week 24 (75% reduction from baseline to Week 24). The key secondary endpoints are

- F-VASI 50 at Week 24 (50% reduction)
- F-VASI 90 at Week 24 (90% reduction)
- T-VASI 50 at Week 24 (50% reduction)
- VNS Response (4=a lot less noticeable or 5=no longer noticeable) at Week 24
- Percentage change from baseline in F-BSA at Week 24.

The assessments and endpoint definitions are defined below.

Clinical Outcome Assessment Description(s):
Efficacy was assessed using several clinical outcome assessments (COAs), including the Vitiligo Area Scoring Index on the face (F-VASI) and total body (T-VASI), the Vitiligo Noticeability Scale (VNS), facial body surface area (F-BSA), Facial Physician's Global Vitiligo Assessment Scale (F-PhGVA), Total Body Physician's Global Vitiligo Assessment Scale (T-PhGVA), Facial Patient Global Impression of Change-Vitiligo (F-PaGIC-V), and Total Body Patient Global Impression of Change-Vitiligo (T-PaGIC-V). A description of each COA is given below.

<u>VASI</u>
The VASI is a clinician-reported outcome (ClinRO) instrument designed to assess the severity and extent of vitiligo based on percentage of vitiligo involvement (i.e., areas affected by depigmentation due to vitiligo) and degree of pigmentation. A copy of the instrument can be found in Appendix 14.5.

[‡‡] These are the key eligibility criteria. Other inclusion/exclusion criteria are listed in the study protocols, with the same criteria for both studies 306 and 307; see Section 5 (Study Population) of the protocol for Study 306 at \\cdsesub1\evsprod\NDA215309\0021\m5\53-clin-stud-rep\535-rep-effic-safety-stud\vitiligo\5351-stud-rep-contr\incb18424-306\18424-306-16-1-01.pdf.

The VASI generates two scores: Facial[§§] VASI (F-VASI) and Total Body VASI (T-VASI).

- The F-VASI score ranges from 0 to 3; it is calculated by multiplying the percentage of vitiligo involvement by the percentage of affected skin (depigmentation) for each site on the face in hand units (see below) and summing the values of all sites together.
- The T-VASI score ranges from 0 to 100; it is calculated using a formula that includes contributions from all body regions (possible range, 0-100):

  VASI= Σ [hand units] x [Residual Depigmentation] all body sites

  The body is divided into the following 6 separate and mutually exclusive sites: (1) head/neck, (2) hands, (3) upper extremities (excluding hands), (4) trunk, (5) lower extremities (excluding feet), and (6) feet. The head/neck region was subdivided into two sites: the face and neck and scalp, not including face. The percentage of vitiligo involvement is estimated in hand units (see below) by the same investigator during the entire course of the study. Note: subjects in the study were to have a maximum of 10% BSA involvement, so subject scores could have a maximum T-VASI score of 10 at baseline.

Calculation of hand units:

- To assess the percent BSA involvement, the size of a subject's hand is assumed to correspond to 1% BSA. The investigator mimics the subject's hand size to evaluate the percent BSA involvement.
- The degree of depigmentation for each vitiligo site is estimated to the following nearest percentages: 0, 10, 25, 50, 75, 90, 100.
- For each involvement site, the percent BSA is multiplied by the degree of depigmentation and the scores for each involvement site are summed to calculate the total involvement score.

VNS

The VNS is a single item patient-reported outcome (PRO) instrument designed to assess perceived noticeability of vitiligo on a 5-point verbal rating scale ranging from 1 ("More noticeable") to 5 ("No longer noticeable"). Subjects were shown baseline facial photographs and used a mirror to assess vitiligo of the face. The recall period is a comparison of the current state to an earlier time period. A copy of the instrument is in Appendix 14.5.

F-PhGVA

The F-PhGVA is a single item ClinRO instrument designed to assess facial vitiligo severity on a 5-point verbal rating scale ranging from 0 (Clear) to 4 (Severe disease). The recall period is

[§§] The area "Face" is defined as including the area on the forehead to the original hairline, on the cheek to the jawline vertically to the jawline and laterally from the corner of the mouth to the tragus. The area "Face" will not include surface area of the lips, scalp, ears, or neck but will include the nose and eyelids.

current state. A copy of the instrument is in Appendix 14.5.

T-PhGVA
The T-PhGVA is a single item ClinRO instrument designed to assess total body vitiligo severity on a 5-point verbal rating scale ranging from 0 (Clear) to 4 (Severe disease). The recall period is current state. A copy of the instrument is in Appendix 14.5.

F-PaGIC-V
F-PaGIC-V is a single item PRO instrument designed to assess global improvement of facial vitiligo on a 7-point verbal rating scale ranging from 1 (Very much improved) to 7 (Very much worse). The recall period is a comparison of the current state to an earlier time period. A copy of the instrument is in Appendix 14.5.

T-PaGIC-V
T-PaGIC-V is a single item PRO instrument designed to assess global improvement of total body vitiligo on a 7-point verbal rating scale ranging from 1 (Very much improved) to 7 (Very much worse). The recall period is a comparison of the current state to an earlier time period. A copy of the instrument is in Appendix 14.5.

Statistical Analysis Plan

The primary analysis population was the ITT population, defined as all randomized subjects. The primary endpoint was analyzed with exact logistic regression with terms for treatment group and the stratification factors (region: North America vs. Europe and Fitzpatrick skin type: I and II vs. III – VI). The analysis also included 95% confidence intervals for the odds ratio. Missing data was handled using multiple imputation using a fully conditional specification method, with a regression model including treatment group, stratification factors, and baseline and post-baseline F-VASI scores up to Week 24. The applicant made some changes to the planned multiple imputation analyses after finalization of the statistical analysis plan to improve the stability and accuracy of the results. These changes included:

- Increase the number of imputations in the model from 10 to 30.
- Use predictive mean matching method rather than the regression method when imputing VASI and BSA values in the fully conditional specification method to avoid potential imputation of negative scores.
- Increase the number of burn-in iterations for each imputation from 20 to 30 to allow for proper convergence of the imputation models.

In addition to the primary method (multiple imputation) of handling missing data, analyses using non-responder imputation and LOCF were conducted. Note that the LOCF analyses were conducted only in subjects who had at least one post-baseline assessment, rather than in all randomized subjects. A tipping point analysis was also conducted. For the tipping point analysis, the missing F-VASI75 values at Week 24 in each treatment group were evaluated in multiple scenarios from the most conservative case (all the missing participants in 1.5% BID group are non-responders and all the missing participants in vehicle group are responders) to the most

aggressive case (all the missing participants in 1.5% BID group are responders and all the missing participants in vehicle group are non-responders). For each scenario, between-treatment comparisons were performed using a Fisher's exact test.

The binary secondary endpoints were analyzed using the same methods as the primary endpoint. The percent change in F-BSA at Week 24 was analyzed using ANCOVA with terms for treatment group, stratification factors, and baseline value. Missing data was imputed using multiple imputation similar to how missing data was imputed for the VASI values. The secondary endpoints were analyzed in the sequential order described above to control multiplicity.

Protocol Amendments

The protocols were amended three times. Amendments 1 and 3 included some changes to the endpoints and analyses as follows:

- Amendment 1 – Stratification factor was changed from age to region; the analysis method was clarified as exact logistic regression for the primary and secondary endpoints
- Amendment 2 – minor changes to screening procedures and exclusion criteria that do not impact the design or analysis were made
- Amendment 3 – Key secondary endpoints were reordered and revised

The protocol specified that the primary method of handling missing data would be non-responder imputation. The statistical analysis plan (SAP) changed the planned primary method of handling missing data to multiple imputation. In addition, the SAP changed the primary analysis population. While the protocol specified the analysis population as all randomized subjects, the SAP changed the analysis population to all randomized subjects with at least one post-baseline assessment. After comments from the FDA upon review of the SAP, the applicant changed the primary analysis population back to all randomized subjects. Thus, the all-randomized population (corresponding to what was specified in the protocol) was used as the primary analysis population in the study reports.

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant reported that, “Each of the studies of ruxolitinib cream in participants with vitiligo was conducted in compliance with Good Clinical Practice and ethical principles that have their origin in the Declaration of Helsinki and are consistent with US, European, and International Council on Harmonisation guidelines on drug development” (p. 11 of the Clinical Overview in Module 2 of the sNDA submission).

Financial Disclosure

The Applicant reported no clinical investigators with disclosable financial interests or

arrangements for the covered clinical studies, 306 and 307. See Section 15.2.

Patient Disposition

Study 306 enrolled 330 subjects at 45 centers, 29 centers in North America and 16 centers in Europe. Study 307 enrolled 344 subjects at 49 centers, 32 centers in North America and 17 centers in Europe. In Study 306, 12% of ruxolitinib subjects and 17% of vehicle subjects discontinued treatment during the 24-week vehicle-controlled period. In Study 307, 10% of ruxolitinib subjects and 11% of vehicle subjects discontinued treatment during the 24-week vehicle-controlled period. The most common reasons for discontinuation were loss to follow-up and withdrawal by subject. See Table 3.

Table 3. Disposition of Subjects (Vehicle-Controlled Period)

	Study 306		Study 307	
N (%)	**1.5% BID N=221**	**Vehicle BID N=109**	**1.5% BID N=229**	**Vehicle BID N=115**
Discontinued Treatment	26 (11.8)	18 (16.5)	23 (10.0)	13 (11.3)
Reasons for treatment discontinuation				
Adverse event	0 (0.0)	1 (0.9)	1 (0.4)	0 (0.0)
COVID-19 Pandemic	3 (1.4)	0 (0.0)	3 (1.3)	1 (0.9)
Lack of efficacy	0 (0.0)	1 (0.9)	1 (0.4)	0 (0.0)
Lost to follow-up	14 (6.3)	7 (6.4)	10 (4.4)	6 (5.2)
Pregnancy	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Protocol violation	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawal by subject	8 (3.6)	9 (8.3)	7 (3.1)	5 (4.3)
Other	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
Discontinued Study	28 (12.7)	19 (17.4)	30 (13.1)	16 (13.9)
Reasons for study discontinuation				
Adverse event	0 (0.0)	1 (0.9)	2 (0.9)	0 (0.0)
COVID-19 pandemic	3 (1.4)	0 (0.0)	3 (1.3)	1 (0.9)
Lack of efficacy	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.9)
Lost to follow-up	14 (6.3)	7 (6.4)	11 (4.8)	6 (5.2)
Physician decision	1 (0.5)	0 (0.0)	1 (0.4)	0 (0.0)
Pregnancy	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Protocol violation	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawal by subject	9 (4.1)	10 (9.2)	11 (4.8)	7 (6.1)
Other	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.9)

Source: page 33 of Study Report 306 and page 33 of Study Report 307 and reviewer analysis

Protocol Violations/Deviations

The most common major protocol deviations during the double-blind period were issues with signing the informed consent and issues related to study drug compliance. The proportion of subjects with major protocol deviations was higher on the ruxolitinib arm in Study 306 and higher on the vehicle arm in Study 307. See Table 4.

Table 4. Major Protocol Deviations (Safety Population)

	Study 306		Study 307	
N (%)	**1.5% BID N=221**	**Vehicle BID N=109**	**1.5% BID N=228**	**Vehicle BID N=115**
Any major protocol deviation	38 (17.2)	14 (12.8)	20 (8.8)	18 (15.7)
Assessment-Efficacy	1 (0.5)	1 (0.9)	1 (0.4)	0 (0.0)
Assessment -Safety	3 (1.4)	1 (0.9)	0 (0.0)	0 (0.0)
Exclusion criteria	1 (0.5)	0 (0.0)	1 (0.4)	0 (0.0)
Inclusion criteria	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.9)
Informed consent	15 (6.8)	6 (5.5)	12 (5.3)	11 (9.6)
Study drug	12 (5.4)	5 (4.6)	4 (1.8)	6 (5.2)
Visit window	7 (3.2)	2 (1.8)	0 (0.0)	1 (0.9)
Other	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.9)

Source: page 40 of Study Report 306 and page 40 of Study Report 307 and reviewer analysis.

Demographic Characteristics

Baseline demographic characteristics were generally balanced across treatment arms in both studies, though there were some imbalances in age and sex categories. The studies enrolled similar proportions of male and female subjects. Most subjects were White, with smaller proportions of Black/African American and Asian subjects. The mean age was approximately 39 years, with approximately 11% of subjects less than 18 years of age and 7% of subjects at least 65 years of age. See Table 5.

Table 5. Baseline Demographics

	Study 306		Study 307	
N (%)	**1.5% BID N=221**	**Vehicle BID N=109**	**1.5% BID N=229**	**Vehicle BID N=115**
Age Category				
12-<18 years	25 (11.3)	11 (10.1)	30 (13.1)	6 (5.2)
18-<65 years	180 (81.4)	85 (78.0)	186 (81.22)	106 (92.2)
>=65 years	16 (7.2)	13 (11.9)	13 (5.7)	3 (2.6)
Mean	40.5	39.7	38.6	39.8
Min, Max	12, 79	12, 79	12, 77	13, 68
Sex				
M	85 (38.5)	59 (54.1)	117 (51.1)	55 (47.8)
F	136 (61.5)	50 (45.9)	112 (48.9)	60 (52.2)
Race				
White	180 (81.4)	96 (88.1)	183 (79.9)	93 (80.9)
Black or African American	11 (5.0)	4 (3.7)	12 (5.2)	5 (4.3)
Asian	5 (2.3)	4 (3.7)	12 (5.2)	7 (6.1)
Native HI/Pac Islander	0 (0.0)	0 (0.0)	2 (0.9)	0 (0.0)
Amer. Ind. / AK Native	1 (0.5)	0 (0.0)	1 (0.4)	0 (0.0)
Not Reported	16 (7.2)	3 (2.8)	3 (1.3)	3 (2.6)
Other	8 (3.6)	2 (1.8)	16 (7.0)	7 (6.1)
Fitzpatrick Skin Type				
I	10 (4.5)	3 (2.8)	2 (0.9)	1 (0.87)
II	74 (33.5)	40 (36.7)	57 (24.9)	32 (27.8)
III	89 (40.3)	43 (39.4)	90 (39.3)	45 (39.1)
IV	34 (15.4)	15 (13.8)	55 (24.0)	25 (21.7)
V	11 (5.0)	7 (6.4)	17 (7.4)	10 (8.7)
VI	3 (1.4)	1 (0.9)	8 (3.5)	2 (1.7)
Ethnicity				
Hispanic or Latino	53 (24.0)	20 (18.3)	50 (21.8)	32 (27.8)

Not Hispanic or Latino	151 (68.3)	86 (78.9)	175 (76.4)	80 (69.6)
Not Reported/Unknown/ Other	17 (7.7)	3 (2.8)	4 (1.7)	3 (2.6)
Region				
North America	147 (66.5)	73 (67.0)	161 (70.3)	83 (72.2)
Europe	74 (33.5)	36 (33.0)	68 (29.7)	32 (27.8)

Source: page 35-36 of Study Report 306 and page 35-36 of Study Report 307 and reviewer analysis.

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

Based on the inclusion criteria, subjects were to have an F-VASI score between 0.5 and 3 (inclusive) and a T-VASI score between 3 and 10 (inclusive) at baseline. T-VASI includes the areas on the face and other body regions. The mean F-VASI score at baseline was approximately 0.95 in Study 306 and 0.88 in Study 307. The mean T-VASI score at baseline was approximately 6.47 in Study 306 and 6.89 in Study 307. See Table 6.

Table 6. Baseline Disease Severity

	Study 306		**Study 307**	
	1.5% BID N=221	**Vehicle BID N=109**	**1.5% BID N=229**	**Vehicle BID N=115**
F-VASI				
Mean (SD)	0.93 (0.58)	1.00 (0.59)	0.90 (0.52)	0.83 (0.52)
Median	0.69	0.74	0.70	0.60
Min, Max	0.4, 3.0	0.5, 2.7	0.45, 3.0	0.5, 3.0
T-VASI				
Mean (SD)	6.48 (2.02)	6.42 (1.92)	6.83 (2.06)	7.02 (2.20)
Median	6.38	6.25	7.28	7.30
Min, Max	3.01, 10.0	3.06, 10.0	2.65, 10.0	3.10, 10.0

SD= standard deviation
Source: page 37 of Study Report 306 and page 37 of Study Report 307 and reviewer analysis.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The double-blind treatment period was 24 weeks (168 days). The mean duration of treatment ranged between 153 and 160 days for the two treatment arms in the two studies. The mean treatment duration was longer on the ruxolitinib arm compared to the vehicle arm in Study 306, but the trend is reversed in Study 307. See Table 7.

Table 7. Treatment Duration (Safety Population)

	Study 306		Study 307	
	1.5% BID N=221	**Vehicle BID N=109**	**1.5% BID N=228**	**Vehicle BID N=115**
Duration of treatment (days)				
Mean (SD)	160.0 (32.3)	152.8 (42.6)	157.9 (37.5)	160.3 (34.9)
Min, Max	1, 237	1, 200	1, 220	4, 248

SD= standard deviation
Source: page 37 of Study Report 306 and page 37 of Study Report 307 and reviewer analysis.

Efficacy Results – Primary Endpoint

The primary efficacy endpoint was F-VASI 75 at Week 24, defined as at least a 75% reduction from baseline in facial VASI. The primary analysis population was the ITT population, defined as all randomized subjects. The primary endpoint was analyzed with exact logistic regression with terms for treatment group, geographical region, and Fitzpatrick skin type. Missing data was handled using multiple imputation. Ruxolitinib was superior to vehicle for the primary endpoint in both studies ($p \leq 0.0021$). See Table 8.

Table 8. F-VASI 75 at Week 24 (ITT Population; Multiple Imputation)

Study 306	**1.5% BID N=221**	**Vehicle BID N=109**	**1.5% BID vs Vehicle BID**
F-VASI 75 Rate (%)	29.9	7.5	
p-value			<.0001
Odds ratio (95% CI)			5.30 (2.324, 12.066)
Response rate difference (95% CI)			22.5 (14.18, 30.75)
Study 307	**1.5% BID N=229**	**Vehicle BID N=115**	**1.5% BID vs Vehicle BID**
F-VASI 75 Rate (%)	29.9	12.9	
p-value			0.0021
Odds ratio (95% CI)			2.86 (1.467, 5.585)
Response rate difference (95% CI)			16.9 (7.84, 26.02)

CI= Confidence interval
Source: page 52 of Study Report 306 and page 52 of Study Report 307 and reviewer analysis.

Missing Data Handling
The applicant conducted sensitivity analyses using non-responder imputation and LOCF as alternate ways of handling missing data. The LOCF analysis was conducted in a subset of the ITT population that excluded subjects with no post-baseline assessments. The results of these sensitivity analyses were similar to the primary analysis. See Table 9.

Table 9. F-VASI 75 at Week 24 - Sensitivity Analyses for Missing Data Handling

	Study 306		Study 307	
Study 306	**1.5% BID N=221**	**Vehicle BID N=109**	**1.5% BID N=229**	**Vehicle BID N=115**
Non-responder imputation n/N (%)	60/221 (27.1)	7/109 (6.4)	63/229 (27.5)	12/115 (10.4)
p-value		<0.0001		0.0003
Odds ratio (95% CI)		5.43 (2.353, 14.655)		3.23 (1.627, 6.889)
LOCF[a] n/N (%)	61/214 (28.5)	7/100 (7.0)	63/218 (28.9)	15/111 (13.5)
p-value		<0.0001		0.0024
Odds ratio (95% CI)		5.25 (2.272,14.189)		2.57 (1.357, 5.148)

CI= Confidence interval
[a] Note: the Applicant's LOCF analysis was conducted in subjects with at least one post-baseline assessment.
Source: page 52 of Study Report 306 and page 52 of Study Report 307 and reviewer analysis.

The applicant also conducted a tipping point analysis for F-VASI 75 at Week 24. In Study 306, 12% of subjects on the ruxolitinib arm and 17% of subjects on the vehicle arm had missing data. In Study 307, 10% of subjects on the ruxolitinib arm and 17% of subjects on the vehicle arm had missing data. The tipping point analysis imputed various proportions of subjects with missing data on the ruxolitinib or vehicle arms as either responders or non-responders. For each imputation scenario the primary endpoint was tested using Fisher's exact test. The imputation scenarios for which nominal statistical significance ($p<0.05$) for the primary endpoint comparison was demonstrated were identified. The most extreme conservative missing data imputation scenario—in which all subjects randomized to vehicle were imputed as responders and all subjects randomized to ruxolitinib were imputed as non-responders—led to an outcome that was not nominally significant in either study. The shaded areas in Table 10 and **Error! Reference source not found.**Table 11 represent the scenarios for which the results were not nominally significant. In particular, these scenarios represent situations where the proportion of vehicle subjects with missing data imputed as responders is at least 38% higher than for ruxolitinib subjects with missing data (e.g., 100% of vehicle subjects imputed as responders and 62% of ruxolitinib subjects imputed as responders). Because these scenarios are implausible based on the observed data, with substantially higher response rates for vehicle subjects than ruxolitinib subjects with missing data, the conclusions for the primary endpoint are robust to the handling of missing data.

Table 10. Tipping Point Scenarios that were not Nominally Significant (Shaded Area) in Study 306

No. of Ruxolitinib Subjects with Missing Data Imputed as Responders	No. of Vehicle Subjects with Missing Data Imputed as Responders																			
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
0																				
1																				
2																				
3																				
4																				
5																				
6																				
7																				
8																				
9																				
10																				
11																				
12																				
13																				
14																				
15																				
16																				
17																				
18																				
19																				
20																				
21																				
22																				
23																				
24																				
25																				
26																				

Source: page 529 of Study Report 306 and reviewer analysis.

Table 11. Tipping Point Scenarios that were Not Nominally Significant (Shaded Area) in Study 307

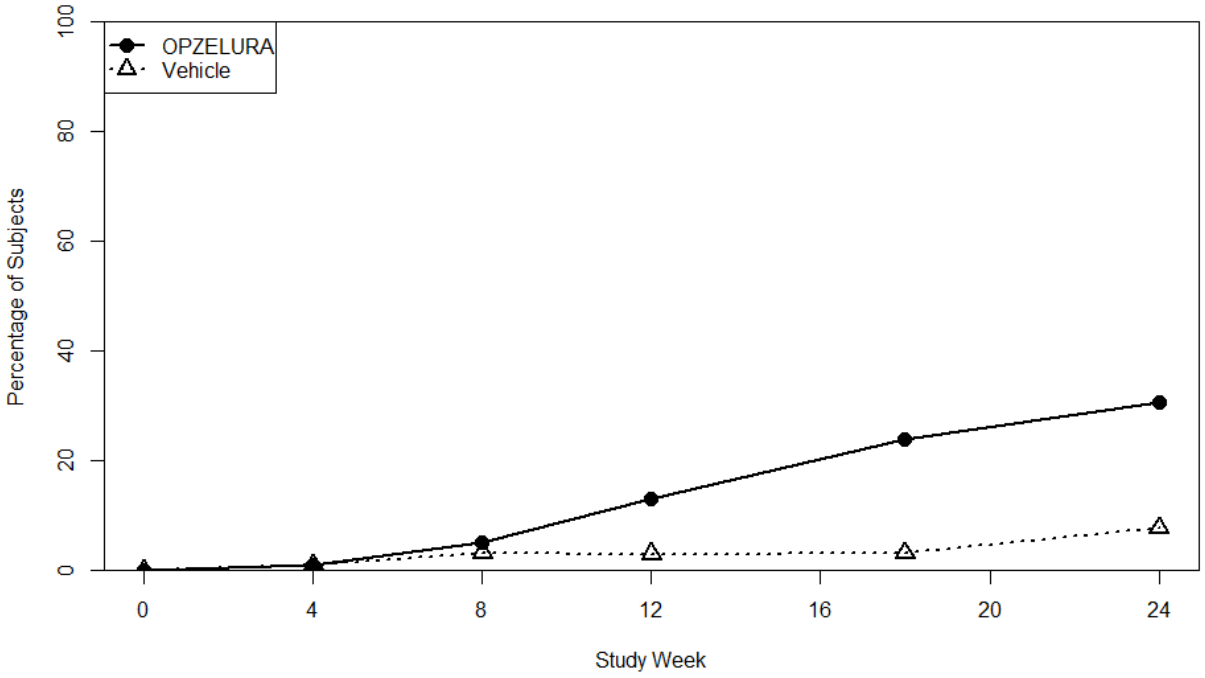
No. of Ruxolitinib Subjects with Missing Data Imputed as Responders	No. of Vehicle Subjects with Missing Data Imputed as Responders														
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
0															
1															
2															
3															
4															
5															
6															
7															
8															
9															
10															
11															
12															
13															
14															
15															
16															
17															
18															
19															
20															
21															
22															
23															

Source: page 541 of Study Report 307 and reviewer analysis.

Efficacy over Time

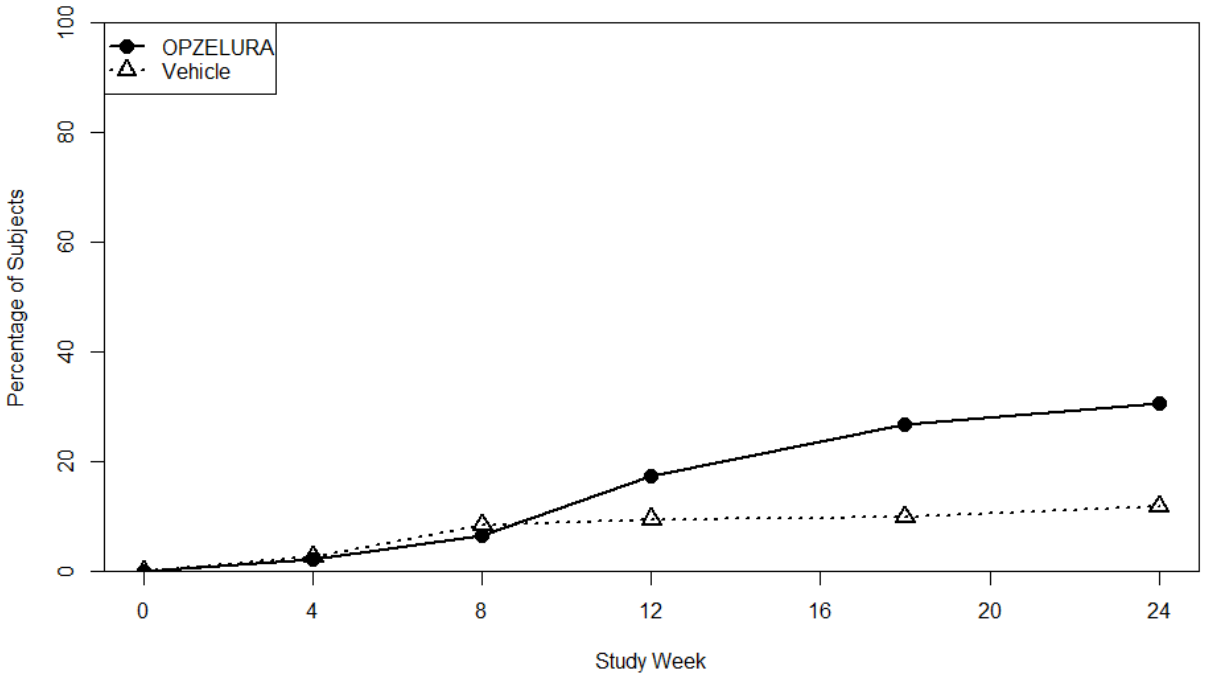
The efficacy results for F-VASI 75 were similar on the ruxolitinib and vehicle arms through Week 8, and the curves started separating after this point through the end of the double-blind period at Week 24. See Figure 4 and Figure 5.

Figure 4. F-VASI 75 by Study Visit in Study 306 (Observed Cases)



Source: reviewer analysis

Figure 5. F-VASI 75 by Study Visit in Study 307 (Observed Cases)

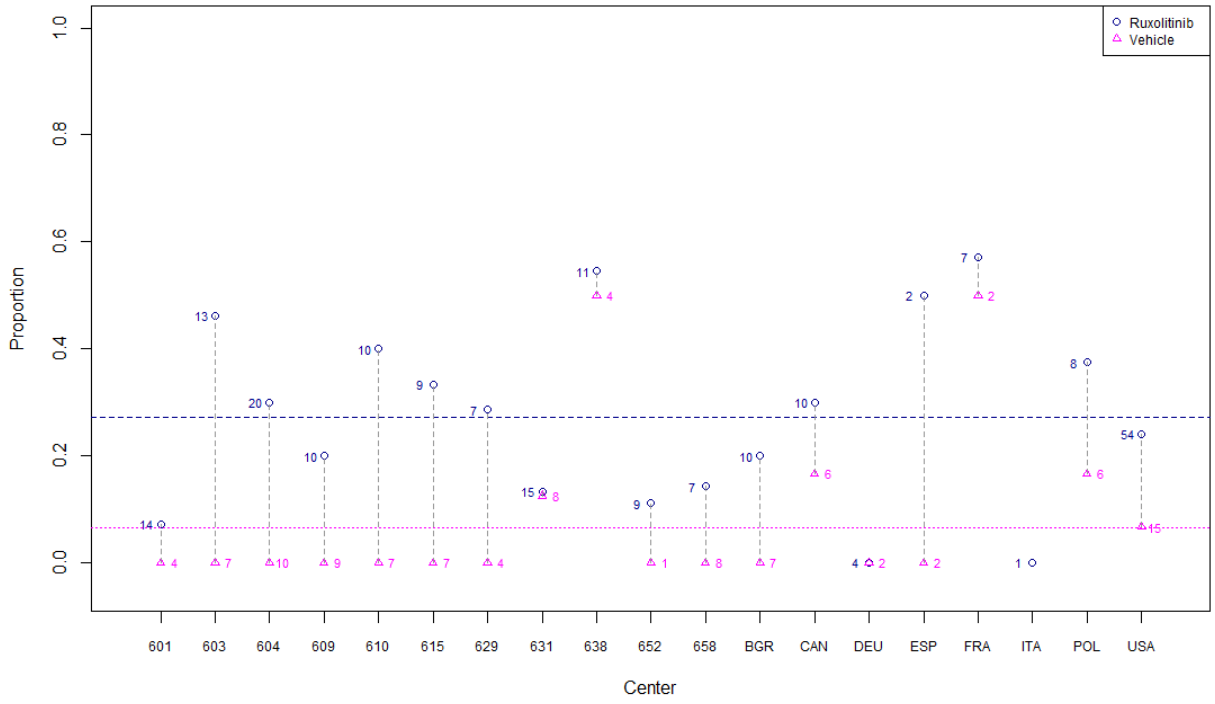


Source: reviewer analysis

Efficacy by Center

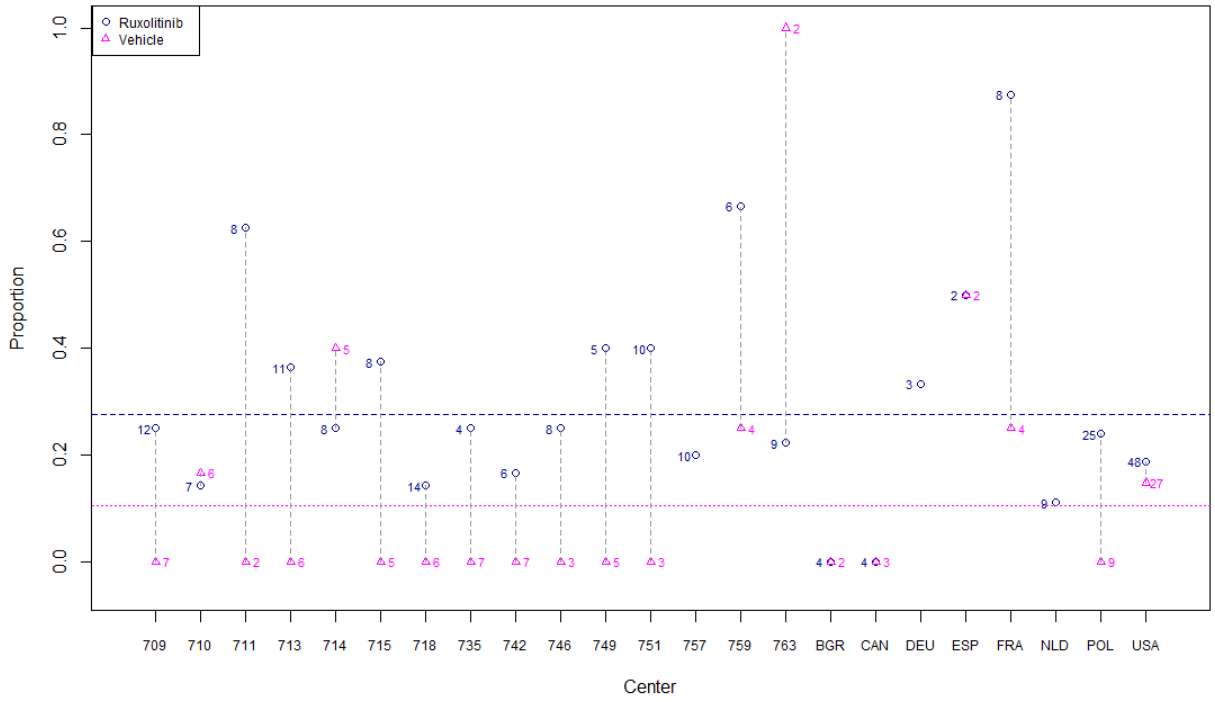
Study 306 enrolled 330 subjects at 45 centers, 29 centers in North America and 16 centers in Europe. Study 307 enrolled 344 subjects at 49 centers, 32 centers in North America and 17 centers in Europe. Because many of the sites in the two studies enrolled relatively few subjects, Figure 6 and Figure 7 present the primary endpoint results by site for the sites that enrolled at least 10 subjects. The smaller sites are pooled by country. The results were generally consistent across sites in the two studies. Non-responder imputation was used for this analysis, because of challenges with applying multiple imputation to this subgroup analysis.

Figure 6. F-VASI 75 by Center in Study 306 (Non-responder Imputation)



Numbers represent the number of subjects per treatment arm per center. Centers with fewer than 10 subjects are combined within country.
Source: Reviewer analysis

Figure 7. F-VASI 75 by Center in Study 307 (Non-responder Imputation)



Numbers represent the number of subjects per treatment arm per center. Centers with fewer than 10 subjects are combined within country.
Source: Reviewer analysis

Findings in Subgroup Populations
Treatment effects were generally consistent across age, sex, race, and geographic region subgroups, though many of the racial subgroups were small. Table 12 and Table 13 present the subgroup results for the ITT population using multiple imputation. The applicant's study reports presented results for observed cases only.

Table 12. F-VASI 75 by Demographic Subgroups in Study 306 (Multiple Imputation)

	Response Rate (%)		
Subgroup	**1.5% BID**	**Vehicle BID**	**Response Rate Difference % (SE)**
All Participants	29.9	7.5	22.5 (4.23)
Age Category			
12-<18 years	32.0	0	32.0 (9.33)
18-<65 years	30.6	8.4	22.2 (4.91)
>=65 years	18.8	7.7	11.1 (12.24)
Sex			
M	30.0	8.4	21.6 (6.61)
F	29.9	6.3	23.5 (5.39)
Race			
White	27.6	7.2	20.5 (4.53)
Black or African American	45.5	0	45.5 (15.01)
Asian	40.0	4.2	35.8 (25.51)
Not Reported	31.3	33.3	-2.1 (29.58)
Other	49.3	5.0	44.3 (25.93)
Region			
North America	30.7	4.1	26.6 (4.95)
Europe	28.4	14.3	14.1 (7.90)

Source: reviewer analysis.

Table 13. F-VASI 75 by Demographic Subgroups in Study 307 (Multiple Imputation)

	Response Rate (%)		
Subgroup	**1.5% BID**	**Vehicle BID**	**Response Rate Difference % (SE)**
All Participants	29.9	12.9	16.9 (4.64)
Age Category			
12-<18 years	32.0	0	32.0 (8.81)
18-<65 years	28.3	14.0	14.3 (5.05)
>=65 years	47.4	0	47.4 (14.14)
Sex			
M	23.5	14.3	9.2 (6.78)
F	36.5	11.7	24.8 (6.39)
Race			
White	27.3	11.8	15.5 (4.91)
Black or African American	34.4	29.3	5.1 (26.84)
Asian	25.0	3.3	21.7 (16.16)
Not Reported	100.0	0	100.0 (0.00)
Other	43.3	31.0	12.4 (22.18)
Region			
North America	29.4	14.6	14.7 (5.74)
Europe	31.0	8.5	22.5 (7.71)

Source: reviewer analysis.

Data Quality and Integrity

No issues with data quality and integrity were identified during the review.[***]

Efficacy Results – Secondary and other relevant endpoints

The studies evaluated five key secondary endpoints. These endpoints were analyzed in the

[***] Many of the study data in Studies 306 and 307, including VASI results, were directly transferred to datasets without documentation in case report forms. Thus, assessment of data quality from the Clinical reviewer perspective is challenging. The small %BSA values for F-VASI coupled with discontinuous scoring for the degree of depigmentation (0, 10, 25, 50, 75, 90 and 100% of the assessment area being depigmented) and the rounding up used in calculation pose additional potential for inaccuracy which could be difficult to overcome.

following order to control multiplicity:

- F-VASI 50 at Week 24 (50% reduction - face)
- F-VASI 90 at Week 24 (90% reduction - face)
- T-VASI 50 at Week 24 (50% reduction – total body)
- Vitiligo Noticeability Scale (VNS) Response (4 [a lot less noticeable] or 5 [no longer noticeable]) at Week 24
- Percentage change from baseline in F-BSA at Week 24.

All of the key secondary endpoints assessed vitiligo of the face, except for T-VASI 50, which assessed vitiligo on the total body. The binary secondary endpoints were analyzed using the same methods as the primary endpoint. The percent change in F-BSA at Week 24 was analyzed using ANCOVA with terms for treatment group, stratification factors, and baseline value. All of the key secondary endpoints were statistically significant in both studies. During the review, the statistical analyst noted that the point estimates from the multiple imputation procedure for several of the endpoints differed slightly (up to one half of a percent) depending on which SAS platform (desktop or server) was used to run the analyses, even when the same randomization seed and program were used. The reviewers were able to confirm the Applicant's results for all endpoints based on F-VASI or T-VASI using the server platform for SAS. However, even when using the server platform for SAS, the reviewer's multiple imputation results for the VNS response endpoint and the percent change in F-BSA differed slightly from the Applicant's results. Neither the reason for the minor differences between the reviewers and Applicant's analyses for the VNS and F-BSA multiple imputation results nor the reason for difference in results based on the SAS platform used was resolved. However, these minor discrepancies did not impact the conclusions and the overall results are robust to minor variations in handling the missing data. All endpoint results recommended for inclusion in labeling were confirmed by the reviewers. See Table 14 and Table 15.

Table 14. Secondary Endpoints at Week 24 in Study 306 (ITT population; Multiple Imputation)

Endpoint	1.5% BID N=221	Vehicle BID N=109	1.5% BID vs Vehicle BID
F-VASI 50 Rate (%)	51.5	17.2	
p-value			<.0001
Response rate difference (95% CI)			34.2 (24.06, 44.40)
F-VASI 90 Rate (%)	15.5	2.2	
p-value			0.0035
Response rate difference (95% CI)			13.3 (7.49, 19.08)
T-VASI 50 Rate (%)	20.6	4.9	
p-value			0.0015
Response rate difference (95% CI)			15.7 (8.68, 22.65)
VNS 4 or 5 Rate (%)[a]	24.5	3.8	
p-value			0.0004
Response rate difference (95% CI)			20.7 (13.43, 27.92)
Percent Change in F-BSA [LSM (SE)]	-28.8 (2.30)	-9.5 (3.36)	
p-value			<.0001
Mean difference (95% CI)			-19.3 (-27.24, -11.37)

[a] Reviewer results differed slightly from the Applicant's results. The Applicant's results were: 24.5 vs. 3.3 (p=0.0002)
LSM=least squares mean, SE = standard error, CI=confidence interval
Source: page 53-55 of Study Report 306 and reviewer analysis.

Table 15. Secondary Endpoints at Week 24 in Study 307 (ITT population; Multiple Imputation)

Endpoint	1.5% BID N=229	Vehicle BID N=115	1.5% BID vs Vehicle BID
F-VASI 50 Rate (%)	51.4	23.4	
p-value			<.0001
Response rate difference (95% CI)			27.9 (17.31, 38.56)
F-VASI 90 Rate (%)	15.4	1.9	
p-value			0.0159
Response rate difference (95% CI)			13.5 (7.66, 19.31)
T-VASI 50 Rate (%)	26.1	11.3	
p-value			0.0038
Response rate difference (95% CI)			14.8 (6.29, 23.33)
VNS 4 or 5 Rate (%)[a]	21.8	6.5	
p-value			0.0012
Response rate difference (95% CI)			15.4 (7.97, 22.74)
Percent Change in F-BSA [LSM (SE)][b]	-16.6 (4.57)	1.8 (6.48)	
p-value			0.0209
Mean difference (95% CI)			-18.5 (-34.15, -2.79)

[a] Reviewer results differed slightly from the Applicant's results. The Applicant's results were: 21.9 vs. 6.6 (p=0.0015)
[b] Reviewer results differed slightly from the Applicant's results. The Applicant's results were: -16.3 (4.65) vs. 2.3 (6.56) (p=0.0221)
LSM=least squares mean, SE = standard error, CI=confidence interval
Source: page 53-55 of Study Report 307 and reviewer analysis.

At the End of Phase 2 Meeting (minutes dated 5/6/2019), FDA raised concerns that F-VASI 50 and T-VASI 50 may not represent clinically meaningful improvement, particularly for subjects with extensive disease. Considering the concerns that a 50% improvement may not be clinically meaningful, endpoints based on F-VASI 50 and T-VASI 50 may not be suitable for labeling. T-VASI 50 is the only key secondary endpoint based on total body vitiligo rather than face vitiligo. Higher levels of improvement on the T-VASI, including T-VASI 75, were evaluated as exploratory secondary endpoints at all timepoints. At Week 24, the estimated T-VASI 75 response rates in Study 306 were 4.1% vs. 1.8% (ruxolitinib vs. vehicle; p=0.2920) and in Study 307 were 10.3% vs. 5.4% (ruxolitinib vs. vehicle; p=0.1548). Too few subjects were able to achieve at least 75% improvement on the total body during the 24-week vehicle-controlled treatment period to adequately assess whether treatment with ruxolitinib would lead to a clinically meaningful effect on total body vitiligo. See the subsection Additional Analyses Conducted on the

Individual Trial, below for further evaluation of total body vitiligo during the follow-up period (after Week 24).

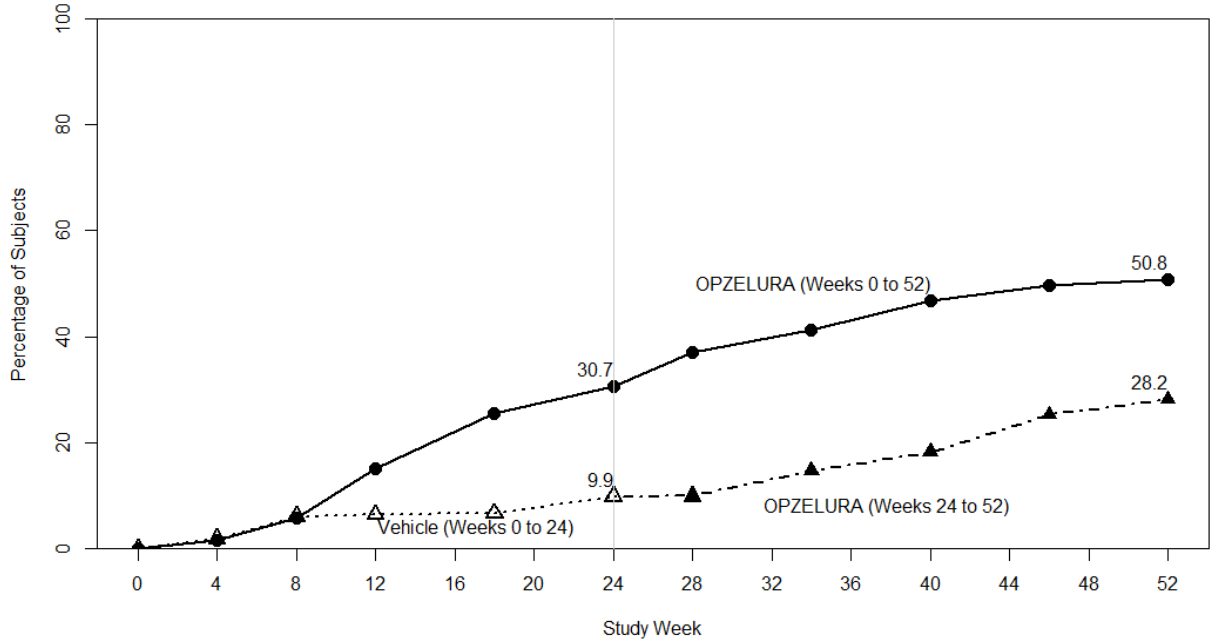
Dose/Dose Response

The applicant conducted a Phase 2 study (INCB 18424-211) that evaluated the following treatment arms: 0.15% QD, 0.5% QD, 1.5% QD, and 1.5% BID versus vehicle in 157 subjects. The 1.5% QD and 1.5% BID treatment arms had the largest treatment effect for the primary efficacy endpoint of F-VASI 50. Based on the primary endpoint results and supportive results from F-VASI 75 and T-VASI 50, the applicant selected the 1.5% BID dose for phase 3 development. Both Phase 3 studies evaluated ruxolitinib 1.5% BID versus vehicle BID.

Durability of Response

The studies were designed with a 24-week vehicle-controlled period and a 28-week follow-up period where all subjects were treated with ruxolitinib. Thus, any treatment comparisons after Week 24 compared subjects continuously treated with ruxolitinib versus subjects who crossed over from vehicle to ruxolitinib treatment. Figure 8 presents F-VASI 75 results through Week 52 for the two studies combined. The proportion of subjects achieving F-VASI 75 response continued to increase among subjects treated with ruxolitinib throughout the study. Among subjects who were initially treated with vehicle and switched to ruxolitinib at Week 24, the proportion of subjects achieving F-VASI 75 response increased after the switchover at Week 24. Comparable proportions of subjects achieved F-VASI 75 response after 28 weeks of ruxolitinib treatment following the treatment switch from vehicle to ruxolitinib at Week 24, as subjects treated with ruxolitinib from baseline through Week 24. Specifically, the F-VASI 75 response rate at Week 24 for subjects who were originally randomized to ruxolitinib is 30.7% compared to 28.2% at Week 52 for subjects originally randomized to vehicle and switched to ruxolitinib at Week 24.

Figure 8. F-VASI 75 by Study Visit through Week 52 (Combined Studies; Observed Cases)



Source: reviewer analysis

Additional Analyses Conducted on the Individual Trials

T-VASI 75

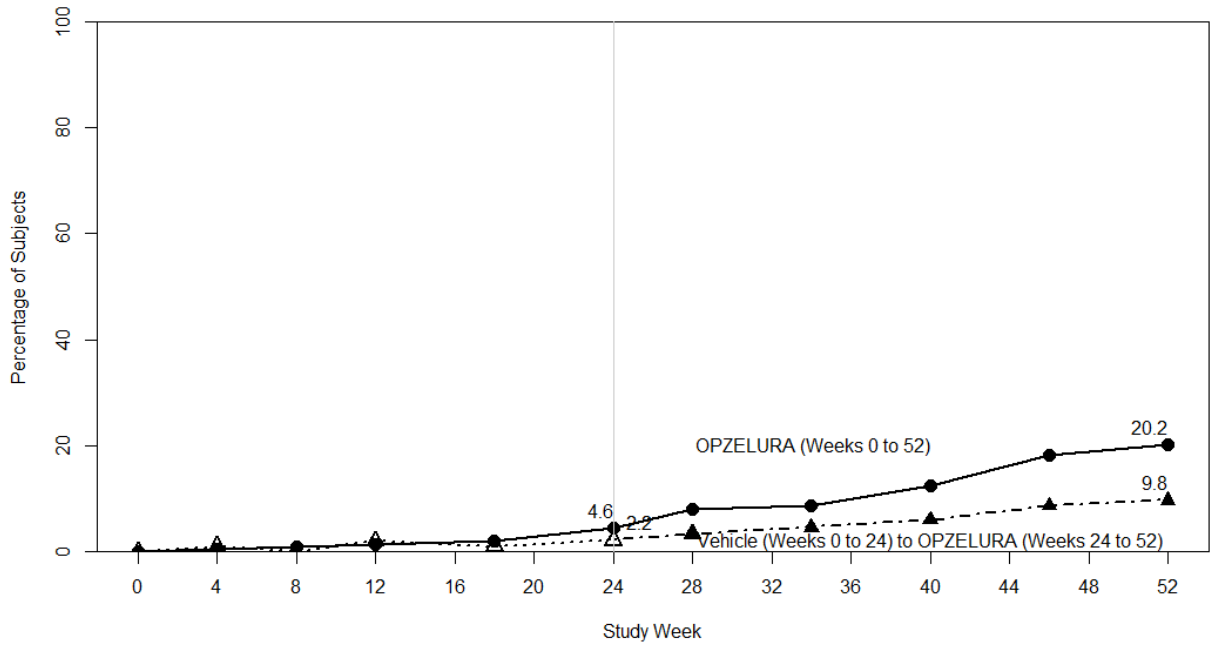
The Applicant is seeking an indication for nonsegmental vitiligo that is not restricted to treatment on the face. To support the broader indication, the studies need to provide sufficient evidence that ruxolitinib has a clinically meaningful effect on vitiligo in body regions other than the face. The T-VASI scale, which incorporates assessments of both facial and non-facial areas, is an assessment in the studies that measures vitiligo in non-facial areas. T-VASI 50 at Week 24 was evaluated as a multiplicity-controlled key secondary endpoint. T-VASI 25/50/75/90 at each visit through Week 52 were evaluated as uncontrolled exploratory endpoints. Because the primary endpoint was based on a 75% improvement from baseline for vitiligo on the face (F-VASI 75) and few subjects achieved T-VASI 75 by Week 24, T-VASI 75 was further evaluated at timepoints later than Week 24. At Week 24, subjects on the vehicle arm switched to ruxolitinib, so the control arm represents 24 weeks of vehicle treatment followed by 28 weeks of ruxolitinib treatment, rather than 52 weeks of vehicle treatment. Thus, it may be reasonable to assume that treatment effects representing ruxolitinib versus vehicle for the full 52 weeks would be at least as large as those observed in Studies 306 and 307 where the vehicle subjects were switched to ruxolitinib at Week 24.

Figure 9 and Figure 10 present T-VASI 75 observed case results through Week 52 for the two studies. The proportion of subjects achieving T-VASI 75 response continued to increase among subjects treated with ruxolitinib throughout the study. **Error! Reference source not found.**

presents the estimates and p-values for the ITT analysis for F-VASI at Week 52. The p-values for the two studies for T-VASI 75 for the treatment comparison of 52 weeks of ruxolitinib treatment versus 24 weeks of vehicle plus 28 weeks of ruxolitinib were 0.0675 and 0.024 with response rate differences of 9.6% and 10.8.

The pre-specified and multiplicity-controlled secondary endpoint of T-VASI 50 at Week 24 was statistically significant (see Table 14 and Table 15), indicating that ruxolitinib has a non-zero effect on total body vitiligo. However, there are concerns that a 50% improvement may not be clinically meaningful. Through Week 52, the treatment effect estimates for T-VASI 75 continued to increase among subjects treated with ruxolitinib. The treatment effect estimates were similar in the two studies, and the p-value for full ruxolitinib treatment versus partial ruxolitinib treatment control was <0.05 for Study 307 and <0.10 for Study 306. Thus, the finding of a statistically significant, but potentially not clinically meaningful effect at Week 24 (T-VASI 50)[†††] is further supported by the findings from the exploratory analyses at Week 52 using a more stringent endpoint, T-VASI 75, indicating that ruxolitinib treatment has a clinically meaningful effect on total body vitiligo over the 52-week treatment period. See Table 16.

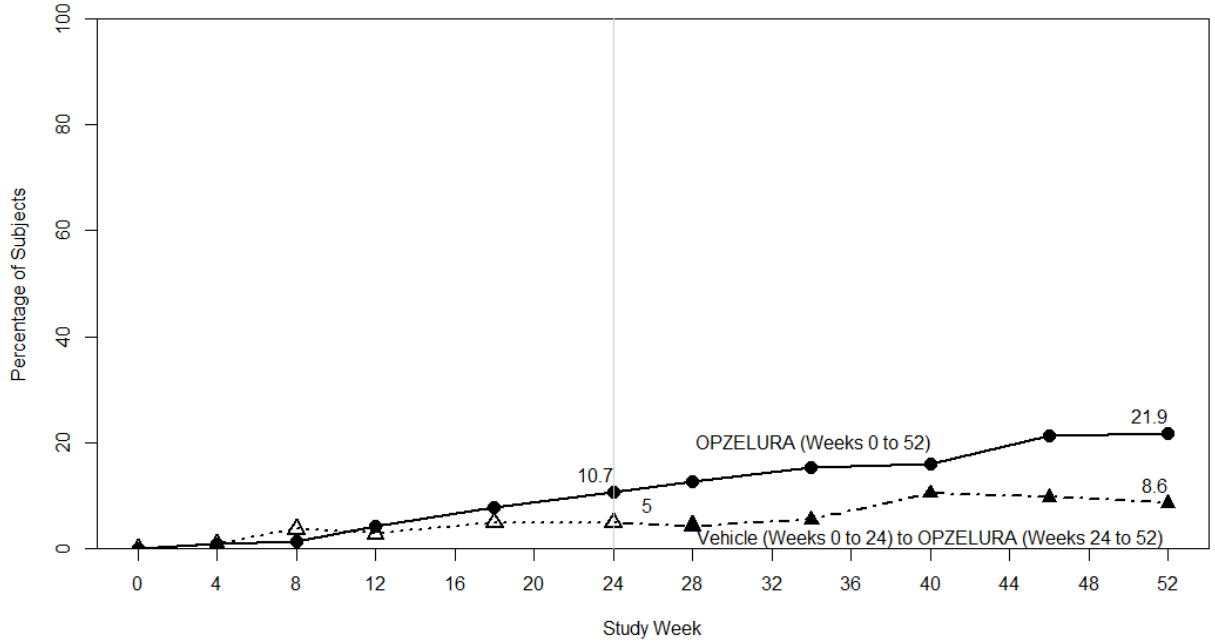
Figure 9. T-VASI 75 by Study Visit through Week 52 in Study 306 (Observed Cases)



Source: reviewer analysis

[†††] See COA review on clinical meaningfulness of T-VASI 50 below under Integrated Assessment of Effectiveness (Section 8.1.3)

Figure 10. T-VASI 75 by Study Visit through Week 52 in Study 307 (Observed Cases)



Source: reviewer analysis

Table 16. T-VASI 75 at Week 52 (Multiple Imputation)

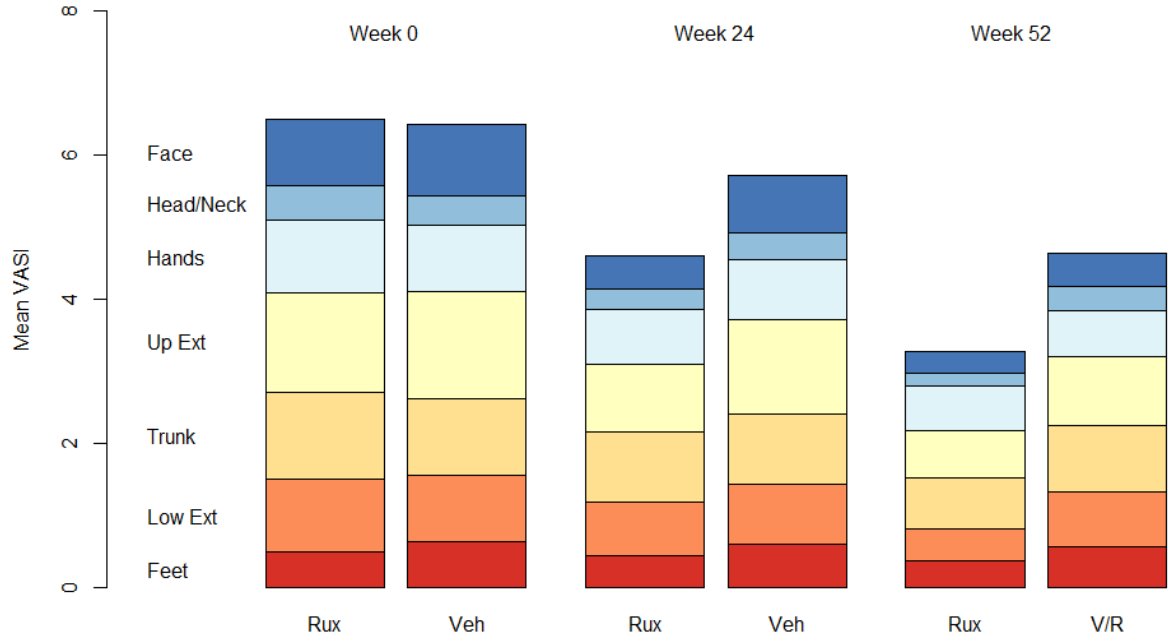
Endpoint	1.5% BID	Vehicle/ 1.5% BID	1.5% BID vs Vehicle/1.5% BID
Study 306	N=221	N=109	
T-VASI 75 Rate (%)	20.3	10.8	
p-value			0.0675
Odds ratio (95% CI)			2.13 (0.947, 4.780)
Response rate difference (95% CI)			9.6 (0.59, 18.55)
Study 307	N=229	N=115	
T-VASI 75 Rate (%)	20.7	9.9	
p-value			0.0240
Odds ratio (95% CI)			2.39 (1.121, 5.094)
Response rate difference (95% CI)			10.8 (2.76, 18.93)

Source: reviewer analysis.

Assessments by Body Region

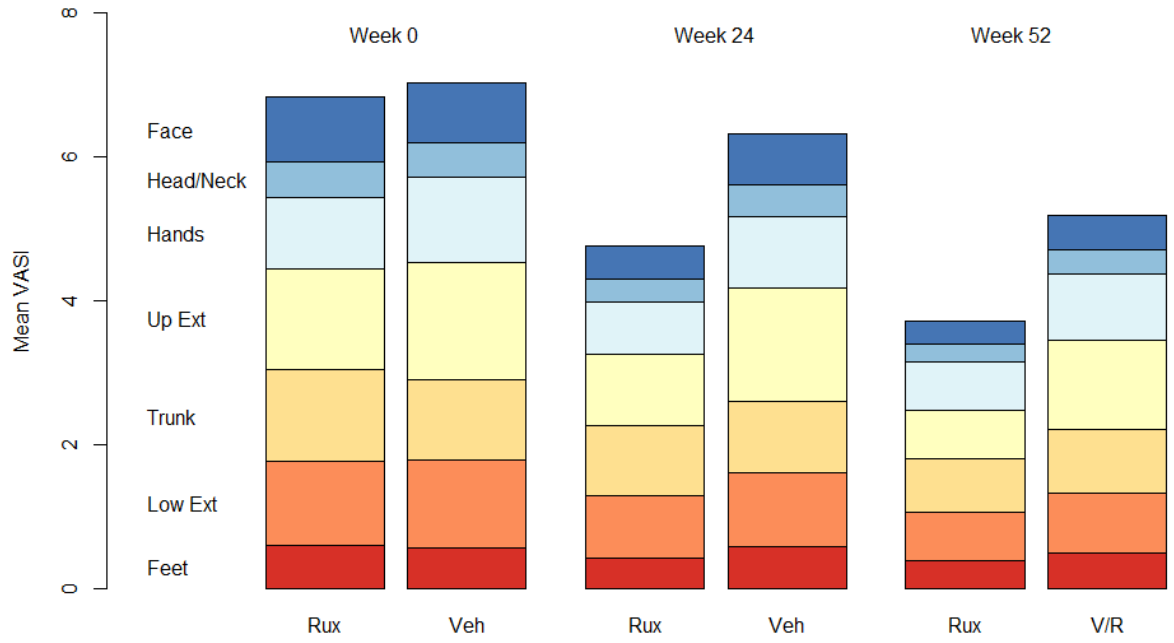
T-VASI is the summation of VASI assessments on seven regions: face, head and neck (neck and scalp, not including face), hands, upper extremities, trunk, lower extremities, and feet. Figure 11 and Figure 12 present the mean T-VASI scores at baseline, Week 24, and Week 52 broken down by the contribution of each body region to the total score. Some body regions, such as the face and upper and lower extremities showed greater improvement following ruxolitinib treatment that other body regions, such as the feet and hands.

Figure 11. Mean VASI by Body Region in Study 306 (Observed Cases)



V/R = Vehicle/Ruxolitinib; Up Ext = upper extremities, Low Ext = lower extremities
Source: reviewer analysis

Figure 12. Mean T-VASI by Body Region in Study 307 (Observed Cases)



V/R = Vehicle/Ruxolitinib; Up Ext = upper extremities, Low Ext = lower extremities
Source: reviewer analysis

8.1.3. Integrated Assessment of Effectiveness

The primary efficacy endpoint, defined as at least a 75% reduction in F-VASI (F-VASI 75) from baseline to Week 24, was statistically significant in both studies. The results for F-VASI 75 at Week 24 were consistent across subgroups and plausible assumptions for missing data handling.

The results for the key secondary endpoints were also statistically significant in both studies under the multiplicity control scheme. The key secondary endpoints included at least a 50% reduction in F-VASI from baseline to Week 24 (F-VASI 50), at least a 90% reduction in F-VASI from baseline to Week 24 (F-VASI 90), at least a 50% reduction in T-VASI from baseline to Week 24 (T-VASI 50), response on the patient-reported Vitiligo Noticeability Scale at Week 24, and percent change in facial BSA from baseline to Week 24. The primary and key secondary endpoints are summarized in Table 17.

Table 17. Primary and Key Secondary Endpoint Results

	Study 306		Study 307	
Study 306	**1.5% BID N=221**	**Vehicle BID N=109**	**1.5% BID N=229**	**Vehicle BID N=115**
F-VASI 75 Rate (%)	29.9	7.5	29.9	12.9
p-value		<.0001		0.0021
F-VASI 50 Rate (%)	51.5	17.2	51.4	23.4
p-value		<.0001		<.0001
F-VASI 90 Rate (%)	15.5	2.2	15.4	1.9
p-value		0.0035		0.0159
T-VASI 50 Rate (%)	20.6	4.9	26.1	11.3
p-value		0.0015		0.0038
VNS 4 or 5 Rate (%)	24.5	3.8	21.8	6.5
p-value		0.0004		0.0012
Percent Change in F-BSA [LSM (SE)]	-28.8 (2.30)	-9.5 (3.36)	-16.6 (4.57)	1.8 (6.48)
p-value		<.0001		0.0209

While the primary endpoint and the majority of key secondary endpoints evaluated vitiligo on the face, one of the key secondary endpoints evaluated vitiligo on the total body (T-VASI 50 at Week 24). This key secondary endpoint was statistically significant, however, FDA has concerns that a 50% improvement on T-VASI may not be clinically meaningful. The findings from exploratory analyses demonstrated that the proportion of subjects treated with ruxolitinib with at least 75% improvement of vitiligo on the total body (T-VASI 75) continued to increase through Week 52. Even though subjects on the control arm were treated with 24 weeks of vehicle followed by 28 weeks of ruxolitinib rather than continuous vehicle treatment, treatment effects for T-VASI 75 at Week 52 of 9.6% (20.3% vs. 10.8%, p=0.0675) in Study 306 and 10.8% (20.7% vs. 9.9%, p=0.0240) were observed for the two studies, and the observed effects would likely be larger if the studies had been designed with a 52-week vehicle-controlled period. Together these analyses indicate that ruxolitinib treatment has a clinically meaningful effect on total body vitiligo over the 52-week treatment period.

Thus, the totality of evidence from the two phase 3 trials supports the efficacy of ruxolitinib cream, 1.5% in the treatment of nonsegmental vitiligo in adult and pediatric patients 12 years of age and older.

Additional Efficacy Considerations

Review of COAs for Evaluation of Clinical Benefit
The FDA reviewed the Applicant's qualitative and quantitative evidence for the VASI. The VASI was reviewed for content validity and other measurement properties (reliability, construct validity, responsiveness), as well as score interpretability.

Content Validity
The Applicant obtained patient input via qualitative interviews to evaluate the content validity of the VASI.

The review team evaluated the data generated from the qualitative interviews. Patient input confirmed that the content of the VASI assess important aspects of vitiligo. The submitted qualitative data supports that depigmentation is a bothersome concept for patients with facial vitiligo. While the applicant's qualitative study did not identify the most important and/or bothersome signs and symptoms of total body vitiligo, it is noted that repigmentation and reduction of size of the affected area were important characteristics of an ideal treatment from the patient perspective. Further, the Voice of the Patient report[‡‡‡] from the FDA Patient-Focused Drug Development meeting supports that location of depigmentation and amount or extent of depigmentation are bothersome aspects of vitiligo (including face and total body). It is noted that the Applicant did not conduct qualitative interviews with clinicians. Therefore, it is unclear whether the VASI is well-understood and interpreted appropriately across clinicians.

Refer to the full COA review by Mira Patel, Ph.D, the Division of Clinical Outcome Assessment (DCOA) dated June 23, 2022, for detailed results of the content validity of these COAs.

Other Measurement Properties (Reliability, Construct validity, Responsiveness)
The Applicant evaluated other measurement properties of the VASI using data from Study INCB 18424-211 and Studies MVT-601-3101 and MVT-601-3102.

For the assessment of reliability (test-retest reliability) and other measurement properties of the VASI (F-VASI and T-VASI) using data from Study INCB 18424-211 and Studies MVT-601-3101 and MVT-601-3102, the results were generally within acceptable and within reasonable range. It is noted that the Applicant did not evaluate inter-rater reliability of the VASI. However, for the context of this development program this data may not be as critical as the same investigator in Studies INCB 18424-306 and -307 estimated the percentage of vitiligo involvement for the same patient during the entire course of the study (refer to the clinical trial

[‡‡‡] https://www.fda.gov/media/155068/download

protocols (Studies 306 and 307)[§§§]).

Refer to the full review by Mira Patel, Ph.D, DCOA, dated June 23, 2022 for detailed discussion of the other measurement properties of these COAs.

Score Interpretability

The Applicant performed the following analyses using data from Studies INCB 18424-306 and -307 to derive a meaningful within-patient score change in the VASI scores:

- Anchor-based analyses
- Distribution-based analyses
- Qualitative methods (exit interviews)

The Applicant proposed the following thresholds for meaningful within-patient score change for each VASI-based endpoint:

- F-VASI: The applicant proposed a 75% reduction from baseline to Week 24 to be a meaningful within-patient score change in the F-VASI.
- T-VASI: The applicant proposed a 50% reduction from baseline to Week 24 to be a meaningful within-patient score change in the T-VASI.

Due to FDA's concerns regarding the threshold for the T-VASI, the review team focused on evaluating the score interpretability of the T-VASI, specifically the clinical meaningfulness of the T-VASI50 endpoint. Refer to Sections 15.4.1 and 15.4.2 of this unireview for discussion of the results of the anchor-based analyses and exit interviews. The results for the distribution-based analyses are not discussed in this unireview as distribution-based methods (e.g., effect sizes, certain proportions of the standard deviation and/or standard error of measurement) are only considered supportive to anchor-based methods.

Refer to the full review by PFSS (dated July 6, 2022) for detailed discussion of the quantitative anchor-based analyses. Refer to the full COA review by the DCOA (dated June 23, 2022) for detailed results of the score interpretability of the T-VASI.

Conclusions

The VASI and its corresponding endpoints could potentially support labeling claims related to the improvements in the severity and extent of vitiligo on the face and total body, if supported by the clinical trial study design and analysis.

[§§§] Both protocols provide the same methodology. Source: \\cdsesub1\evsprod\NDA215309\0021\m5\53-clin-stud-rep\535-rep-effic-safety-stud\vitiligo\5351-stud-rep-contr\incb18424-306\18424-306-16-1-01.pdf Section 8.2.2 - "The percentage of vitiligo involvement is estimated in hand units (% of BSA) by the same investigator during the entire course of the study."

8.2. Review of Safety

8.2.1. Safety Review Approach

The integrated safety database consists of 830 subjects from 3 studies:

- 157 subjects from phase 2 study 211
- 330 subjects from phase 3 study 306
- 343 subjects from phase 3 study 307 (of 344 subjects randomized, 343 received study treatment).

The Applicant provided analyses of safety data for these subjects according to 5 pools, as presented below in Table 18.

Table 18. Pooled Populations and Treatment Groups*

Pooled Population	Studies	Treatment Groups (No. of Participants)	Comments
Pool 1: Phase 3 Vitiligo Vehicle-Controlled Population (N = 673)	INCB 18424-306 and -307	• Vehicle cream BID (224) • Ruxolitinib 1.5% cream BID (449)	Safety data are summarized for the vehicle-controlled DB periods (Day 1 through Week 24) of the Phase 3 studies only.
Pool 2a: Phase 2/3 Vitiligo Vehicle-Controlled Population (N = 738)	INCB 18424-211, -306, and -307	• Vehicle cream BID (256) • Ruxolitinib 1.5% cream BID (482)	Safety data are summarized for the vehicle-controlled DB period (Day 1 through Week 24) of the Phase 2 and 3 studies.
Pool 2b: Phase 2/3 Vitiligo Population With at Least 1 Dose of Ruxolitinib 1.5% Cream BID in the Second Period (N = 624)	INCB 18424-211, -306, and -307	• Vehicle cream BID (196) • Lower strengths (6) • Vehicle cream BID to ruxolitinib 1.5% cream BID (196) • Lower strengths to ruxolitinib 1.5% cream BID (6) • Ruxolitinib 1.5% cream BID (422) • Ruxolitinib 1.5% cream BID total (624)	Safety data from Day 1 to Week 52 are summarized for participants who applied ruxolitinib 1.5% cream BID at least once in the second period (ie, TE period [Weeks 24-52] of Studies INCB 18424-306 and -307 and DB extension period [Weeks 24-52] of Study INCB 18424-211). • For participants who crossed over from vehicle cream to ruxolitinib cream, safety data from each period are presented by the treatment regimen for each respective period. • For participants who applied ruxolitinib cream at different strengths and/or application frequencies in different periods of Study INCB 18424-211 (eg, ruxolitinib 0.15% cream QD during the vehicle-controlled DB period and ruxolitinib 1.5% cream BID during the DB extension period), safety data from each period are presented by the treatment regimen for each respective period.
Pooled Population	**Studies**	**Treatment Groups (No. of Participants)**	**Comments**
Pool 2c: Phase 2 Vitiligo Population With Long-term Exposure to Ruxolitinib 1.5% Cream BID (N = 98)	INCB 18424-211	• Vehicle cream BID (17) • Lower strengths (65) • Vehicle cream BID to ruxolitinib 1.5% cream BID (4) • Lower strengths to ruxolitinib 1.5% cream BID (65) • Ruxolitinib 1.5% cream BID (29) • Ruxolitinib 1.5% cream BID total (98)	Safety data from Day 1 through the data cutoff date are summarized for participants who applied ruxolitinib 1.5% cream BID for more than 52 weeks in Study INCB 18424-211. • For participants who crossed over from vehicle cream to ruxolitinib cream, safety data from each period are presented by the treatment regimen for each respective period. • For participants who applied ruxolitinib cream at different strengths and/or application frequencies in different periods of Study INCB 18424-211 (eg, ruxolitinib 0.15% cream QD during the vehicle-controlled DB period and ruxolitinib 1.5% cream BID during the open-label extension period), safety data from each period are presented by the treatment regimen for each respective period.
Pool 2: Phase 2/3 Vitiligo Population (N = 830)	INCB 18424-211, -306, and -307	• Vehicle cream BID (256) • Ruxolitinib 0.15% cream QD (31) • Ruxolitinib 0.5% cream QD (45) • Ruxolitinib 1.5% cream QD (44) • Ruxolitinib 1.5% cream BID (767) • Ruxolitinib cream total (789)	Safety data are summarized for all study periods. • For participants who crossed over from vehicle cream to ruxolitinib cream, safety data from each period are presented by the treatment regimen for each respective period. • For participants who applied ruxolitinib cream at different strengths and/or application frequencies in different periods of Study INCB 18424-211 (eg, ruxolitinib 0.15% cream QD during the vehicle-controlled DB period and ruxolitinib 1.5% cream BID during the open-label extension period), safety data from each period are presented by the treatment regimen for each respective period.

*Source: Table 4 Summary of Clinical Safety

The Applicant conducted the primary safety analysis on Pool 1, which consisted of data through Week 24 from the phase 3 studies (306 and 307), the double-blind, vehicle-controlled period of those studies. Pool 1 consists of 673 subjects: 449 (67%) were in the ruxolitinib 1.5% group,

and 224 (33%) were in the vehicle group. This enrollment ratio reflects the planned randomization of 2:1 (ruxolitinib cream:vehicle) for the phase 3 studies.

The discussion in the safety review focuses on Pool 1, as this was the primary safety data pool. All other pools include data from the Phase 2 study, 211, and these data support the safety of ruxolitinib cream 1.5% in the target population. For long-term exposures, the safety review considered Pools 2b, 2c, and 2. Analysis of data reflecting exposures up to 52 weeks is provided from all 3 studies and is captured in Pool 2b. Exposures > 52 weeks is captured in Pool 2c and is provided from study 211. Pool 2 reflects analyses of data from subjects who applied study treatment (ruxolitinib or vehicle) at least once. Thus, Pool 2 reflects all exposures to study treatment, and it consists of the 830 subjects who constitute the safety database.

The long-term safety data may not have been complete because of the data cut-off date, when studies were ongoing.

Data from use in adolescents (12 to < 18 years of age) was provided only by studies 306 and 307 (study 211 only enrolled adults).

8.2.2. Review of the Safety Database

Overall Exposure

The 830 subjects in the integrated safety database (Pool 2) applied study treatment at least once in the 3 vitiligo studies (306, 307, and 211). Of the 830, 789 subjects applied ruxolitinib cream of any concentration (0.15%, 0.5%, or 1.5%) and frequency i.e., once daily (QD) or twice daily (BID) (only the 1.5% was used BID). A total of 767 subjects applied ruxolitinib cream, 1.5% BID. See Table 19.

Table 19. Number of Subjects Who Applied Ruxolitinib Cream by Regimen and Overall in Integrated Safety Database*

Study	Ruxolitinib Cream Regimen				Total Number of Participants Who Applied Ruxolitinib Cream at Least Once	Total Number of Participants Who Applied Study Drug at Least Once
	0.15% QD	0.5% QD	1.5% QD	1.5% BID		
INCB 18424-211	31	45	44	130	152	157
INCB 18424-306	0	0	0	311	311	330
INCB 18424-307	0	0	0	326	326	343
Total for pooled studies	**31**	**45**	**44**	**767**	**789**	**830**

*Source: Table 6 Summary of Clinical Safety

Table 20 presents the durations of exposures for the integrated safety database. Of the 767 subjects who applied ruxolitinib 1.5% cream BID, 589 subjects had exposure to this dosing

regimen for ≥ 24 weeks, 220 subjects had exposure for ≥ 52 weeks, and 51 subjects were exposed for ≥ 104 weeks. These numbers exceed the minimum recommended for the 6-month and one-year timepoints in the International Council for Harmonisation (ICH) E1A guideline.

Table 20. Summary of Exposure (Pool 2 Population)*

	Treatment Group					
Variable	Vehicle BID (N=256)	0.15% QD (N=31)	0.5% QD (N=45)	1.5% QD (N=44)	1.5% BID (N=767)	Rux Cream Total (N=789)
Duration of treatment (days)						
n	256	31	45	44	767	789
Mean	156.21	215.45	304.82	268.30	282.48	315.44
STD	39.371	117.979	85.691	117.841	200.331	260.356
Min	1.0	1.0	84.0	1.0	1.0	1.0
Median	168.00	173.00	364.00	347.00	246.00	247.00
Max	248.0	371.0	375.0	429.0	1186.0	1192.0
<8 weeks	13(5.1)	3(9.7)	0(0.0)	4(9.1)	48(6.3)	54(6.8)
>=8 - <24 weeks	41(16.0)	3(9.7)	1(2.2)	1(2.3)	130(16.9)	129(16.3)
>=24- <52 weeks	202(78.9)	15(48.4)	18(40.0)	19(43.2)	369(48.1)	361(45.8)
>=52- <104 weeks	0(0.0)	10(32.3)	26(57.8)	20(45.5)	169(22.0)	161(20.4)
>= 104 weeks	0(0.0)	0(0.0)	0(0.0)	0(0.0)	51(6.6)	84(10.6)

*Source: Table 3.1.1.2 Integrated Summary of Safety

The phase 3 studies provided the data for subjects 12 to < 18 years of age i.e., adolescents. A total of 55 adolescent subjects were exposed to ruxolitinib 1.5% BID for ≥ 24 weeks, and 12 were exposed for ≥ 52 weeks.

Table 21. Summary of Exposure in Subject 12 to < 18 Years of Age Group (Pool 2 Population)*

Age Group: 12-<18 years

	Treatment Group					
Variable	Vehicle BID (N=17)	0.15% QD (N=0)	0.5% QD (N=0)	1.5% QD (N=0)	1.5% BID (N=70)	Rux Cream Total (N=70)
Duration of treatment (days)						
n	17				70	70
Mean	160.47				209.86	209.86
STD	30.077				104.936	104.936
Min	54.0				3.0	3.0
Median	168.00				198.50	198.50
Max	190.0				377.0	377.0
<8 weeks	0(0.0)				8(11.4)	8(11.4)
>=8 - <24 weeks	3(17.6)				7(10.0)	7(10.0)
>=24- <52 weeks	14(82.4)				43(61.4)	43(61.4)
>=52- <104 weeks	0(0.0)				12(17.1)	12(17.1)
>= 104 weeks	0(0.0)				0(0.0)	0(0.0)

*Source: Integrated Summary of Safety Table 3.1.1.2.1

In Pool 1, median duration of BID treatment through Week 24, in number of days, was the same for both treatment groups, at 168 days. Median total amount of study product used over the 24-week period was higher in the ruxolitinib group compared to vehicle by approximately 18 grams (609.10 and 591.05, respectively). Median daily amounts of study product applied were similar between treatment groups, vehicle group: 3.90 g and ruxolitinib group: 4.07. See Table 22.

Table 22. Summary of Study Drug Exposure (Pool 1)*

Variable	Vehicle Cream BID (N = 224)	Ruxolitinib 1.5% Cream BID (N = 449)	Total (N = 673)
Duration of treatment (days)			
Mean (SD)	156.62 (38.942)	158.94 (34.974)	158.16 (36.331)
Median	168.00	168.00	168.00
Min, max	1.0, 248.0	1.0, 237.0	1.0, 248.0
Total weight of medication applied (g)			
Mean (SD)	642.23 (357.348)	682.54 (383.105)	669.13 (374.945)
Median	591.05	609.10	607.80
Min, max	23.0, 1517.1	11.2, 1442.7	11.2, 1517.1
Average weight of medication applied daily (g)			
Mean (SD)	7.13 (22.957)	7.36 (25.230)	7.28 (24.480)
Median	3.90	4.07	4.03
Min, max	0.3, 236.3	0.4, 237.1	0.3, 237.1

*Source: Table 7 Summary of Clinical Safety

Adequacy of the safety database:

The safety database was adequate in size and extent of drug exposures to permit an assessment of the safety of ruxolitinib 1.5% cream in subjects ≥ 12 years of age with vitiligo. Although the number of adolescent subjects (12 to < 18 years) was limited (n=55), safety is supported by data for the approval for use of the product in adolescents with AD.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

No issues were identified regarding data integrity or overall submission quality that precluded substantive review.[****]

Categorization of Adverse Events

[****] Many of the study data including laboratory findings were directly transferred from electronic data capture to datasets. Thus, the case report forms lack important information for clinical review. This poses a challenge requiring recovery of the information from datasets or data listings instead of the specific subject's data consolidated in the case report forms. It also presents difficulty in assessing data quality when the data are dispersed.

The Applicant coded treatment-emergent adverse events (TEAEs) for the pooled analyses using Medical Dictionary for Regulatory Activities (MedDRA) v23.1 and tabulated TEAEs by MedDRA preferred term (PT) and system organ class (SOC). The Applicant assessed severity of TEAEs using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.03 for study 211 and v5.0 for studies 306 and 307.

The Integrated Summary of Safety Statistical Analysis Plan (ISS SAP) defined a TEAE as below:

A TEAE is any AE either reported for the first time or worsening of a pre-existing event between the first application date and 30 days after last application date. For participants who cross over treatments, the first application date is period-specific, and the end date is 30 days after the last application date in this period, or the first application date in the next period, whichever comes first.

Analysis of TEAEs was limited to events that met the above definition; however, data listings included all adverse events (AEs), regardless of their timing in relation to last study drug application.

The Applicant searched the safety pools for TEAEs of interest for oral ruxolitinib and other JAK inhibitors as adverse events of interest. Per the ISS SAP, these events were:

- Cytopenias: anemia, thrombocytopenia, neutropenia
- Herpes zoster
- Viral skin infections
- Skin neoplasms
- Venous and arterial thromboembolic events
- Thrombocytosis and elevated mean platelet volume
- Liver Function Tests elevations.

Routine Clinical Tests

Safety assessments were performed according to the schedule presented in Table 23. The nature and frequency of the safety assessments were acceptable.

Table 23. Safety Assessments in the Phase 2 and 3 Studies of Ruxolitinib Cream in Participants With Vitiligo*

Assessment	INCB 18424-306 and -307	INCB 18424-211
Hematology and chemistry assessments[a]	Screening; Day 1; Weeks 4, 8, 12, 18, 24/EOT1, 28, 34, 40, 46, and 52/EOT2; and the safety follow-up visit (30 [+ 7] days after the last study drug application)	Screening; Day 1; Weeks 4, 8, 12, 18, 24, 28, 34, 40, 46, 52/EOT/ET, 56, 68, 80, 92, 104, 116, 128, 140, and 156/ET/EOT; and 1-, 3-, and 6-month follow-up
Vital signs[b]	Screening; Day 1; Weeks 4, 8, 12, 18, 24/EOT1, 28, 34, 40, 46, and 52/EOT2; and the safety follow-up visit (30 [+ 7] days after the last study drug application)	Screening; Day 1; Weeks 4, 8, 12, 18, 24, 28, 34, 40, 46, 52/EOT/ET, 56, 68, 80, 92, 104, 116, 128, 140, and 156/EOT; and 1-, 3-, and 6-month follow-up
Height and weight	Screening and Weeks 24 and 52/EOT2	Screening
Physical examination	Comprehensive: screening and Weeks 24/EOT1 and 52/EOT2. Targeted: Day 1 and Weeks 4, 8, 12, 18, 24/EOT1, 28, 34, 40, 46, and 52/EOT2	Comprehensive: screening and Weeks 24, 52/EOT/ET, and 156/EOT/ET Targeted: Day 1; Weeks 4, 8, 12, 18, 28, 34, 40, 46, 56, 68, 80, 92, 104, 116, 128, and 140; and 1-, 3-, and 6-month follow-up
Pregnancy test	Screening; Day 1; Weeks 4, 8, 12, 18, 24/EOT1, 28, 34, 40, 46, and 52/EOT2; and the safety follow-up visit (30 [+ 7] days after the last study drug application)[c]	Screening; Day 1; Weeks 4, 8, 12, 18, 24, 28, 34, 40, 46, 52/EOT/ET, 56, 68, 80, 92, 104, 116, 128, 140, and 156/EOT/ET; and 1-, 3-, and 6-month follow-up[d]

*Source: Table 2 Summary of Clinical Safety
[a] Including a complete blood cell count and differential count and chemistry panel; early termination (ET), end of treatment (EOT)
[b] Blood pressure, pulse, respiratory rate, and body temperature.
[c] Female participants of childbearing potential had a serum test at screening and the safety follow-up visit (30 + 7 days after EOT; EOT1 or EOT2 as applicable) and a urine test at all other visits. A positive urine test was to be confirmed by a serum test.
[d] Female participants of childbearing potential had a serum test at screening and a urine test at all other visits. A positive urine test was to be confirmed by a serum test.

8.2.4. Safety Results

Deaths

There were no deaths in the development program.

Serious Adverse Events

The Applicant defined serious adverse event (SAE) as any untoward medical occurrence that, at any dose, resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, or was a congenital anomaly/birth defect. Other situations (important medical event) that could be classified as an SAE were events that may have been considered serious when, based on appropriate medical judgment, the event may have jeopardized the

participant and may have required medical or surgical intervention to prevent one of the outcomes listed in the above definition. The Applicant's definition was acceptable.

A total of 9 serious adverse events (SAEs) were reported in the phase 3 studies through Week 24 (Pool 1): one in the vehicle group (0.4%) and 8 in the ruxolitinib 1.5% group (1.8%). There were only single reports of all SAEs i.e., no one type of SAE was reported in more than one subject. Based on the provided information, ruxolitinib cream does not appear to be clearly implicated in causation in any of the events. For some SAEs, there were other factors in the subject's history that predisposed the subject to the SAE i.e., in the absence of exposure to ruxolitinib cream. Investigators assessed that there was not "a reasonable possibility" that ruxolitinib caused any of the SAEs. This reviewer agrees with that assessment. For most subjects, no action was taken with study treatment or treatment was briefly interrupted. One subject withdrew himself from the study for unstated reasons.

Table 24. Summary of Serious Treatment-Emergent Adverse Events by Preferred Term (Pool 1)

MedDRA PT	**Vehicle Cream BID (N = 224) n (%)**	**Ruxolitinib 1.5% Cream BID (N = 449) n (%)**
Participants with any serious TEAE	*1 (0.4)*	*8 (1.8)*
Anal fistula	0	1 (0.2)
Appendicitis	0	1 (0.2)
Concussion	0	1 (0.2)
Coronary artery stenosis	0	1 (0.2)
Hepatitis infectious mononucleosis	0	1 (0.2)
Kidney contusion	0	1 (0.2)
Myocarditis	0	1 (0.2)
Ureterolithiasis	0	1 (0.2)
Tibia fracture	1 (0.4)	0

*Source: Table 25 Summary of Clinical Safety

Narrative information on the subjects who experienced SAEs in the ruxolitinib group (1.5% BID) in Pool 1:

- Subject (b) (6): anal fistula

A 32-year-old male (race not reported) was hospitalized for "anus pain" on Day 58. He underwent "anus fistula flattening (incision)" on Day 59, and the SAE was considered recovered/resolved on Day 61; he was discharged. No action was taken with study treatment.

- Subject (b) (6): kidney contusion

A 14-year-old White male was hospitalized for a left kidney contusion on Day 5. The trauma was sustained from a "kick scooter accident." The SAE was considered recovered/resolved on Day 16. He discontinued study treatment on Day 238 due to "withdrawal by participant" (reason not provided).

- Subject (b) (6): appendicitis

A 34-year-old White male experienced abdominal pain on Day 169 and was diagnosed with appendicitis and hospitalized that same day. The event was considered resolved on Day 171, following appendectomy; he was discharged the same day. No action was taken with study treatment.

- Subject (b) (6): concussion

A 27-year-old White male experienced a concussion on Day 151 following head trauma sustained at work. He was hospitalized as a precaution. The event was considered resolved on Day 154, and he was discharged. No action was taken with study treatment (although he did not receive study product during his hospitalization).

- Subject (b) (6): hepatitis infectious mononucleosis

A 23-year-old female (race not reported) experienced hepatitis infectious mononucleosis (Epstein-Barr virus hepatitis) on Day 148 and was hospitalized. Study treatment was interrupted the same day. Onset of the SAE was reported as Day 147, with no additional history provided regarding onset. She had progressive elevations of aspartate aminotransferase (AST) alanine transaminase (ALT), with improvement noted by Day 153; gamma-glutamyl transferase (GGT) was not discussed for this period. She was treated and monitored, and study treatment was resumed on Day 154. AST and ALT were in the normal ranges by Day 171, and GGT was elevated, but had improved by Day 177. The event was considered recovered/resolved on Day 177.

- Subject (b) (6): myocarditis

A 59 -year-old White male experienced interscapular back pain on Day 61, 3 hours after lifting a heavy dresser. He developed chest pain and shortness of breath that same day (temporal relationship of these events to furniture lifting was not more specifically stated). On Day 63, he "experienced" the SAE of acute perimyocarditis. Electrocardiogram (ECG) that day in the Emergency Department (ED) showed diffuse ST elevation. He also had an upper respiratory infection, ongoing since Day 31. Emergency core angiography and a cardiac catheterization showed mild coronary artery disease and preserved left ventricular systolic function. He was hospitalized with ST elevation myocardial infarction (STEMI); however, the ECG changes were

suggestive of perimyocarditis. Laboratory tests revealed troponin <0.012 ng/mL (normal range 0 to 0.034), C-reactive protein (CRP) 14.9 mg/dL (normal range 0.0 to 0.8), and creatine kinase (CK) 36 U/L (normal range 0 to 170). A 2D ECHO on Day 63 showed: estimated ejection fraction of 55% to 60% with no regional wall motion abnormalities; left ventricular diastolic function parameters were normal; and no pericardial effusion. Chest X-ray showed normal size heart and no evidence of congestive heart failure (CHF) or pleural effusion. He was treated medically, and the acute perimyocarditis was considered resolved on Day 64, the day of discharge. He had applied study drug 124 times prior to onset of the SAE, with last application prior to event being on Day 62. No action was taken with study drug due to the SAE, and he completed study treatment.

Comment: *This subject's history is somewhat confusing relative to "myocarditis," which was reported as being "resolved" just one day following diagnosis. Whether the back and chest pain and shortness of breath related to the myocarditis is unclear. However, the temporal relationship of the back pain and furniture lifting suggest muscle strain as a possibility.*

- Subject (b) (6): ureterolithiasis

A 27-year-old White male experienced ureterolithiasis (right ureter) on Day 120 and was hospitalized for severe pain. The calculus was "broken by laser" and was considered recovered/resolved on Day 121, and he was discharged. No action was taken with study drug.

- Subject (b) (6): coronary artery stenosis

A 57-year-old White male had 90% stenosis of the left anterior descending artery reported on Day 78. He had experienced 2-3 weeks of substernal chest pain, which radiated to the back and worsened on physical activity (coughing). The chest pain was associated with shortness of breath and was relieved with rest. An exercise stress test done on Day 78 was abnormal and was terminated due to chest pain. He was hospitalized on Day 80 for stent placement, and the stenosis was considered recovered/resolved that same day. He had applied study drug 142 times prior to onset of the SAE, with last application prior to event being on Day 77. Additionally, he resumed treatment with ruxolitinib cream, 1.5% on Day 80, and he completed study treatment on Day 358. Anti-platelet therapy was recommended (day unclear), and he started a lipid-lowering agent on Day 90. Reported risk factors for coronary artery disease included a history of hyperlipidemia and hypertension, and a family history of cardiac disease (father underwent coronary artery bypass graft surgery at 78 years; brother underwent percutaneous coronary intervention at 60 years).

Comment: *This subject had several risk factors for cardiovascular disease. Ths reviewer does not consider it reasonable to consider ruxolitinib use as having a causative role in his significant cardiovascular disease after 78 days of use.*

With exposure up to 52 weeks (Pool 2b), an additional 5 subjects who were treated with ruxolitinib experienced SAEs, and no type of event occurred in more than one subject: hypersensitivity and subacute combined cord degeneration (both events in one subject), prostate cancer, papillary thyroid cancer, appendiceal abscess, and rhabdomyolysis. Two of these subjects had crossed over from vehicle to treatment with 1.5% cream treatment (subjects with appendiceal abscess and prostate cancer). Investigators again assessed that there was not a reasonable possibility of the SAEs being caused by study treatment. This reviewer agrees. Information regarding the 5 subjects who experienced SAEs with exposure ≥ 24 weeks up to 52 weeks is provided below:

- Subject (b) (6) hypersensitivity and subacute combined cord degeneration

A 66-year-old White female applied ruxolitinib 1.5% cream BID during the double-blind and treatment extension periods. Day 178 was the last study drug application before onset of the SAEs. On Day 179, she presented to the ED with a severe allergic reaction (details not provided) and numbness and tingling that started on the distal aspects of lower extremities and progressed proximally to the waist. She was hospitalized and treated with systemic corticosteroids, and the "severe allergic reaction" recovered/resolved the same day. Her presentation included "unspecified neurological symptoms (neurological presentation)." Imaging studies of the spine on Day 179 revealed subacute combined degeneration. On an unknown date, she was found to have a low B12 level, and she was treated with B12 supplements. Study treatment was interrupted due to the SAE of hypersensitivity on Day 179 and resumed on Day 184. No action was taken with the ruxolitinib 1.5% cream BID due to the SAE of subacute combined cord degeneration. The SAE of subacute combined degeneration was not recovered/not resolved. However, the day of this assessment was not specified.

Comment: *The sequence of events in the narrative was somewhat difficult to follow. Additionally, the narrative was lacking in details pertaining to the hypersensitivity reaction, including the subject's presentation and possible trigger for the reaction. The narrative was focused on the cord degeneration, which seems likely due to her B12 deficiency. However, ruxolitinib was clearly and reasonably not believed to be causative in either event as study treatment was resumed and continued. The reviewer agrees with the investigator assessment that it was not reasonably possible that either event was related to ruxolitinib cream.*

- Subject (b) (6) prostate cancer

A 66-year-old White male applied vehicle cream BID during the double-blind period and ruxolitinib 1.5% cream BID during the treatment-extension period. The last study drug application before onset of the SAE was on Day 323, and no action was taken with the study drug due to the SAE. On an unspecified date, he reported to the study site that he had a prostate specific antigen of 4. Also, on an unspecified date, he had an ultrasound and multiple biopsies, and he was ultimately diagnosed with prostate cancer on Day 323. He completed

study treatment on Day 358 (completed the study on Day 394). On Day 370, he had a consultation with an oncologist. The SAE of prostate cancer was not recovered/not resolved.

- Subject (b) (6) papillary thyroid cancer

A 31-year-old White female applied ruxolitinib 1.5% cream BID during the double-blind and treatment-extension periods. The last application of study drug before onset (or day of biopsy diagnosis) of the SAE was on Day 173. On an unspecified date, she had a thyroid ultrasound to follow-up on an asymptomatic thyroid nodule that she had had for "many years." Ultimately, the lesion was biopsied, and the results revealed papillary thyroid cancer (Grade 3) on Day 174. For unspecified reasons, the surgery that was initially recommended was "postponed" and "surveillance follow up" was the decided course. The SAE was not recovered/not resolved as of Day 181. No action was taken with study treatment.

- Subject (b) (6) appendiceal abscess

A 52-year-old White female applied vehicle cream BID during the double-blind period and ruxolitinib 1.5% cream BID during the treatment-extension period. The last application of study drug before onset of the SAE was on Day 290. She felt "unwell" on Day 291 (no symptoms were described). She went to the ED on Day 292 and was sent home, following a negative abdominal x-ray. She returned to the ED on Day 294 with increased abdominal pain and still feeling "unwell." A CT scan revealed appendicitis with abscess, and she was hospitalized. Treatment included intravenous antibiotics. On Day 295, she underwent a laparoscopic appendectomy. The SAE was recovered/resolved on Day 296, and she was discharged. No action was taken with study treatment due to the SAE.

- Subject (b) (6) rhabdomyolysis

A 26-year-old White male applied ruxolitinib 1.5% BID during the double-blind and treatment-extension periods. The last study drug application before onset of the SAE was on Day 207. On Day 204, he had a session with a personal trainer and reported vomiting during the session due to the difficulty of the workout. He experienced muscle soreness for 4 days following the workout. On Day 208, the event of rhabdomyolysis was reported. That day, he had presented to the study site for the Week 28 visit, and protocol-specified labs were collected. On Day 209, results revealed a creatine kinase (CK) level of 22,000 IU/L (normal range 39 to 308 IU/L). He was hospitalized, and intravenous fluids were begun. On Day 209, the CK had increased to 26,279 IU/L. On Day 210, CK had decreased and continued to progressively decrease over subsequent days. His CK was 4,699 IU/L (normal range 30 to 300 IU/L) on Day 212, and the SAE was considered recovered/resolved on that day. No action was taken with the study drug due to the SAE.

Comment: *Rhabdomyolysis has been reported in association with use of JAK inhibitors, as discussed in the Integrated Assessment of Safety (see Section 8.2.11).*

No SAEs that occurred in study 211 and beyond Week 24 in the phase 3 studies were considered treatment related; this reviewer agrees. Those SAEs were seizure, esophageal achalasia, coronary artery occlusion, and subdural hematoma. Additional details regarding the subject who experienced the coronary artery occlusion are presented below; the subject continued study treatment:

- Subject (b) (6) coronary artery occlusion

A 56-year-old White male completed treatment with ruxolitinib 0.5% cream QD through Week 52 (Day 357). His past medical history included hyperlipidemia and hypertension. He had no history of diagnosed cardiac ischemia. His last dose of study drug prior to the event was on Day 327. On Day 318, he experienced periodic chest pain (Grade 2 angina pectoris), which was treated with low-dose aspirin. On Day 327, sestamibi nuclear stress test revealed, "significant left anterior descending artery (LAD) territory infarct with minimal peri-infarct ischemia." That same day he had T wave inversions in some leads, and troponin was normal, and the event, termed "angina pectoris" was apparently considered recovered/resolved on Day 327 (the narrative is unclear). He was evaluated by his cardiologist on Day 328 and hospitalized with unstable angina and for additional workup. On Day 329, he had a transthoracic echocardiogram and a cardiac catheterization, which revealed a blockage ("20 mm (L), 95% stenosis"), corrected by angioplasty. He had a successful stent placement and also received medical therapies. He was discharged on Day 330, and the SAE of "coronary blockage" was considered recovered/resolved. Study treatment continued unchanged.

Comment: *The subject's narrative is somewhat confusing. The stress test apparently showed signs of a significant infarct. However, there is no further mention of "infarct" beyond the findings reported for the stress test. It is possible that the "infarct" not have been acute, as troponin was normal (the timepoint of testing is unclear; there is no mention of serial testing). The chest pain that led to the stress test was ultimately referred to as "angina pectoris" that "resolved/recovered." The case report form lists the event as "coronary blockage" The narrative describes events pertaining to the SAE of coronary blockage, and his risk factors included his age, and his history of hyperlipidemia and hypertension.*

The Summary of Clinical Safety describes the following SAEs as having been reported in subjects treated for > 52 weeks, data only from study 211 (Pool 2c): acute cholecystitis, esophageal achalasia, and osteoarthritis. However, the Week 104 interim study report (presents data from Weeks 52 through 104 for study 211) does not include discussion of an SAE of acute cholecystitis for this period. Additionally, the recorded start date for the SAE of esophageal achalasia was Day 295, and this event was discussed in the Week 52 interim study report for study 211 (seemingly appropriately, as the SAE occurred during the 52-week treatment exposure period). One subject (Subject 007009 in Study 21) had an SAE for osteoarthritis which resulted in hospitalization for left hip replacement (start date at Study Day 852, beyond Week 104). SAEs that may relate to safety concerns with JAK inhibitors that were discussed in the

Week 104 interim study reports (and the only 2 narratives for SAEs included in that report) were:

- Subject (b) (6): cerebrovascular accident

A 71-year-old White female applied ruxolitinib 0.5% cream QD during the vehicle-controlled and double-blind extension periods and applied ruxolitinib 1.5% cream BID during the open-label extension period. Her last study drug application before onset of the SAE was on Day 707. The narrative provided limited information regarding the SAE. The subject had missed her one month follow-up visit. When the study site was able to contact her, she reported that she had experienced a stroke on Day 754 (47 days after the last application of study drug). She was hospitalized the same day. The SAE of left middle cerebral artery stroke was considered to be recovering/resolving, and the investigator indicated that the subject would not completely recover from the stroke. No additional information was available regarding the event, per the narrative. Her reported risk factors for ischemic stroke included advanced age, hyperlipidemia, and family history (heart disease and stroke in her mother). The subject had an unconfirmed history of stroke, prior to beginning study treatment. Her vascular evaluation reportedly revealed no significant atherosclerotic disease.

Comment: *This SAE was not recorded as a TEAE, as it occurred outside of the 30-day post-treatment window that defined the endpoint for TEAE classification, per the ISS SAP. This subject had multiple risk factors for CVA. The investigator assessed that there was not a reasonable possibility that "study procedure/study conduct contributed to the event." Based on the available information, this reviewer considers the investigator's assessment to be reasonable.*

- Subject (b) (6) breast cancer

A 63-year-old White female applied ruxolitinib 0.15% cream QD during the vehicle-controlled period, ruxolitinib 1.5% cream QD during the double-blind extension period, and ruxolitinib 1.5% cream BID during the open-label extension period. On an unspecified date, she felt a lump in her breast, and the lesion was biopsied on Day 551, with the pathology reported as "triple-positive breast cancer." The last study drug application before onset of the SAE was on Day 550. She was discontinued from study drug due to the SAE of breast cancer on Day 562. On an unspecified date, a diagnosis of invasive ductal carcinoma was confirmed, and she was found to have an associated ductal carcinoma in situ (DCIS) of high nuclear grade. Disease was found to be extensive in the left breast on Day 558. Subsequent additional workup identified a possible liver lesion, and malignancy could not be excluded. Past medical history included hormone replacement therapy for 15 years. Her age at the birth of her 3 children and age of menarche were not provided. She reportedly drank socially and had no family history of breast cancer. Her body mass index was 29.33 kg/m^2. The outcome of the SAE was reported as unknown, and she was lost to follow-up, as of Day 664.

Comment: *The investigator assessed that there was not a reasonable possibility that study drug had caused this SAE. This seems a reasonable assessment to the reviewer.*

The pattern in occurrence of SAEs with longer term exposure (i.e., > 24 weeks) raised no new safety concerns relative to the up to 24-week exposure.

4-Month Safety Update

The 4-month safety update provided for an additional SAE from study 307:

- Subject (b) (6) joint dislocation

A 31-year-old White male sustained injuries to his right shoulder secondary to a fall from his bicycle. Final diagnosis was rupture of "the coracoclavicular ligament in acromioclavicular joint disruption according to Tossy III." Study treatment continued unchanged.

The 4-month safety update also included SAEs from study 308. Investigators assessed that SAEs as not reasonably caused by study treatment. Subjects enrolled in this study after completion of participation in the pivotal studies 306 and 307:

- Subject (b) (6): cholecystolithiasis and cholecystitis

A 38-year-old female was hospitalized for cholecystolithiasis on Day 392. She was treated and discharged on Day 393. On Day 394 (Day 31 of study 308), she "experienced" cholecystitis and was hospitalized, treated, and released on Day 395, with surgery planned for Day 402. She underwent a laparoscopic cholecystectomy on Day 402 and was discharged on Day 404. Both SAEs resolved. Study treatment continued unchanged.

- Subject (b) (6) hip fracture

A 44-year-old White female was hospitalized on Day 454 (Day 90 of study 308) for a hip fracture sustained during a fall. The fracture was surgically repaired on the same day. The SAE was considered resolved on Day 561. Study treatment was withdrawn for unspecified reasons.

- Subject (b) (6): angina pectoris

A 58-year-old male experienced worsening angina pectoris on Day 369 (Day 6 of study 308), presented to the ED, and was hospitalized the same day. His past medical history included angina pectoris, coronary artery disease, hyperlipidemia, transient ischemic attack, coronary angioplasty, coronary artery bypass, and hypertension. Work-up for myocardial infarction was negative. He was treated, and the chest pain ultimately resolved. He was discharged on Day 370 (Day 7 of 308). Study treatment continued unchanged.

Comment: *The Applicant included the same narrative information in the Appendix to the Summary of Clinical Safety as an SAE that occurred in study 308 (which enrolls subjects from the phase 3 studies, 306 and 307). This subject experienced the nonserious events of right bundle branch block, worsening hypertension, and chest pain during study 307.*

- Subject (b) (6) cystocele, rectocele, uterine prolapse

A 65-year-old White female experienced uterine prolapse, midline cystocele, and rectocele on Day 525 (Day 160 of study 308). On the same day, she was hospitalized and underwent bilateral oophorectomy and hysterectomy as treatment. She was considered to be recovered from the events on Day 526 and was discharged that same day. Study treatment was interrupted.

- Subject (b) (6): pelvic prolapse

A 68-year-old White female was hospitalized for surgery for pelvic floor depression on Day 381 (Day 17 of study 308). She apparently had the surgery (day not specific), and the event was considered resolved on Day 386. Study treatment continued unchanged.

Dropouts and/or Discontinuations Due to Adverse Effects

The incidence of discontinuation from treatment in Pool 1 due to a TEAE was 0.4% in each treatment group.

Table 25. Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of Study Drug (Pool 1)*

MedDRA PT, n (%)	**Vehicle Cream BID (N = 224)**	**Ruxolitinib 1.5% Cream BID (N = 449)**
Participants with any TEAE leading to discontinuation of study drug	*1 (0.4)*	*2 (0.4)*
Application site rash	0	1 (0.2)
Fatigue	0	1 (0.2)
Headache	1 (0.4)	0
Nausea	1 (0.4)	0

*Source: Table 28 Summary of Clinical Safety

The subject who discontinued from ruxolitinib 1.5% cream group due to a reaction at the treatment site is discussed below:

- Subject (b) (6) was a 44-year-old male in the ruxolitinib group who experienced a Grade 1 application site irritation “in the neck region” on Day 25. No action was taken with study treatment, nor was the irritation treated. The investigator assessed the TEAE

as being possibly related to study treatment. The reaction did not resolve; however, the period over which the reaction did not resolve was not specified. On Day 75, the subject had a Grade 2 application site rash (unclear whether it was the same reaction that was present on Day 25), and study treatment was discontinued that same day. The subject was treated with intramuscular and topical corticosteroids, and the event was considered resolved on Day 110. The investigator assessed the application site rash as being unlikely related to study treatment and associated with an unnamed concomitant medication (aside from the treatment for the rash, the only other listed concomitant medication in the narrative is escitalopram).

Comment: *That the application site reaction was treated with systemic and topical corticosteroids and resulted in discontinuation of study treatment indicates that the rash was highly clinically significant. No other products were specifically cited as potential causes of the application site reaction.*

- Subject (b) (6) was a 62-year-old White female who discontinued due to application site eczema.

No subject who applied ruxolitinib 1.5% BID for longer than 52 weeks (Pool 2c) experienced a TEAE leading to discontinuation of treatment.

The incidence of discontinuation of ruxolitinib 1.5% BID treatment due to a TEAE was low and did not meaningfully increase over time (through Week 52).

Significant Adverse Events

Treatment-related adverse events and Grade 3 or higher severity adverse events are discussed below.

Treatment-Related Adverse Events

Overall, treatment-related TEAEs were reported in a higher proportion of subjects in the ruxolitinib arm compared to vehicle: 66 (14.7%) and 17 (7.6%), respectively. In Pool 1, treatment-related TEAEs were reported in the following SOCs in the ruxolitinib group and vehicle groups, respectively, as follows:

- Gastrointestinal disorders: 1 (0.2%) and 1 (0.4%),
- General disorders and administration site conditions: 56 (12.5%) and 10 (4.5%),
- Infections and infestations: 5 (1.1%) and 2 (0.9%),
- Investigations: 0 (0.0%) and 1 (0.4%),
- Nervous system disorders: 2 (0.4%) and 1 (0.4%), and
- Skin and subcutaneous tissue disorders: 5 (1.1%) and 4 (1.8%).

In both treatment groups, most treatment-related TEAEs occurred in the General disorders and administration site conditions SOC [ruxolitinib arm 56 subjects (12.5%) and vehicle arm 10

subjects (4.5%), respectively], and most events in this SOC were ASRs. Application site acne was the most common ASR that was assessed as treatment-related in the ruxolitinib arm and was reported in 22 subjects (4.9%) compared to 2 subjects (0.9%) the vehicle arm. In the ruxolitinib arm, application site pruritus occurred at essentially the same incidence as application site acne: 21 subjects (4.7%) and 22 subjects (4.9%), respectively. Application site folliculitis was the only treatment-related TEAE that was reported for more than one subject in the Infections and infestations SOC, and all reports of this event were in the ruxolitinib arm: 3 subjects (0.7%). Somewhat interestingly, treatment-related TEAEs in the Skin and subcutaneous tissue disorders SOC were reported at a higher incidence in the vehicle group compared to ruxolitinib: 4 subjects (1.8%) and 5 subjects (1.1%), respectively. No TEAE was reported in more than one subject in the Skin and subcutaneous tissue disorders SOC.

Grade 3 or Higher Severity Adverse Events

The overall incidence of TEAEs of grade 3 severity or higher was similar between treatment groups, but slightly higher in the ruxolitinib arm through Week 24 in Pool 1. Investigators did not assess any of the TEAEs of grade 3 severity or higher as being treatment related. No TEAE of grade 3 severity or higher was reported in more than one subject.

A full narrative was not provided for the subject who experienced ovarian cancer and was in the ruxolitinib treatment arm. The event was recorded as nonserious. However, in the Summary of Clinical Safety, she was described as a 56-year-old female who had a history of right ovarian cancer and hysterectomy with bilateral oophorectomy (Subject 7 (b) (6)).

Table 26. Summary of Treatment-Emergent Adverse Events of Grade 3 or Higher Severity (Pool 1)

MedDRA PT, n (%)	Vehicle Cream BID (N = 224)	Ruxolitinib 1.5% Cream BID (N = 449)
Participants with any ≥ Grade 3 TEAE	*4 (1.8)*	*10 (2.2)*
Anal fistula	0	1 (0.2)
Anal stenosis	0	1 (0.2)
Appendicitis	0	1 (0.2)
Concussion	0	1 (0.2)
Coronary artery stenosis	0	1 (0.2)
Hepatitis infectious mononucleosis	0	1 (0.2)
Hypertension	0	1 (0.2)
Localized infection	0	1 (0.2)
Ovarian cancer	0	1 (0.2)
Tooth impacted	0	1 (0.2)
Electrolyte imbalance	1 (0.4)	0
Hyperglycemia	1 (0.4)	0
Hyperkalemia	1 (0.4)	0
Pilonidal cyst	1 (0.4)	0
Tibia fracture	1 (0.4)	0

*Source: Table 22 Summary of Clinical Safety

Treatment Emergent Adverse Events and Adverse Reactions[††††]

Table 27 presents an overall summary of TEAEs that occurred in Pool 1.

[††††] The Applicant has distinguished "Adverse Drug Reactions" (ADRs, and referred to as "Adverse Reactions" in this review) from simple treatment-related TEAEs which are identified via Investigator considerations for relationship to treatment. The details for qualifying as an ADR instead of a treatment-related TEAE are discussed in Section 7.1.3 of the Clinical Summary of Safety document and the legend to Table 59 in that section: "*ADRs were identified based on the frequency of reporting during the vehicle-controlled DB period of the Phase 3 studies a higher incidence and IR (when data from the Phase 2 study and the TE period of the Phase 3 studies were included) among participants who applied active treatment versus vehicle, and the fact that a relationship to application of ruxolitinib cream is plausible*." (Section 2.7.4 of Module 2). They are also to be distinguished from, but may overlap with, application site reactions (ASRs) discussed below.

Table 27. Overall Summary of Treatment-Emergent Adverse Events (Pool 1)*

Category, n (%)	Vehicle Cream BID (N = 224)	Ruxolitinib 1.5% Cream BID (N = 449)
Participants who had a TEAE	79 (35.3)	214 (47.7)
Participants who had a treatment-related TEAE	17 (7.6)	66 (14.7)
Participants who had a Grade 3 or higher severity TEAE	4 (1.8)	10 (2.2)
Participants who had a treatment-related Grade 3 or higher severity TEAE	0	0
Participants who had a serious TEAE	1 (0.4)	8 (1.8)
Participants who had a treatment-related serious TEAE	0	0
Participants who had a serious TEAE with a fatal outcome	0	0
Participants who had a TEAE leading to study drug interruption	4 (1.8)	6 (1.3)
Participants who had a TEAE leading to study drug discontinuation	1 (0.4)	2 (0.4)
Participants who had an application site reaction	13 (5.8)	67 (14.9)

*Source: Table 16 Summary of Clinical Safety

TEAEs were most frequently reported in the Infections and Infestations SOC in Pool 1: 98 subjects (21.8%) in the ruxolitinib arm and 37 subjects (16.5%) in the vehicle arm. Nasopharyngitis was the commonly reported TEAE in this SOC vehicle- 5 subjects (2.2%), and ruxolitinib 1.5% cream- 19 (4.2%). The SOC that was second in most commonly reported TEAEs was General disorders and administration site conditions (ASRs were captured in this SOC): 74 subjects (16.5%) in the ruxolitinib arm and 15 subjects (6.7%) in the vehicle arm. Application site acne was the most commonly reported TEAE in this SOC (and overall) for subjects in the ruxolitinib group: vehicle- 2 subjects (0.9%) and ruxolitinib cream- 26 subjects (5.8%).

Table 28 presents the TEAEs that occurred in at least 1% of subjects in the ruxolitinib arm in Pool 1 and at a greater incidence than in the vehicle arm. The most common TEAEs in the ruxolitinib groups were application site acne and application site pruritus, both of which occurred at a higher rate in the active group compared to vehicle. Additionally, other ASRs met the criteria for inclusion in the table, namely application site rash and application site erythema. Other TEAEs that occurred at a higher incidence in the ruxolitinib arm compared to vehicle included common AEs such as nasopharyngitis, headache, and upper respiratory tract infection.

Also see discussion of ASRs below.

Table 28. Adverse Reaction Occurring in ≥ 1% of Subjects in the Ruxolitinib Arm and at a Higher Incidence than Vehicle (Pool 1)*

Adverse Reaction	Vehicle Cream BID (N=224) n (%)	Ruxolitinib 1.5% Cream BID (N=449) n (%)
*Subjects with any TEAE**	*79 (35.3)*	*214 (47.7)*
Application site acne	2 (0.9)	26 (5.8)
Application site pruritus	6 (2.7)	23 (5.1)
Nasopharyngitis	5 (2.2)	19 (4.2)
Headache	6 (2.7)	17 (3.8)
Upper respiratory tract infection	5 (2.2)	13 (2.9)
Urinary tract infection	1 (0.4)	7 (1.3)
Application site rash	2 (0.9)	7 (1.6)
Application site erythema	1 (0.4)	7 (1.6)
Influenza	1 (0.4)	6 (1.3)
Pyrexia	0	6 (1.3)
Alanine aminotransferase increased	1 (0.4)	5 (1.1)

*Source Table 3.2.3.1.2.1 Integrated Summary of Safety

Application Site Reactions (ASRs)

The Applicant developed a list of 86 MedDRA PTs for assessment of ASRs and applied those PTs in searches performed on each of the pooled databases. From review of the list, this reviewer concluded that it allowed for comprehensive assessment of ASRs.

ASRs occurred in a higher percentage of subjects treated with ruxolitinib cream, 1.5% BID compared to vehicle in all pools except Pool 2c, which consisted only of subjects in the phase 2 study, 211. This may relate to reporting practices in study 211, in which not all TEAEs that occurred at application sites were recorded as ASRs. Study 211 also included evaluation of lower strengths of ruxolitinib cream.

The 2 most commonly reported ASRs (except Pool 2c) and in order of frequency were application site acne and application site pruritus. None of the ASRs were SAEs and all were of Grade 1 or 2 severity. The Applicant reported that most resolved with no action taken with study treatment and did not recur. However, many application site acne events did not resolve. As noted, Grade 2 was the highest severity level for any ASRs, and Grade 2 ASRs were reported with active and vehicle treatment. However, treatment was discontinued for one subject due to an ASR (this subject has been previously discussed). Additionally, a 35-year-old-male (709020) had ruxolitinib treatment interrupted due to Grade 2 application site acne (face and neck) and resumed treatment after one month with the event ongoing. The signal for application site acne was not seen in the AD program (even with long-term use).

In Pool 1, ASRs were reported in 13 subjects (5.8%) in the vehicle group and 67 subjects (14.9%) in the ruxolitinib group.

Table 29 presents the ASRs that were reported for Pool 1.

Table 29. Summary of Application Site Reactions (Pool 1)

MedDRA PT, n (%)	Vehicle Cream BID (N (N= 224)	Ruxolitinib 1.5% BID (N = 449)
Any application site TEAE	*13 (5.8)*	*67 (14.9)*
Application site acne	2 (0.9)	26 (5.8)
Application site pruritus	6 (2.7)	23 (5.1)
Application site erythema	1 (0.4)	7 (1.6)
Application site rash	2 (0.9)	7 (1.6)
Application site dermatitis	0	4 (0.9)
Application site exfoliation	1 (0.4)	4 (0.9)
Application site discolouration	0	3 (0.7)
Application site dryness	1 (0.4)	3 (0.7)
Application site folliculitis	0	3 (0.7)
Application site irritation	1 (0.4)	2 (0.4)
Application site pain	0	2 (0.4)
Application site bruise	0	1 (0.2)
Application site eczema	0	1 (0.2)
Application site papules	1 (0.4)	1 (0.2)
Application site paraesthesia	1 (0.4)	1 (0.2)
Application site urticaria	0	1 (0.2)

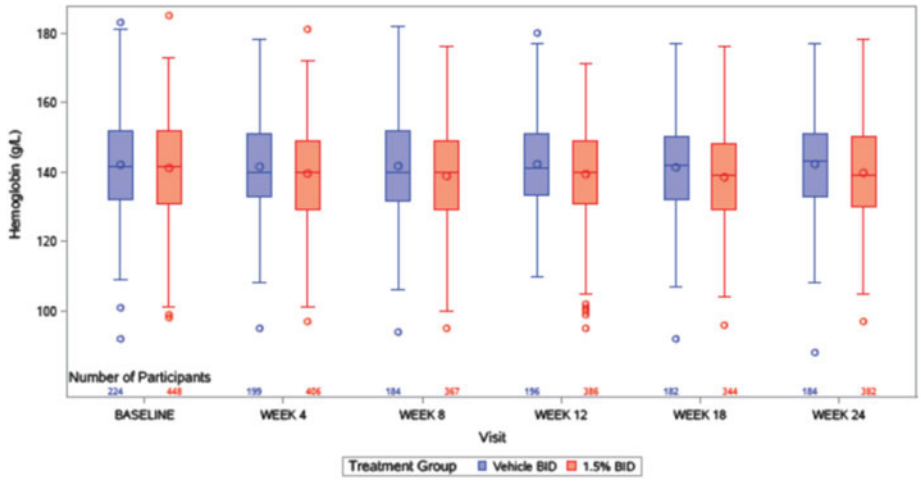
*Source: Table 30 Summary of Clinical Safety

Laboratory Findings

The label for oral ruxolitinib includes a Warning and Precaution describing that treatment can cause thrombocytopenia, anemia and neutropenia. The Applicant's examination of laboratory data for platelets, hemoglobin and neutrophils in the phase 3 studies through Week 24 (Pool 1) identified no clinically meaningful changes in these parameters with treatment with ruxolitinib cream 1.5% BID.

In Pool 1, mean hemoglobin, platelet, and neutrophil levels were similar between treatment groups at each test visit (Baseline through Week 24). See Figures 13, 14, and 15, respectively.

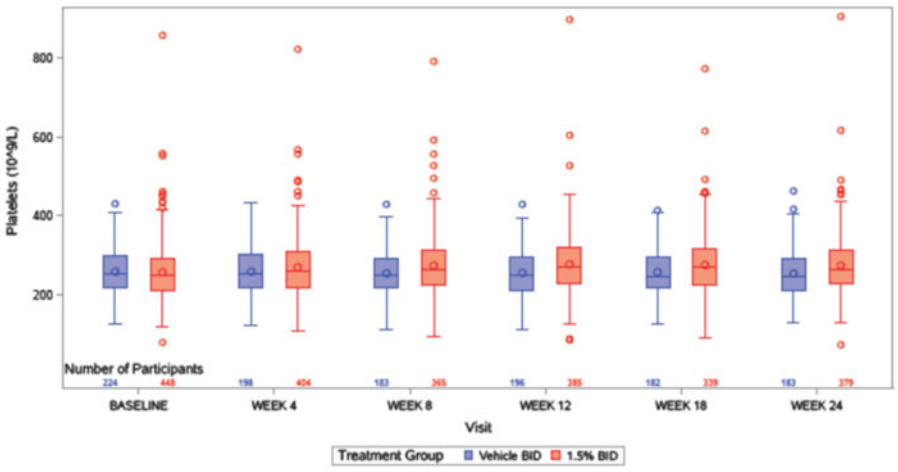
Figure 13. Box Plot of Hemoglobin Levels by Visit and Treatment Group (Pool 1)*



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

Regarding hemoglobin concentration, 418 subjects (93.1%) in the ruxolitinib group in Pool 1 were categorized as Grade 0 at Baseline, and a shift to Grade 2 for one subject (0.2%) was the worst shift reported for these subjects. In the vehicle group, 205 subjects (91.5%%) were in the Grade 0 category at Baseline, and the worst shift was to Grade 1 for 16 subjects (7.8%).

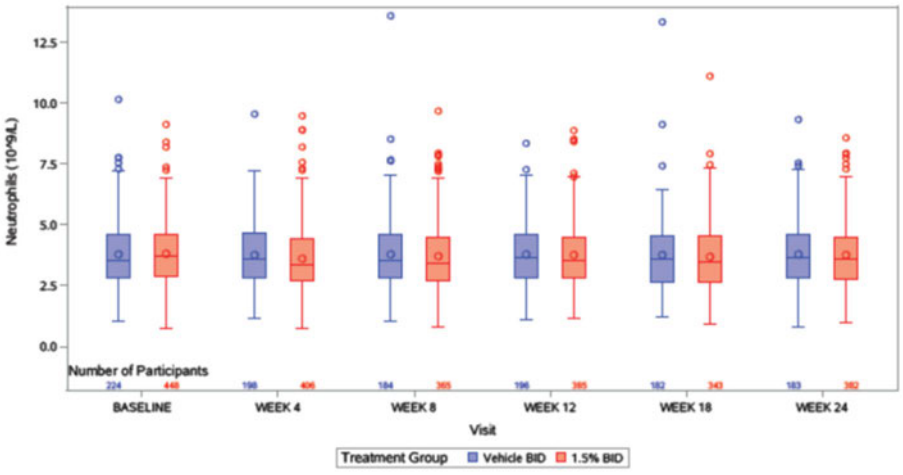
Figure 14. Box Plot of Platelet Counts by Visit and Treatment Group (Pool 1)*



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

Regarding platelet counts, 443 subjects (98.7%) in the ruxolitinib group in Pool 1 were categorized as Grade 0 at Baseline, and a shift to Grade 1 for 2 subjects (0.5%) was the worst shift reported in this group. In the vehicle group, 223 subjects (99.6%%) were in the Grade 0 category at Baseline, and the worst shift was to Grade 1 for 1 subject (0.4%).

Figure 15. Box Plot of Neutrophil Counts by Visit and Treatment Group (Pool 1)*



* Source: Figure 6 Summary of Clinical Safety

Regarding neutrophil counts, 432 subjects (96.2%) in the ruxolitinib group in Pool 1 were categorized as Grade 0 at Baseline, and a shift to Grade 3 for one subject (0.2%) was the worst shift reported in this group. Six subjects (1.4%) had a shift to Grade 2. In the vehicle group, 218

subjects (97.3%%) were in the Grade 0 category at Baseline, and the worst shift was to Grade 3 for 1 subject (0.5%). One subject in each treatment group experienced a Grade 3 shift. Five subjects (2.3%) in the vehicle group had a shift to Grade 2.

A 12-year-old female who was treated with ruxolitinib 1.5% cream BID had a Grade 3 shift neutrophil count at Week 28. Her baseline value was 2.74×10^9/L, and her value was 0.57×10^9/L at Week 28. She had had a Grade 1 neutrophil value of 1.65×10^9/L at a screening visit. She had no other abnormal neutrophil values reported during the study. A 71-year-old male had 2 Grade 3 shifts. His baseline neutrophil value was 2.59×10^9/L, and at Week 4 his value 0.88×10^9/L, and at Week 70, his value was 0.98×10^9/L. No other abnormal neutrophil values were reported.

Liver Function Tests

Elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were observed in clinical trials with oral ruxolitinib and some other JAK inhibitors and are discussed in the labels for those products. The Applicant assessed ALT, AST, and bilirubin concentrations as being similar between treatment groups at all visits through Week 24 in Pool 1.

Most shifts in LFT parameters were Grade 1 or 2. Four subjects in Pool 1 had seemingly sporadic Grade 3 post baseline shifts in a single LFT parameter: 3 subjects had a shift in ALT (1 vehicle-treated subject and 2 ruxolitinib-treated subjects), and 1 subject in the ruxolitinib group had shifts in bililrubin. These shifts were accompanied by lesser shifts (Grade 1 or 2) of other LFT parameters. None of these occurrences were SAEs. One of the subjects who experienced a Grade 3 elevation in ALT was also the subject who experienced rhabdomyolysis.

No subjects met Hy's law criteria.

Vital Signs

The Applicant did not summarize vital signs for pooled populations. Per the study reports for studies 306 and 307, most subjects had normal vital signs from Baseline through the treatment extension periods, and no significant trends were noted in changes in vital signs through Week 24. The same was true for study 211 through Week 104, per the interim study report. See Table 23 for the schedule for assessment of vital signs.

TEAEs relating to vital signs in the phase 3 trials through Week 24 were blood pressure fluctuation (1 subject in vehicle group) and hypertension (4 subjects, all in the ruxolitinib group).

Electrocardiograms (ECGs)

ECGs were specified only for the Screening visit in studies 306 and 307. ECGs were specified for the Screening, Week 52, and Week 156 visits in Study 211. The Week 52 interim study report

for study 211 did not include discussion of ECG findings, and no ECGs were obtained between Weeks 52 and 104 (therefore, no new ECGs findings were available for the Week 104 interim report).

In Pool 1, the TEAE of atrial fibrillation was reported for 1 subject (ruxolitinib group). This was the only TEAE relating to ECG findings in Pool 1.

QT

From Section 4.2 of the Summary of Clinical Safety (referencing the original submission (12/21/2020):

A thorough QT study of oral ruxolitinib at a supratherapeutic dose (200 mg), which produced plasma concentrations well above those observed for ruxolitinib 1.5% cream BID, was negative for QT prolongation according to the International Council for Harmonisation E14 Guidance (previously reported in NDA 215309).

From review of the original NDA:

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

Immunogenicity Potential

Not applicable.

8.2.5. Analysis of Submission-Specific Safety Issues

The approved package insert for Opzelura includes a Boxed Warning advising of risks of serious infections, mortality, malignancy, major adverse cardiovascular events (MACE), and thrombosis. These events are largely discussed in the context of JAK inhibitors as a class, specifically those products indicated for treatment of inflammatory conditions. Adverse events of interest are discussed below.

8.2.5.1. Serious Infections and Herpes Zoster

The 2 serious infections that occurred in the phase 3 trials during the initial 24-week period (Pool 1) have been previously discussed, and those events were appendicitis and hepatitis infectious mononucleosis. See Section 8.2.4.

Although not SAEs, 5 herpes zoster events were reported across the development program: 4 herpes zoster events and 1 event of postherpetic neuralgia. All of these events occurred in subjects who had been using ruxolitinib 1.5% cream BID for at least 24 weeks, and all subjects were using the product when the event occurred. Study day of onset of the herpes zoster ranged from Day 224 to Day 345 (it was not reported for one subject). Subjects ranged in age from 47 to 69 years. For 2 subjects the herpes zoster occurred at an application site, and for the other 2 the location was "not applicable." All subjects recovered, including the subject who developed postherpetic neuralgia. The duration of the zoster for 3 subjects ranged from 11 to 22 days (duration was not reported for a 4th subject), and the duration was 30 days for the postherpetic neuralgia. No action was taken with study treatment for any subject. The courses of the herpes zoster events were uncomplicated (except for the postherpetic neuralgia). All subjects were older than forty years of age. The duration of the zoster events was within the general timeframe for zoster.[26]

No additional serious infections or events of herpes zoster were reported in the 4-Month Safety Update.

8.2.5.2. Malignancy and Lymphoproliferative Disorders

Ultraviolet light (UVL) exposure is a known factor in development of non-melanoma skin cancers (NMSC). The absence of the protective effect of melanin at affected sites could raise concerns regarding a potential increased risk for NMSC and melanoma in patients with vitiligo, from exposures to UVL, including therapeutic exposures. An increased risk of skin cancer from long-term PUVA treatment has been established for patients with psoriasis.[34,35] However, similar risks do not appear to attach to NB-UVB.[14] Genetic and autoimmune factors may have protective effects against development of melanoma and NMSC in patients with vitiligo, although additional investigations are required to support reported findings. [14]

In the phase 3 trials, prior therapy included PUVA for 5.2% of subjects and NB-UVB for 20.8% of subjects. In the integrated safety database (Pool 2), 29.6%, had received phototherapy as prior treatment: PUVA for 5.7% of subjects and NB-UVB for 16.9% of subjects.

In Pool 2, 5 subjects experienced 8 treatment-emergent NMSC: 6 basal cell carcinomas (BCC) (in 3 subjects), 1 Bowen's disease, and squamous cell carcinoma (SCC). No melanomas were reported. All 5 subjects were White, and 4 of 5 had Fitzpatrick Type II skin type (the remaining subject had Type I skin type), and 4 of 5 were male. Two of the subjects had a a history of photochemotherapy treatment, and a third subject had a history of phototherapy treatment.

One of the 5 subjects had 4 of the 6 BCCs (at scattered sites). This subject was a 50-year-old White male with Type II skin, and he had a previous history of phototherapy. One of his BCCs was at an application site, and this lesion was apparently diagnosed on the same day as 2 other BCCs that were not at treatment sites. The 4th lesion had been diagnosed 175 days prior to the other BCCs. For the remaining 3 subjects, the NMSC (2 BCC and 1 Bowen's disease) occurred at an application site.

The subject who experienced the SCC was in the vehicle treatment group, and the event "started" on Day 42 and occurred at an application site.

Table 30. Nonmelanoma Skin Neoplasm Treatment-Emergent Adverse Events (Safety Population)*

Study Age/Sex, Race	Treatment Group	Relevant Medical History/Relevant Prior Medications or Therapies and Concomitant Medications	PT (Location)	Grade	Serious (Y/N)	Related (Y/N)	At Application Site (Y/N)	Action Taken With the Study Drug	Study Day Start	Duration (days)
INCB 18424-211 42/F, White (Fitzpatrick Type II skin type)	Ruxolitinib 0.15% cream QD	None/None	Basal cell carcinoma (mid chest)	2	N	N	Y	Drug interrupted (study drug application restarted: yes)	198	31
INCB 18424-211 68/M, White (Fitzpatrick Type II skin type)	Ruxolitinib 0.5% cream QD (vehicle-controlled DB and DB extension periods)/ruxolitinib 1.5% cream BID (open-label extension)	None/Photochemotherapy (prior therapy), tacrolimus (topical, prior medication)	Basal cell carcinoma (left lower leg)[a]	2	N	Y	Y	Drug discontinued	680	134
INCB 18424-211 50/M, White (Fitzpatrick Type II skin type)	Ruxolitinib 1.5% cream BID	Skin lesion (reported term: red lesion on right shoulder)/Phototherapy (prior therapy), tacrolimus (topical, prior medication)	Basal cell carcinoma (right shoulder)	2	N	N	N	Drug interrupted (study drug application restarted: yes)	203	120
			Basal cell carcinoma (left posterior shoulder)	2	N	N	N	Drug interrupted (study drug application restarted: no)	378	106
			Basal cell carcinoma (left upper arm)	2	N	N	N	Drug interrupted (study drug application restarted: no)	378	106
INCB 18424-211 50/M, White (Fitzpatrick Type II skin type) (continued)			Basal cell carcinoma (right neck)	2	N	N	Y	Drug interrupted (study drug application restarted: no)	378	106
INCB 18424-211 52/M, White (Fitzpatrick Type II skin type)	Ruxolitinib 1.5% cream BID	None/Corticosteroids (topical, prior medication), psoralen (oral, prior therapy), UVA (prior therapy)	Bowen disease (unspecified treated area)	2	N	N	Y	No change	1090	Ongoing
INCB 18424-306 66/M, White (Fitzpatrick Type I skin type)	Vehicle cream BID	Skin lesion (reported term: 4 mm raised flaky lesion [right forearm skin])/cortisone (topical, prior medication)	Squamous cell carcinoma of skin (unspecified treated area)	2	N	N	Y	No change	42	27

*Source: Table 41 of Summary of Clincia Safety

[a] This event was preceded by nonserious TEAEs of actinic keratosis (Grade 2, right inferior leg) and lichenoid actinic keratosis (Grade 2, left wrist and right superior leg) with onset on Day 387. None of these events were considered related to the study drug by the investigator, and no action was taken with the study drug due to these events. The events resolved on Day 477.

The size- and exposure-adjusted incidence rates for BCC in Pool 2 were vehicle: 0 (0%) and ruxolitinib cream 3 (0.4%) and for Bowen's disease: vehicle (0%) and ruxolitinib cream, 1 (0.1%) (Table 3.2.3.2.6.1).

This reviewer notes that all of the subjects had fair skin, most of the subjects were male (one subject was female), and most subjects were ≥ 50 years of age (the female subject was 42), factors which may correlate with development of BCC and cutaneous SCC. All subjects

developed the NMSC at what may be considered sun-exposed areas, which also corresponded to application sites for some subjects, including the subject on vehicle treatment who experienced the SCC. Two subjects had a history of photochemotherapy. For the one subject for whom multiple BCC were reported, 3 of the 4 lesions were not at application sites. The available information includes factors that placed each subject at some risk for development of NMSC. A potential contributory role of ruxolitinib in causation atop other risk factors is unclear. However, investigators did not consider any of the lesions to be treatment-related, and this seems a reasonable assessment.

There were single reports of all other malignancies in the integrated safety database (Pool 2), and those other malignancies were breast cancer, ovarian cancer, papillary thyroid cancer, and prostate cancer. All were reported as SAEs (see Section 8.2.4) except the event of ovarian cancer, which was considered nonserious (Subject (b) (6) was a 56-year-old female who had a history of right ovarian cancer, hysterectomy and double ovariectomy. The event was ongoing at the time of data cutoff for the supplement, and no action was taken with study drug because of the event).

No additional malignancies were reported in the 4-Month Safety Update.

8.2.5.3. Thromoembolic and Major Adverse Cardiovascular Events (MACE)

In the integrated safety database (Pool 2), 3 subjects experienced thrombotic or embolic events while on ruxolitinib cream treatment, and no action was taken with study medication for any of these subjects. “Coronary artery occlusion” was the event reported for one of these subjects (024005). The event was an SAE, and this subject has been previously discussed (see Section 8.2.4). For subject 024005, the SAE was recorded as “coronary blockage” on the case report form; “coronary artery occlusion” is the PT reported in the narrative. The SAE for this subject and the investigator assessment appear to pertain to incomplete coronary blockage, (coronary occlusion).

A second subject (b) (6)) was a 54-year-old obese female (BMI 32 kg/m^2) who experienced a thrombus in the left leg 25 days following surgery to remove a torn meniscus from the right knee. It is unclear whether the subject had any mobility limitations in her postoperative course that may have increased her risk for development of a thrombus. The 3rd subject (b) (6)) was a 65-year-old female, with a history of hyperlipidemia for which she was taking lipid lowering agents (ezetimibe and simvastatin), who experienced a nonserious transient ischemic attack on Day 76. Her risk factors for the event include her age and history of hypercholesterolemia.

The Applicant reported that for 2 of these subjects, the plasma ruxolitinib concentrations were below the half-maximal inhibitory concentration (IC_{50}) for JAK2 inhibiton in whole blood assays at testing proximate to the event. For the third subject (subject with thrombus in leg), such PK sampling was not done.

Table 31. Arterial and Venous Thromboembolic Events (Pool 2 Population)*

Study Participant No. Age/Sex, BMI at Baseline	Treatment Group	Relevant Medical History/Relevant Prior and Concomitant Medications	PT	Grade	Serious (Y/N)	Related (Y/N)	Action Taken With the Study Drug Plasma Concentrations	Study Day Start	Duration
INCB 18424-211 024005 56/M, 29.7 kg/m^2	Ruxolitinib 0.5% cream QD (vehicle-controlled DB and DB extension periods); ruxolitinib 1.5% cream BID (open-label extension period)	Hyperlipidemia, hypertension/None	Coronary artery occlusion	3	Y	N	No change Week 28: 11.8 nM (preapplication) and 20.8 nM (2 h postapplication) Week 52: 26.9 nM (preapplication) and 16.2 nM (2 h postapplication)	328	3 days
INCB 18424-211 020007 54/F, 32.0 kg/m^2	Ruxolitinib 1.5% cream BID	Recent knee surgery (meniscus removal)/None	Thrombosis (verbatim term: left lower leg blood clot)	2	N	N	No change 203 to 669 nM	980	177 days
INCB 18424-307 723007 65/F, 25.6 kg/m^2	Ruxolitinib 1.5% cream BID	Hypercholesterolemia/ Ezetimibe and simvastatin	Transient ischaemic attack	2	N	N	No change 63.2 nM	76	1 day

*Source: Table 42 Summary of Clinical Safety

This reviewer could not find that the Applicant expressly defined "MACE." MACE was not included in the list of adverse events of interest (or elsewhere) in the ISS SAP, dated "18 MAR 2021," nor were MACE discussed at the pre-sNDA meeting on 07/29/2021. In the approved Opzelura package insert, MACE is defined as "cardiovascular death, non-fatal myocardial infarction (MI), and non-fatal stroke" (the discussion in the package insert is in the context of events observed in clinical trials of JAK inhibitors used to treat inflammatory conditions). To identify MACE in the vitiligo program, the Applicant searched the integrated safety database using 40 PTs to identify events that could be categorized as MACE. This reviewer considers that the Applicant's search terms allowed for a comprehensive assessment of the database. The Applicant identified no MACE under the search criteria.

However, one subject experienced a MACE (as defined by the Applicant's search criteria and as defined in the package insert): Subject (b) (6) was a 71-year-old White female who experienced a cerebrovascular accident. However, as the stroke occurred 47 days after the last application of ruxolitinib cream, it occurred beyond the 30-day, post-treatment window that defined the period for TEAE. This subject and the SAE has been previously discussed (see Section 8.2.4).

No new thromboembolic events or MACE were reported in the 4-Month Safety Update.

<u>Thrombocytosis/elevated mean platelet volume</u>

The Applicant references literature reports of transient increases in platelet count with baricitinib in the rheumatoid arthritis population. (Note: The baricitinib package insert does not include discussion of this observation.)

The Applicant searched the integrated clinical database for AEs of platelet count increased, MPV increased, and thrombocytosis and identified 3 subjects under the terms of the search. One subject appeared to have an elevated baseline platelet count. All of the events were nonserious, and no action was taken with study treatment for any of the subjects. See Table 32:

Table 32. Treatment-Emergent Thrombocytosis Events (Pool 2)*

Study Age/Sex	Relevant Medical History/Relevant Prior and Concomitant Medications	PT	Severity Serious (Yes/No)	Onset Duration	Laboratory Value at Baseline	Laboratory Value at Onset[a]	Worst Laboratory Value	Action Taken With the Study Drug Investigator Assessment of Relationship to Study Drug
Ruxolitinib 1.5% cream BID								
INCB 18424-306 45/F	Thrombocytosis, /None	Thrombocytosis (worsening)	Grade 2 No	Day 319 Ongoing	Platelets: 552×10^9/L	Platelets: 692×10^9/L	Platelets: 701×10^9/L	No action (advised to see a hematologist) Not related
INCB 18424-307 49/F	Obesity, Type 2 diabetes mellitus, Hyperlipidemia/Metformin, fenofibrate	Platelet count increased	Grade 1 No	Day 29 64 days	Platelets: 342×10^9/L	Platelets: 416×10^9/L	Platelets: 443×10^9/L	No action Not related
Ruxolitinib 1.5% cream QD (vehicle-controlled DB and DB extension periods)								
INCB 18424-211 46/F	None/None	Platelet count increased	Grade 1 No	Day 169 1 day	Platelets: 301×10^9/L	Platelets: 428×10^9/L	Platelets: 428×10^9/L[b]	No action Not related

*Source: Table 43 Summary of Safety
[a] Laboratory result on the day of onset or the last result before onset.
[b] Worst value through Week 52.
Normal range: 130-400 10^9/L

No additional events of platelet count increased, MPV increased, and thrombocytosis were reported in the 4-Month Safety Update

8.2.5.4. Cytopenias

The package insert for oral ruxolitinib includes a Warning and Precaution that treatment with the product can cause thrombocytopenia, anemia and neutropenia, and the label for the topical product reflects that these events were observed in the clinical trials for the AD program. Cytopenic events that occurred in Pool 1 (through Week 24 of the vitiligo phase 3 studies) are presented in Table 33. For subjects in the 1.5% cream group, the day of onset of the cytopenic event ranged from Day 57 to Day 132, and no action was taken with study treatment for any of these subjects. None of the events were serious, and none were considered as being related to treatment. All of the events were ongoing at the time of data cutoff except for one event of "Hemoglobin decreased" that had a duration of 112 days. No events of thrombocytopenia were reported through Week 52. Mean steady-state ruxolitinib plasma concentrations (C_{ss}) were generally low (less than 125 nM) for these subjects except for subject (b) (6) (TEAE: "anemia") who had a $C_{SS} > 95^{th}$ percentile, at C_{ss} 295 nM.

Table 33. Summary of Erythropenia, Neutropenia, and Thrombocytopenia

Treatment-Emergent Adverse Events in Decreasing Order of Frequency (Pool 1)*

MedDRA PT, n (%)	Vehicle Cream BID (N = 224)	Ruxolitinib 1.5% Cream BID (N = 449)
Any erythropenia TEAE	*1 (0.4)*	*4 (0.9)*
Hemoglobin decreased	0	2 (0.4)
Anemia	1 (0.4)	1 (0.2)
Microcytic anemia	0	1 (0.2)
Any neutropenia TEAE	*1 (0.4)*	*0*
Neutrophil count decreased	1 (0.4)	0
Any thrombocytopenia TEAE	*0*	*0*

*Source: Table 34 Summary of Clinical Safety

Additional details regarding these subjects are presented below in Table 34.

Table 34. Subjects With Cytopenias in Pool 1*

Study Age/Sex	PT	Severity Serious (Y/N)	Onset Duration	Laboratory Value at Baseline	Laboratory Value at Onset	Worst Laboratory Value During the 24-Week Vehicle-Controlled DB Period	Action Taken With the Study Drug Treated with Concomitant Medication (Y/N) Investigator Assessment of Relationship to Study Drug
Vehicle cream BID							
INCB 18424-307 38/F	Anemia	N	Day 1 90 days	Hemoglobin[a]: 101 g/L	Hemoglobin: 101 g/L	Hemoglobin: 101 g/L	No change Y Not related
INCB 18424-306 37/M	Neutrophil count decreased	N	Day 54 141 days	Neutrophils[b]: 1.5×10^9/L	Neutrophils: 1.07×10^9/L	Neutrophils: 1.07×10^9/L	Drug interrupted (study drug application restarted: yes) N Not related
Ruxolitinib 1.5% cream BID							
INCB 18424-306 79/F	Hemoglobin decreased	N	Day 57 112 days	Hemoglobin[a]: 126 g/L	Hemoglobin: 104 g/L	Hemoglobin: 95 g/L (Day 85)	No change N Not related
INCB 18424-306 16/F	Microcytic anemia	N	Day 130 Ongoing	Hemoglobin[a]: 121 g/L	Hemoglobin: 109 g/L	Hemoglobin 106 g/L (Day 169)	No change N Not related
INCB 18424-307 43/F	Anemia	N	Day 85 Ongoing	Hemoglobin[a]: 107 g/L	Hemoglobin: 99 g/L	Hemoglobin: 99 g/L	No change Y Not related
INCB 18424-307 33/F	Hemoglobin decreased	N	Day 132 Ongoing	NR	NR	NR	No change N Not related

*Source: Table 35 Summary of Clinical Safety
NR = not reported.
[a] Normal range for hemoglobin: 120 to 156 g/L.
[b] Normal range for neutrophils: 1.8 to 8×10^9/L.

The occurrence of cytopenia events in the phase 3 trials did not significantly change with longer term exposure up to Week 52. The Applicant provided exposure-adjusted incidence rates for this treatment-extension period, as presented in Table 35 below.

Table 35. Summary of Exposure-adjusted Incidence Rates of Cytopenias by MedDRA Preferred Term (Pool 1 Population Including TE Period)*

MedDRA Preferred Term - n (Exposure-adjusted IR: Per 100 PY)[1]	Treatment Group	
	Vehicle BID (N=224)	1.5% BID (N=637)
Person-years of exposure		
Study 306	45.59	193.40
Study 307	50.47	197.02
Total	96.05	390.41
Any TEAE	2(2.1)	11(2.8)
Neutropenia	0(0.0)	3(0.8)
Anaemia	1(1.0)	2(0.5)
Haemoglobin decreased	0(0.0)	2(0.5)
Neutrophil count decreased	1(1.0)	2(0.5)
Microcytic anaemia	0(0.0)	1(0.3)
Platelet count decreased	0(0.0)	1(0.3)

*Source: Table 99.3.2.3.6.1 Integrated Summary of Safety
TE= treatment extension

Thus, an increase in rates of cytopenia events was not observed with longer term exposure to ruxolitinib cream.

Also, see "Laboratory Findings" in Section 8.2.4.

Four subjects experienced cytopenia events that were reported in the 4-Month Safety Update. All subjects were being treated with ruxolitinib 1.5% cream BID (the only ongoing dosing regimen). All events were nonserious. The TEAEs were: 2 reports of Grade 1 anemia (Days 488 and 391), a Grade 1 event of hematocrit decreased and hemoglobin decrease (one subject), and a Grade 2 event of neutropenia (Day 427). The neutropenia event was the only one that was considered to be treatment related. Treatment was not interrupted for any of these subjects. All events were ongoing at the time of data cut-off.

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

No COA analyses were conducted to inform safety/tolerability in the vitiligo studies.

8.2.7. Safety Analyses by Demographic Subgroups

The discussion below pertains to Pool 1.

The limited numbers of subjects 12 to < 18 years of age and ≥ 65 years of age allowed only limited comparisons to the majority of subjects who were 18 to < 65 years of age. Overall TEAEs occurred in progressively decreasing rates in the ruxolitinib groups from 12 to < 18 years of age (56.4%), 18 to < 65 years (47%), and ≥ 65 years (39.3%). Treatment-related AEs were reported in 9 subjects (16.4%) 12 to < 18 years of age, and all subjects were in the ruxolitinib group. However, no TEAEs in ruxolitinib-treated subjects 12 to < 18 years of age led to interruption of study drug or discontinuation from the study. In subjects ≥ 65 years of age, treatment-related AEs occurred in 14.3% of subjects in the ruxolitinib group compared to 18.8% of subjects in the vehicle group. Two subjects ≥ 65 years of age in the ruxolitinib group experienced AEs that led to temporary interruption of treatment.

Overall AEs occurred at a lower rate in males (42.3%) compared to females (52%) in the ruxolitinib groups, and the same pattern was noted in the rates of treatment-related AEs 10.0% in males and 18.5% in females. Severe AEs (≥ Grade 3) occurred at similar rates in males and females 2.0% and 2.4%, respectively. SAEs occurred at a higher rate in males at 3.5% and 0.4% in females.

The numbers of non-White subjects permitted only limited comparisons between racial groups. The majority of subjects were White (81.9%). Regarding race, the highest overall incidence of TEAEs in the ruxolitinib group was in the "not reported" group at 89.5%.

Table 36. Overall Summary of Treatment-Emergent Adverse Events by Demographic Characteristic Subgroup (Pool 1)*

Demographic Characteristic	Subgroup	Treatment Group	N	Treatment-Emergent Adverse Events, n (%)						
				All	Treatment-Related	≥ Grade 3	Serious	With Fatal Outcome	Leading to Study Drug Interruption	Leading to Study Drug Discontinuation
Age	12 to < 18 years	Vehicle cream BID	17	6 (35.3)	0	1 (5.9)	0	0	2 (11.8)	0
		Ruxolitinib 1.5% cream BID	55	31 (56.4)	9 (16.4)	0	1 (1.8)	0	0	0
	18 to < 65 years	Vehicle cream BID	191	64 (33.5)	14 (7.3)	3 (1.6)	1 (0.5)	0	2 (1.0)	1 (0.5)
		Ruxolitinib 1.5% cream BID	366	172 (47.0)	53 (14.5)	10 (2.7)	7 (1.9)	0	4 (1.1)	2 (0.5)
	≥ 65 years	Vehicle cream BID	16	9 (56.3)	3 (18.8)	0	0	0	0	0
		Ruxolitinib 1.5% cream BID	28	11 (39.3)	4 (14.3)	0	0	0	2 (7.1)	0
Sex	Male	Vehicle cream BID	114	29 (25.4)	3 (2.6)	1 (0.9)	1 (0.9)	0	3 (2.6)	1 (0.9)
		Ruxolitinib 1.5% cream BID	201	85 (42.3)	20 (10.0)	4 (2.0)	7 (3.5)	0	4 (2.0)	1 (0.5)
	Female	Vehicle cream BID	110	50 (45.5)	14 (12.7)	3 (2.7)	0	0	1 (0.9)	0
		Ruxolitinib 1.5% cream BID	248	129 (52.0)	46 (18.5)	6 (2.4)	1 (0.4)	0	2 (0.8)	1 (0.4)
Race	White	Vehicle cream BID	189	67 (35.4)	14 (7.4)	3 (1.6)	1 (0.5)	0	4 (2.1)	0
		Ruxolitinib 1.5% cream BID	362	174 (48.1)	53 (14.6)	8 (2.2)	6 (1.7)	0	4 (1.1)	2 (0.6)
	Black or African American	Vehicle cream BID	9	1 (11.1)	0	0	0	0	0	0
		Ruxolitinib 1.5% cream BID	23	8 (34.8)	1 (4.3)	0	0	0	0	0
	Asian	Vehicle cream BID	11	0	0	0	0	0	0	0
		Ruxolitinib 1.5% cream BID	17	4 (23.5)	1 (5.9)	0	0	0	1 (5.9)	0
	Not reported	Vehicle cream BID	6	5 (83.3)	1 (16.7)	1 (16.7)	0	0	0	0
		Ruxolitinib 1.5% cream BID	19	17 (89.5)	8 (42.1)	2 (10.5)	2 (10.5)	0	1 (5.3)	0
	Other	Vehicle cream BID	9	6 (66.7)	2 (22.2)	0	0	0	0	1 (11.1)
		Ruxolitinib 1.5% cream BID	28	11 (39.3)	3 (10.7)	0	0	0	0	0

*Source: Table 53 Summary of Clinical Safety

8.2.8. Specific Safety Studies/Clinical Trials

This section is not applicable.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The package insert for ***oral ruxolitinib*** (JAKAFI oral tablets) includes the following discussion in the "Warnings and Precautions" section:

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

Basal cell and squamous cell carcinomas were observed in subjects treated with ***ruxolitinib cream*** in clinical trials, and these were the only malignancies that were reported in more than one subject (including the subject who experienced Bowen's disease). Also see Section 8.2.5.2. Malignancies that were SAEs are discussed in Section 8.2.4.

Opzelura currently has Boxed Warning and Warnings and Precautions for malignancies in the Prescribing Information consistent with JAK inhibitor class labeling concerning the observation of lymphoma and other malignancies.

Human Reproduction and Pregnancy

Pregnant or lactating women were excluded from all clinical studies. Study subjects were required to use appropriate effective contraception to avoid pregnancy or fathering a child, unless the females were of non-childbearing potential or the subjects were prepubescent adolescents. Six pregnancies occurred by the data cut-off date for the supplement, 2 in study subjects and 4 in partners of study subjects. Outcomes were known for 3 of the pregnancies, and all were term births with healthy infants.

Table 37. Pregnancies in Studies of Ruxolitinib Cream*

Subject	Treatment Group	Method of Contraception Used	Pregnancy Outcome
INCB 18424-211			
Partner of male participant (b) (6))	Ruxolitinib 0.15% cream QD	Withdrawal	Term birth/healthy infant
013011[a]	Vehicle cream BID, then ruxolitinib 0.5% cream QD, then ruxolitinib 1.5% cream BID	Medroxyprogesterone	Unknown – ultrasound during pregnancy was normal
Partner of male participant (b) (6)	Ruxolitinib 0.5% cream QD, then ruxolitinib 1.5% cream BID	Barrier method	Term baby/healthy infant
INCB 18424-306			
Partner of male participant (b) (6))	Ruxolitinib 1.5% cream BID	None	Unknown
INCB 18424-307			
(b) (6)	Ruxolitinib 1.5% cream BID	Barrier method	Term baby/healthy infant
Partner of male participant (b) (6))	Ruxolitinib 1.5% cream BID	Barrier method	Unknown

*Source: Table 58 Summary of Clinical Safety
[a] This pregnancy occurred between Weeks 52 and 104 of the study.

The approval letter of the original NDA 215309 for the AD indication included postmarketing requirements for the Applicant to conduct:

- A Pregnancy Exposure Registry

- An additional pregnancy study that uses a different design from the Pregnancy Registry to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in the female population with atopic dermatitis exposed to ruxolitinib cream during pregnancy compared to an unexposed control population

The timelines detailed in the approval letter are the same for both studies:

Draft Protocol Sumbission: 02/2022
Final Protocol Submission: 08/2022
Study Completion: 08/2032
Final Report Submission: 08/2033

The Applicant submitted draft protocols in accordance with the timelines detailed in the approval letter.

Pediatrics and Assessment of Effects on Growth

Ruxolitinib cream, 1.5% is approved for use in patients 12 years and older for the atopic dermatitis indication.

The phase 3 trials for vitiligo included adolescents, considered as subjects 12 to < 18 years of age in the analyses. The studies did not include assessment of effects on growth. Generally, the safety profile appeared to be similar in subjects ≥ 18 years of age and those 12 to < 18 years.

Consistent with the Agreed initial Pediatric Study Plan (iPSP), the Applicant requests:

- A partial waiver for study of the 0 to < 2 years age group on the grounds that studies are highly impracticable because of the extremely low prevalence of nonsegmental vitiligo in this patient population.

- A deferral of pediatric assessments in the ≥ 2 years to < 12 years age group until additional safety or effectiveness data have been collected in the ≥ 12 to < 17 years age group and adults. Note: The upper limit of "< 17 years" in the deferral request aligns with the Center for Drug Evaluation and Research's general definition for the upper bound for pediatric patients.[36] Evaluation in the ≥ 2 years to < 12 years age group will initiate after approval of an application for ruxolitinib cream for treatment of vitiligo in patients 12 years of age and older to allow for complete review of safety and effectiveness in subjects in the older age groups.

The Applicant's waiver and deferral requests are reasonable. The Applicant will be required to conduct the deferred pediatric study as a postmarketing requirement under the Pediatric Research Equity Act. The Applicant's plans have been presented to PeRC which found them acceptable.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

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

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant submitted the first quarterly Periodic Adverse Drug Experience Report (PADER) on 01/19/2022, which covered the period of 09/21/2021 to 12/20/2021. The Applicant received 27 reports that included 46 AEs, and all of the AEs were nonserious and unexpected AEs. The Applicant concluded that the reports revealed "no new significant safety issue." This reviewer agrees with that assessment. The most commonly reported event was "off-label use" (12 reports; uses unspecified).

Expectations on Safety in the Postmarket Setting

Local skin reactions are a possibility with topical products. Application site acne was the most common TEAE in ruxolitinib-treated subjects in the vitiligo studies and seems likely to present in the postmarket setting.

With sufficient systemic exposure, the safety profile could be similar to that of oral ruxolitinib or other JAK inhibitors indicated for treatment of inflammatory conditions, and the approved package insert for ruxolitinib cream includes extensive discussion of safety in the context of systemic exposure in the Warnings and Precautions section (as well as a Boxed Warning). The likelihood of this is unclear.

8.2.11. Integrated Assessment of Safety

The Applicant comprehensively evaluated the safety of ruxolitinib 1.5% cream in subjects with nonsegmental vitiligo. The types and frequency of safety evaluations were adequate to identify local TEAEs that might be observed with ruxolitinib 1.5% cream. The safety evaluations were also adequate to evaluate for systemic TEAEs that might be seen with oral ruxolitinib or with oral JAK inhibitors that are approved for treatment of other inflammatory conditions and that might reflect systemic exposure to ruxolitinib from use of the Applicant's product for treatment of nonsegmental vitiligo.

The Division and Applicant did not discuss the specific size of the safety database to include in this supplement, including the number of adolescents. However, the total number of subjects in the safety database exceeded the minimum recommendations in the ICH E1A guideline for population exposures for assessment of safety for products intended for long-term use for non-life-threatening conditions. Indeed, the timepoint for assessment of primary efficacy, Week 24, itself reflected chronic use of the product. Although a limited number of subjects 12 to < 18

years of age was evaluated in the vitiligo studies, this reviewer considers that the safety of use of the product in this population is supported by the safety data from adolescent exposure in the AD population. The reviewer does not consider there to be sufficient inherent differences in the vitiligo and AD populations, such that safety data from the latter would not support the former. Additionally, ruxolitinib 1.5% cream will have safety labeling similar to upadacitinib, an oral JAK inhibitor that is approved for treatment of patients 12 years and older with refractory, moderate to severe atopic dermatitis whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies are inadvisable. The available information suggests that the safety profile in adolescents is similar to that in adults. The one SAE that occurred in an adolescent subject resulted from a scooter accident. The one adverse event of interest that was reported in Pool 1 in an adolescent (16-year-old female) was microcytic anemia that was assessed as not being related to treatment and resulted in no action being taken with study treatment.

There were only single reports of all SAEs i.e., no one type of SAE was reported in more than one subject. Investigators assessed SAEs as not being reasonably possibly caused by ruxolitinib cream. From the available information, this reviewer agrees with that assessment. Based on the provided information, ruxolitinib cream did not appear to be implicated in causation in any of the events, and, for some events, there were other factors in the subjects' history that predisposed the subject to the SAE i.e., in the absence of exposure to ruxolitinib cream. The pattern and occurrence of SAEs with longer term exposure raised no new safety concerns.

Investigators did not assess any of the TEAEs of grade 3 severity or higher as being treatment related in Pool 1, and the incidence of such events was similar between the vehicle and ruxolitinib 1.5% cream BID groups. No TEAE of grade 3 severity or higher was reported in more than one subject. In Pool 1, mean hemoglobin, platelet, and neutrophil levels were similar between treatment groups at each test visit (Baseline through Week 24). The Applicant assessed ALT, AST, and bilirubin concentrations as being similar between treatment groups at all visits through Week 24 in Pool 1. The comprehensive assessment of adverse events of interest (relating to oral ruxolitinib or systemic JAK inhibitors for other indications) raised no new safety concerns, and events were of low incidence. No TEAEs of MACE were reported (the one reported MACE, a stroke, occurred beyond the 30-day post-treatment window that defined the period for TEAE).

TEAEs were most frequently reported in the Infections and Infestations SOC, with nasopharyngitis being the most commonly reported TEAE in this SOC. The SOC that was second in most commonly reported TEAEs was General disorders and administration site conditions, and ASRs were captured in this SOC. Application site acne was the most commonly reported ASR in the ruxolitinib group, followed by application site pruritus.

Application site acne was the most commonly reported TEAE in ruxolitinib-treated subjects overall. Application site acne was not reported in the AD program. However, "acneiform dermatitis" is reported in the package insert as having occurred in < 1% of subjects with AD in the ruxolitinib 1.5% cream group and none in the vehicle group. "Acne" is a labeled adverse

reaction for both abrocitinib and upadacitinib and occurred in a dose-related pattern for both products. It is listed as an adverse reaction that occurred in ≥ 1% of subjects for the AD and psoriatic arthritis populations in the upadacitinib label. The Applicant did not discuss possible mechanisms for application site acne, and the reviewer found no information on possible mechanisms (based on a limited literature search).

One TEAE of rhabdomyolysis occurred in the vitiligo clinical trials, and it was an SAE. Rhabdomyolysis has been previously reported in association with use of JAK inhibitors. King et al. described 2 subjects who experienced this SAE while receiving brepocitinib in a phase 2a study evaluating the product for treatment of alopecia areata.[36] For both subjects, strenuous physical activity preceded the SAEs, which resolved without sequelae. This history and outcome is similar to the subject in the vitiligo studies (see Section 8.2.4). Guttman-Yassky et al. reported one case of rhabdomyolysis in a 23-year-old male who received upadacitinib in a clinical trial evaluating the product for treatment of AD.[37] The AE was thought to have been potentially triggered by jet skiing. The authors further stated that a "few cases" of rhabdomyolysis had been reported in clinical development programs for upadacitinib across different indications "generally alternative causes were presented for these events" and cited "Liu J, unpublished." The significance of rhabdomyolysis in the context of use of JAK inhibitors, if any, is unclear.

The Applicant proposes to have an instruction to the label that includes not for "ophthalmic" use, later proposing "ocular" as an alternative to "ophthalmic." Such an instruction (with either term) would preclude use of ruxolitinib cream on the eyelids. However, the eyelids are specifically included in the definition of F-VASI, the instrument used for assessment of primary efficacy. If the eyelids were part of the assessment area, then they were, presumably, included in the treatment area. The phase 3 protocols did not include an instruction against use of study product on the eyelids. Five events related to the eyelids were reported in 449 ruxolitinib-treated subjects in the phase 3 database (one event each in 5 subjects), and 3 of these events occurred at an application site area: dryness (eyelid), chalazion-lower left eyelid, and stye on left lower eyelid, making for a frequency of 0.7%. Thus, the submitted safety data do not suggest that use of ruxolitinib cream on the eyelids should be excluded, and the Applicant finally agreed to the phrase "Not for intraocular use."

The Applicant proposes that the current labeled restriction to use of no more than 60 g of product per week (for the AD indication) would apply to the proposed new nonsegmental vitiligo indication. Based on pooled data from the phase 3 studies, the average daily amount of ruxolitinib 1.5% cream usage was 65.8 mg, which equates to an average use of 30.7 g per week. If the maximum 10% body surface area (BSA), proposed in the label for the vitiligo indication, were treated, the average weekly amount of product used would be 42.0 g. The average % BSA treated in the phase 3 studies was 7.31%, and > 97% of subjects used less than 60 g of product per week. (See Section 6.3.2 for details of the clinical pharmacology review.) Thus, the Applicant's proposal regarding a maximum of 60 g per week for the vitiligo indication is acceptable.

The Agency approved NDA 215309/S-002 on April 15, 2022, which allowed for a 100 g container size for ruxolitinib 1.5% cream. For the new container size, the Applicant proposed the following instruction (b) (6) Therefore, the Agency recommends the more convenient instruction of (b) (6) which would still allow a total amount close to, but not exceeding, the recommended limit in the amount of use per week in the currently approved label.

In summary, ruxolitinib 1.5% cream was well tolerated in the study population, and the available safety data support use of the product for treatment of nonsegmental vitiligo in patients 12 years and older.

8.3. Statistical Issues

No significant statistical issues were identified regarding the primary efficacy endpoint of F-VASI 75 at Week 24 or the secondary endpoints related to vitiligo assessments on the face.

The primary and secondary endpoints support the efficacy of ruxolitinib in the treatment of vitiligo of the face. The efficacy of ruxolitinib for vitiligo on the total body is supported by the pre-specified secondary endpoint of T-VASI 50 at Week 24 and exploratory analyses of T-VASI 75 at Week 52.

The applicant made changes to the multiple imputation method used as the primary method of missing data handling after finalizing the statistical analysis plan that include increasing the number of imputations, modifying the imputation method, and increasing the number of burn-in iterations for each imputation. The applicant justified these modifications as necessary to improve the stability and accuracy of the results.

In addition, the statistical analyst identified the issue that the point estimates from the multiple imputation procedure differed slightly (by a fraction of a percent) depending on which SAS platform (desktop or server) was used to run the analyses. However, these minor discrepancies did not impact the conclusions and the overall results are robust to minor variations in handling the missing data and the post-hoc adjustments to the procedure. The issues with the specific details of the multiple imputation procedure do not impact the overall study findings.

8.4. Conclusions and Recommendations

The totality of the data supports that the benefits of ruxolitinib cream, 1.5%, outweigh its risks for treatment of nonsegmental vitiligo in patients 12 years and older.

The review team recommends approval of this application.

9 Advisory Committee Meeting and Other External Consultations

An Advisory Committee meeting was not held for this supplement.

10 Pediatrics

See Section 8.2.9.

The Agency agrees with partial waiver for studying the use of OPZELURA in pediatric patients 0 to <2 years of age and deferral in pediatric patients 2 to <12 years of age. The following postmarketing requirement with estimated dates for the study has been accepted by the Applicant:

4304-1 Conduct a randomized, double-blind, vehicle-controlled 24-week trial of ruxolitinib 1.5% cream followed by a 28-week long-term safety extension period. The trial should enroll 150 pediatric subjects ≥ 2 years to < 12 years of age with nonsegmental vitiligo covering up to 10% body surface area (BSA) and minimum depigmentation involvement of at least 0.5% BSA on the face and at least 3% BSA on non-facial areas.

* Completion of trial including the extension period, not completion of the primary endpoint data collection at Week 24

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Labeling negotiations were underway as this review was ongoing. Class labeling is to be implemented to align with current labeling for JAK inhibitors approved for treatment of inflammatory conditions. On July 12, 2022, the Applicant submitted agreed-upon Prescribing Information and Medication Guide to the Agency with the new indication for "nonsegmental vitiligo":

- OPZELURA is indicated for the topical treatment of nonsegmental vitiligo in adult and pediatric patients 12 years of age and older.

12 Risk Evaluation and Mitigation Strategies (REMS)

None.

13 Postmarketing Requirements and Commitment

See Sections 8.2.9 and 10 concerning the postmarketing requirement to comply with the Pediatric Research Equity Act (PREA). Upon the Applicant's deferral request for PREA compliance, there will be one randomized, double-blind, vehicle-controlled 24-week trial of ruxolitinib 1.5% cream followed by a 28-week long-term safety extension period in pediatric patients 2 to <12 years of age with nonsegmental vitiligo covering up to 10% body surface area (BSA) and minimum depigmentation involvement of at least 0.5% BSA on the face and at least 3% BSA on non-facial areas.

14 Division Director (Clinical) Comments

I concur with the review team's recommendation for approval of Opzelura (ruxolitinib) cream, 1.5% for the topical treatment of nonsegmental vitiligo in patients 12 years of age and older. Opzelura is to be applied as a thin layer twice daily to affected areas of up to 10% body surface area.

Vitiligo is a chronic disorder of depigmentation, characterized by destruction of melanocytes; it is plausible that the immunosuppressive effects of ruxolitinib could treat an underlying autoimmune process. As noted by the review team, there is a need for approved pharmacologic repigmentation therapies in vitiligo.

Ruxolitinib is a selective JAK1 and JAK2 inhibitor, first approved in 2011 as JAKAFI oral tablets for the treatment of myelofibrosis, and subsequently approved for polycythemia vera and acute and chronic graft-versus-host disease. Topical ruxolitinib cream, 1.5% (Opzelura) was approved in 2021 for the topical short-term and non-continuous chronic second-line treatment of mild to moderate atopic dermatitis in non-immunocompromised patients 12 years and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Thus, there is prior safety experience with topical and oral formulations of ruxolitinib to inform the current program.

Effectiveness was demonstrated in two identical randomized, double-blind, vehicle-controlled Phase 3 trials, in which subjects aged 12 years or older with nonsegmental vitiligo were randomized (2:1) to Opzelura or vehicle twice daily for 24 weeks; after this period, subjects on vehicle were crossed over to active treatment and subjects on active treatment remained on their treatment for an additional 28 weeks. In both trials, a statistically significant treatment

effect was observed with respect to the primary endpoint, the proportion of subjects achieving 75% reduction from baseline to Week 24 in the F-VASI score (F-VASI75), which was derived from an estimate of face depigmentation and percentage of body surface area involvement from vitiligo, as assessed by the investigator (see Section 8.1.1). Subgroup analyses and key secondary endpoints at Week 24 (e.g., F-VASI50, F-VASI90, T-VASI50, VNS response [patient-reported outcome] and percentage change in F-BSA) supported results of the primary endpoint. The primary endpoint and three of the five key secondary endpoints were specific to the face region, the most important area for treatment expressed by most patients at a vitiligo Patient-Focused Drug Development meeting (3/8/2021).

The reviewers considered the interpretability and meaningfulness of the T-VASI50 score, a summed score of six regions including the face. Several issues were raised in this review, including: 1. Lack of precision in the VASI degree of depigmentation scale (see Section 8.1.1); and 2. Whether a 50% reduction in the T-VASI is clinically meaningful to patients. Based on quantitative anchor-based analyses and exit interviews with a proportion of subjects from the pivotal trials, the Clinical Outcome Assessment reviewers concluded that the Applicant's pre-specified ≥50% reduction in T-VASI score responder threshold is representative of a clinically meaningful improvement for patients with total body vitiligo at Week 24.

However, according to the Voice of the Patient Report (published December 2021) of the Vitiligo Patient-Focused Drug Development meeting (3/8/2021), "Many participants indicated that 50% repigmentation was too low of a threshold for them to consider taking the medication and they wanted a higher percentage of repigmentation….One participant said, "We definitely want a high percentage [of repigmentation], …. So typically, in the 80 to 100 percent, mainly because there's also a pattern of progression of the vitiligo."

In considering a higher response threshold, the T-VASI75 score (i.e., 75% reduction in total VASI score) at Week 24 showed a smaller proportion of responders that, while favorable for active treatment, was not statistically significant; however, exploratory analyses beyond Week 24 showed that the proportion achieving T-VASI75 continued to increase, suggesting further improvement over time.

The safety in the vitiligo program has been adequately characterized and supports topical use of Opzelura cream, 1.5% in patients with nonsegmental vitiligo as per labeling instructions.

15 Appendices

15.1. References

1. Opzelura package insert.

2. Clinical Overview; Module 2 of NDA 215309/S-001.

3. Ezzedine K, V Eleftheriadou, M Whitton, and N van Geel. Vitiligo. Lancet 2015;386:74–84.

4. Iannella G, A Greco, D Didona, B Didona, G Granata, A Manno, B Pasquariello, and G Magliulo. Vitiligo: Pathogenesis, Clinical Variants and Treatment Approaches. Autoimmun Rev 2016;15:335-343.

5. Alikhan A, LM Felsten, M Daly, and V Petronic-Rosic. Vitiligo: A Comprehensive Overview Part I. Introduction, Epidemiology, Quality of Life, Diagnosis, Differential Diagnosis, Associations, Histopathology, Etiology, and Work-up. J Am Acad Dermatol 2011;65:473-91.

6. Felsten LM, A Alikhan, and V Petronic-Rosic. Vitiligo: A Comprehensive Overview Part II: Treatment Options and Approach to Treatment. J Am Acad Dermatol 2011;65:493-514.

7. Talsana N, B Lamb and A Bewley. Vitiligo is More Than Skin Deep: A Survey of Members of the Vitiligo Society. Clin Exp Dermatol 2010;35(7):736–739.

8. Sampogna F, D Raskovic, L Guerra, C Pedicelli, S Tabolli, L Leoni, L Alessandroni and D Abeni. Identification of Categories at Risk for High Quality of Life Impairment in Patients with Vitiligo. Br J Dermatol 2008 159;2:351–359.

9. Silverberg JI and NB Silverberg. Quality of Life Impairment in Children and Adolescents with Vitiligo. Pediatr Dermatol 2014 31;3:309–318.

10. Kruger C and KU Schallreuter. A Review of the Worldwide Prevalence of Vitiligo in Children/Adolescents and Adults. Int J Dermatol 2012;51:1206–1212.

11. Taieb A and M Picardo. Vitiligo. N Engl J Med 2009;360:160-9.

12. James WD, Berger TG, Elston DM. Chapter 36. Disorders of Pigmentation. In: *Andrews' Diseases of the Skin: Clinical Dermatology*, *11e*.Saunders Elsevier; 2011.

13. Bergqvist C and K Ezzedine. Vitiligo: A Review. Dermatology 2020;236:571–592.

14. Rodrigues M. Skin Cancer Risk (Nonmelanoma Skin Cancers/Melanoma) in Vitiligo Patients. Dermatol Clin 2017;35:129–134.

15. Grimes PE. Vitiligo: Pathogenesis, Clinical Features, and Diagnosis. In: UpToDate, Tsao H (Ed), UptoDate, Waltham MA (Accessed on March 07, 2021).

16. Dahir AM and SF Thomsen. Comorbidities in Vitiligo: Comprehensive Review. Int J Dermatol 2018;57:1157–1164.

17. Rodrigues M, K Ezzedine, I Hamzavi, AG Pandya, and JE Harris. New Discoveries in the Pathogenesis and Classification of Vitiligo. J Am Acad Dermatol 2017;77:1-13.

18. Anbar TS, MM El-Badry, JA McGrath, and ES Abdel-Azim. Most Individuals with Either Segmental or Non-segmental Vitiligo Display Evidence of Bilateral Cochlear Dysfunction. Br J of Dermatol 2015;172:406–411.

19. Ma SH, MD Ang, YT Chang, and YX Dai. Association Between Vitiligo and Hearing Loss. J Am Acad Dermatol 2021;85:1465-72.

20. van Geel N, I Mollet, L Brochez, M Dutre´, S De Schepper, E Verhaeghe, J Lambert and R Speeckaert. New Insights in Segmental Vitiligo: Case Report and Review of Theories. Br J Dermatol 2012;166:pp240–246.

21. Ezzedine K, Y Gauthier, C Leaute-Labreze, S Marquez, S Bouchtnei, T Jouary, and A Taieb. Segmental Vitiligo Associated with Generalized Vitiligo (Mixed Vitiligo): A Retrospective Case Series of 19 Patients. J Am Acad Dermatol 2011;65:965-71.

22. Gawkrodger DJ, AD Ormerod, L Shaw, I Mauri-Sole, ME Whitton, MJ Watts, AV Anstey, J Ingham and K Young. Guideline for the Diagnosis and Management of Vitiligo. Br J of Dermatol 2008;159:1051–1076.

23. Rodrigues M, K Ezzedine, I Hamzavi, AG Pandya, and JE Harris. Current and Emerging Treatments for Vitiligo. J Am Acad Dermatol 2017;77:17-29.

24. Voice of the Patient Report for Vitiligo Patient-Focused Drug Development Initiative Vitiligo; report date 12/2021.

25. Benoquin package insert.

26. Hsu JTS. Chapter 46. Vitiligo. In: Arndt KA, Hsu JTS, Bhatia A, Chilkukuri S. eds. *Manual of Dermatologic Therapeutics, 8e* Philadelphia, PA: Wolters Kluwer; 2014.

27. Grimes PE. Vitiligo: Management and Prognosis. In: UpToDate, Tsao H (Ed), UptoDate, Waltham MA (Accessed on March 07, 2021).

28. Tacrolimus ointment package insert.

29. Pimecrolimus cream package insert.

30. Gambichler T, F Breuckmann, S Boms, P Altmeyer, and A Kreuter. Narrowband UVB Phototherapy in Skin Conditions Beyond Psoriasis. J Am Acad Dermatol 2005;52:660-70.

31. Taieb A, A Alomar, M. Bohm, ML Dell'Anna, A De Pase, V Eleftheriadou, K Ezzedine, Y Gauthier, DJ Gawkrodger, T Jouary, G Leone, S Moretti, L Nieuweboer-Krobotova, MJ Olsson, D Parsad, T Passeron, A Tanew, W van der Veen, N van Geel, M Whitton, A Wolkerstorfer, and M Picardo. Guidelines for the Management of Vitiligo: the European Dermatology Forum Consensus. Br J Dermatol 2013;168:5–19.

32. Nicolaidou E, C Antoniou, AJ Stratigos, C Stefanaki, and AD Katsambas. Efficacy, Predictors of Response, and Long-Term Follow-Up in Patients with Vitiligo Treated with Narrowband UVB Phototherapy. J Am Acad Dermatol 2007;56:274-8.

33. Yones SS, RA Palmer, TM Garibaldinos, and JLM Hawk. Randomized Double-blind Trial of Treatment of Vitiligo. Arch Dermatol 2007;143:578-584.

34. Stern RS. The Risk of Squamous Cell and Basal Cell Cancer Associated with Psoralen and Ultraviolet A Therapy: A 30-year Prospective Study. J Am Acad Dermatol 2012;66:553-562.

35. Patel RV, LN Clark, M Lebwohl, and JM Weinberg. Treatments for Psoriasis and the Risk of Malignancy. J Am Acad Dermatol 2009;60:1001-17.

36. Guidance for Industry. *Pediatric Information Incorporated into Human Prescription Drug and Biological Product Labeling*. March 2019.

37. Guidance for Industry. *Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format*. January 2006.

38. King B, E Guttman-Yassky, E Peeva, A Banerjee, R Sinclair, AB Pavel, L Zhu, LA Cox, B Craiglow, L Chen, C Banfield, K Page, W Zhang, and MS Vincent. A Phase 2a Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of the Oral Janus Kinase Inhibitors Ritlecitinib and Brepocitinib in Alopecia Areata: 24-week results. J Am Acad Dermatol 2021;85:379-87.

39. Guttman-Yassky E, HD Teixeira, EL Simpson, KA Papp, AL Pangan, A Blauvelt, D Thaçi, CY Chu, HCH Hong, N Katoh, AS Paller, B Calimlim, Y Gu, X Hu, M Liu, Y Yang, J Liu, AR Tenorio, AD Chu, and AD Irvine. Once-Daily Upadacitinib Versus Placebo in Adolescents and Adults with Moderate-to-Severe Atopic Dermatitis (Measure Up 1 and Measure Up

2): Results from Two Replicate Double-Blind, Randomised Controlled Phase 3 Trials. Lancet 2021;397:2151–68.

15.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): INCB 18424-306 and INCB 18424-307

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 97		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

15.3. OCP Appendices (Technical documents supporting OCP recommendations)

Clinical Pharmacology Studies

Study INCB 18424-211 (Phase 2 – PK assessment)

Title: A Randomized, Double-Blind, Dose-Ranging Study of INCB018424 Phosphate Cream in Subjects with vitiligo

Objectives and endpoints:

Objectives	Endpoints
Primary	
To establish the efficacy of 24 weeks of treatment with ruxolitinib cream in participants with vitiligo.	• Proportion of participants treated with ruxolitinib cream who achieve a ≥ 50% improvement from baseline in facial assessment of the Vitiligo Area and Severity Index score (F-VASI50) at Week 24 compared with participants treated with vehicle cream.
Key Secondary	
To further assess the efficacy of ruxolitinib cream.	• Proportion of participants who achieve a facial assessment of the Physician's Global Vitiligo Assessment (F-PhGVA) of clear or almost clear at Week 24. • Proportion of participants who achieve a ≥ 50% improvement from baseline in total body assessment of the Vitiligo Area and Severity Index score (T-VASI50) at Week 52.

Study methods:

This was a 3-part, randomized, double-blind, vehicle-controlled study in adult participants (aged 18-75 years) with vitiligo. The 3 parts of the study included a 24-week, double-blind, vehicle-controlled treatment period; a 28-week, continued, double-blind treatment period; and a 104-week, open-label extension period.

Participants were randomized in a 1:1:1:1:1 ratio with stratification by age (≤ 30 or > 30 years) to receive 1 of 4 dose strengths of ruxolitinib cream (1.5% twice daily [BID], 1.5% once daily [QD], 0.5% QD, 0.15% QD) or vehicle cream during the 24-week, double-blind, vehicle-controlled treatment period. After completion of the Week 24 assessments, participants randomized to vehicle cream during the 24-week, double-blind, vehicle-controlled treatment period and participants in the ruxolitinib 0.15% cream QD treatment group who did not achieve a ≥ 25% improvement from baseline on facial assessment of the Vitiligo Area and Severity Index (F-VASI) were rerandomized to 1 of the 3 higher active treatment- group in a 1:1:1 ratio while maintaining the blind. All other participants remained on the same dose regimen through Week 52.

After completion of the Week 52 assessments, participants who continue to be eligible for the study were offered the opportunity to receive an additional 104 weeks of open-label treatment with ruxolitinib 1.5% cream BID. In the open-label extension, which was ongoing at the time of preparation of this interim report, participants may be offered low-dose narrow-band

ultraviolet B phototherapy in addition to ruxolitinib cream in consultation with the investigator and sponsor.

Study population:

Approximately 150 participants were planned, and 157 participants were enrolled and randomized into the study. All participants were analyzed for efficacy and safety, 149 participants were analyzed for pharmacokinetics, and 135 participants were analyzed for translational assessments (which included serum samples and skin tape stripping for proteomic and whole RNA transcript analysis, respectively).

Dosing regimen, study duration and PK sampling:

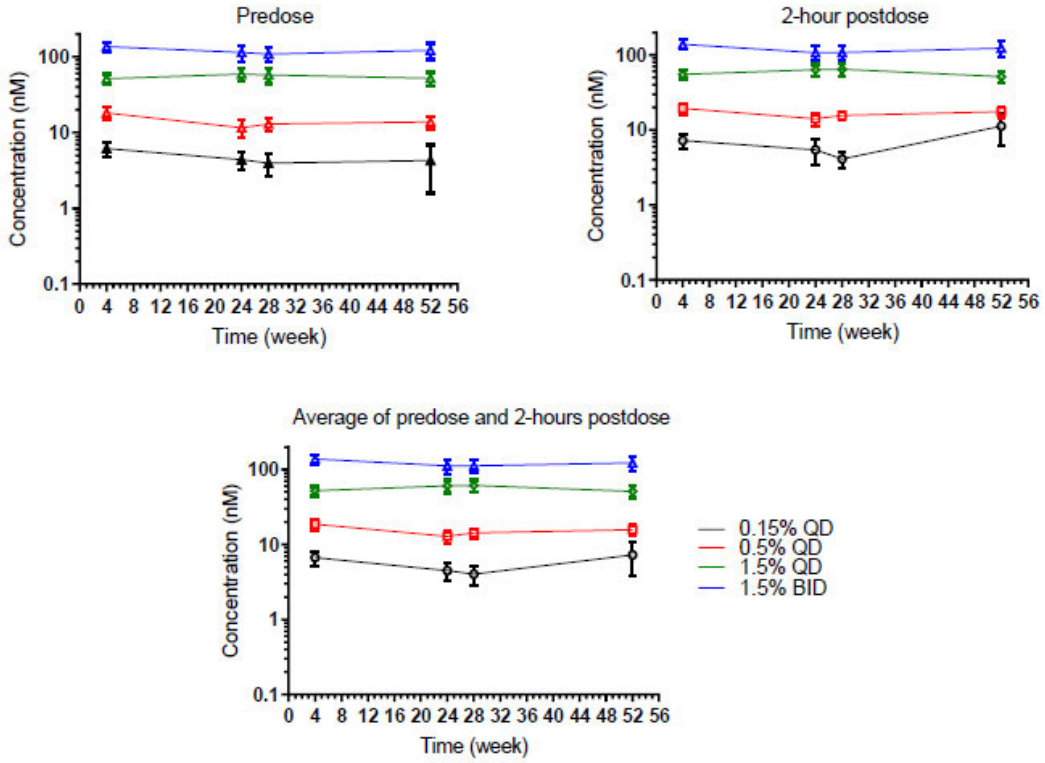
Ruxolitinib drug product was provided as ruxolitinib 1.5% cream (w/w free base equivalent), ruxolitinib 0.5% cream, ruxolitinib 0.15% cream, or vehicle cream packaged as 15 g per tube. Study drug was applied as a thin film BID, with applications at least 8 hours apart. Duration of treatment for an individual participant was up to approximately 184 weeks (4 weeks for screening and baseline, 156 weeks of treatment, and 24 weeks of safety follow-up).

Blood samples for the measurement of plasma concentrations of ruxolitinib were collected before and 2 hours after study drug application at Weeks 4, 24, 28, and 52.

Results:

A total of 157 participants were randomized to 1 of 4 dose strengths of ruxolitinib cream (1.5% BID, 1.5% QD, 0.5% QD, and 0.15% QD) or vehicle in a 1:1:1:1:1 ratio and stratified by age (≤ 30 or > 30 years). Plasma PK data were available from 149 participants. Plasma ruxolitinib concentrations were similar at Weeks 4, 24, 28, and 52 after treatment with ruxolitinib cream (**Figure 16**).

Figure 16. Mean Plasma Concentrations of Ruxolitinib (Mean ± SE) Following Dermal Administration of Ruxolitinib Cream in Study INCB 18424-211



Source: Figure 1. Summary of Clinical Pharmacology Studies (Vitiligo)

Application of ruxolitinib cream 0.15% QD, 0.5% QD, 1.5% QD, and 1.5% BID resulted in a mean Css of 5.62 ± 5.76 nM (geometric mean of 3.18 nM), 14.9 ± 13.2 nM (geometric mean of 10.1 nM), 55.3 ± 49.2 nM (geometric mean of 36.0 nM), and 111 ± 120 nM (geometric mean of 57.3 nM), respectively, from Week 4 to 52 (**Table 38**). Plasma concentrations increased as dose strength and frequency of dosing were increased.

Table 3. Summary of Steady-State Plasma Concentrations of Ruxolitinib and Bioavailability in Study INCB 18424-211

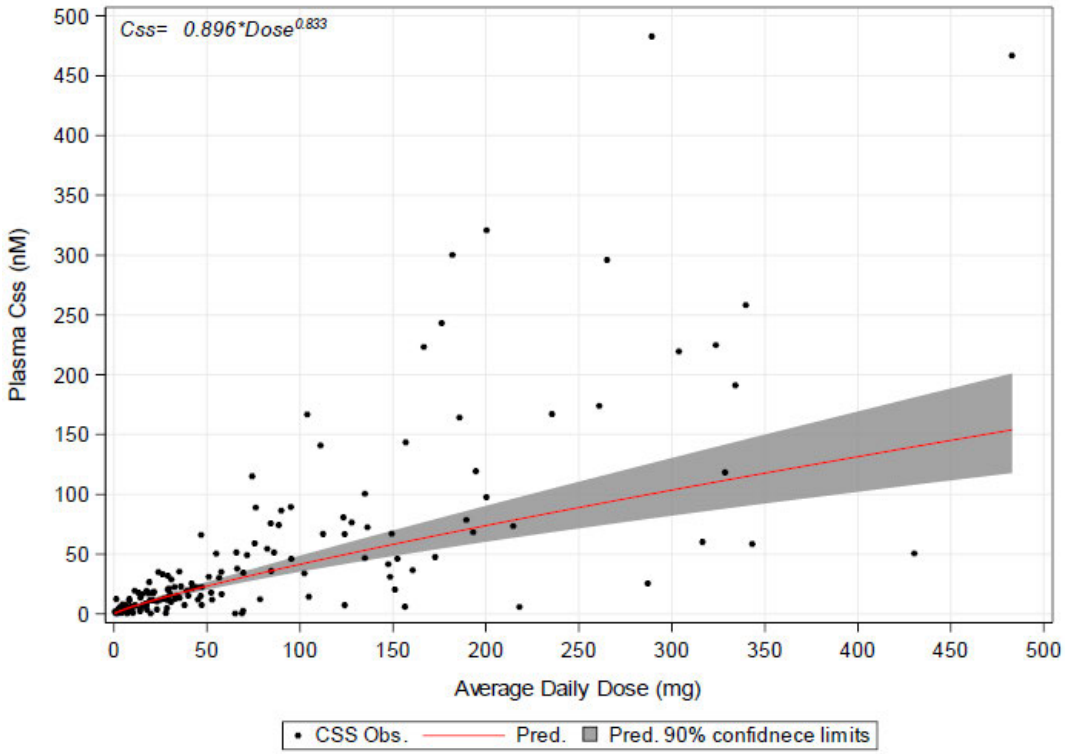
Treatment	Number of Participants	%BSA	C_{ss} (nM)	Topical Bioavailability (%)
0.15% QD	28	16.6 ± 10.9 (14.4)	5.62 ± 5.76 (3.18, 166%)	13.0 ± 21.8 (7.19)
0.5% QD	45	21.0 ± 19.1 (16.3)	14.9 ± 13.2 (10.1, 132%)	7.92 ± 5.26 (5.89)
1.5% QD	41	24.2 ± 19.2 (17.0)	55.3 ± 49.2 (36.0, 137%)	7.64 ± 4.70 (6.86)
1.5% BID	44	23.1 ± 17.5 (17.3)	111 ± 120 (57.3, 233%)	6.67 ± 4.87 (6.14)

Note: Values are presented as mean ± STD (geometric mean, CV%) for concentration and mean ± STD (median) for %BSA and bioavailability.

Source: Table 2. Summary of Clinical Pharmacology Studies (Vitiligo)

The relationship of average daily dosage and ruxolitinib Css was demonstrated in **Figure 17**.

Figure 17. Relationship of Average Daily Dosage of INCB018424 and Css of ruxolitinib cream



Source: Figure 2. DMMB-20.34.2

Reviewer's comments:

1. *Following topical application of ruxolitinib cream (0.15% QD, 0.5% QD, 1.5% QD, and 1.5% BID) in subjects with vitiligo in the Phase 2 study, trough plasma ruxolitinib concentrations were similar at Weeks 4, 24, 28 and 52, which indicates steady state was reached at or likely before Week 4.*
2. *The ruxolitinib plasma trough concentration exhibited large interparticipant variability (CV% > 100%) within each dose strength cohort (1.5% BID, 1.5% QD, 0.5% QD, and 0.15% QD, **Table 1**), which at least in part attributes to a broad range of % BSA treated and a wide span of application rate, ranging from 3.5% to 10% on %BSA treated and from 0.19 to 4.56 mg/cm^2 on application rate, respectively. Refer to the Pharmacometrics Review for more detailed investigation.*

Study INCB 18424 -306 and -307 Combined (Phase 3 trials – PK assessment)

Title: A Phase 3, Double-Blind, Randomized, Vehicle-Controlled, Efficacy and Safety Study of Ruxolitinib Cream Followed by an Extension Period in Participants with Vitiligo

Objectives:

Objectives	Endpoints
Primary	
To evaluate the efficacy of ruxolitinib cream in participants with vitiligo.	• Proportion of participants achieving ≥ 75% improvement from baseline in Face Vitiligo Area Scoring Index (F-VASI75) at Week 24.
Key Secondary	
To further assess the efficacy of ruxolitinib cream.	• Proportion of participants achieving ≥ 50% improvement from baseline in Face Vitiligo Area Scoring Index (F-VASI50) at Week 24. • Proportion of participants achieving ≥ 90% improvement from baseline in Face Vitiligo Area Scoring Index (F-VASI90) at Week 24. • Proportion of participants achieving ≥ 50% improvement in total body Vitiligo Area Scoring Index (T-VASI50) at Week 24. • Proportion of participants achieving a Vitiligo Noticeability Scale (VNS) of "4 – A lot less noticeable" or "5 – No longer noticeable" at Week 24. • Percentage change from baseline in facial body surface area (F-BSA) at Week 24.

Study population:

Study 306**:** Approximately 300 participants were planned, and 330 participants (36 of whom were adolescents, 10.9%) were randomized into the study. All randomized participants (intent-to-treat population) applied study drug at least once (safety population), and 283 participants applied ruxolitinib cream at least once during the treatment-extension (TE) period (TE evaluable population). Plasma samples from 311 participants during the double-blind (DB) period and 147 participants during the TE period were analyzed for PK (PK/pharmacodynamic evaluable population).

Study 307**:** Approximately 300 participants were planned, and 344 participants (36 of whom were adolescents, 10.5%) were randomized into the study. Of the 344 randomized participants (intent-to-treat population), 343 participants applied study drug at least once (safety population), and 297 participants applied ruxolitinib cream at least once during the TE period (TE evaluable population). Plasma samples from 325 participants during the DB period and 143 participants during the TE period were analyzed for pharmacokinetics (pharmacokinetic/pharmacodynamic evaluable population).

Dosing regimen and study duration:

Ruxolitinib 1.5% cream or matching vehicle cream was applied as a thin film BID to depigmented areas. Duration of study participation for an individual participant was approximately 60 weeks (up to 32 days for screening, 24 weeks in the DB, vehicle-controlled period, 28 weeks in the TE period, and 30 [+ 7] days of safety follow-up).

Methods:

Both Phase 3 studies were identical in terms of methodology. This is a randomized, DB, vehicle-controlled study in adolescent and adult participants (≥ 12 years old) with nonsegmental vitiligo. Approximately 300 participants were planned to receive blinded treatment for up to 52 weeks to examine the efficacy, safety, and tolerability of ruxolitinib cream.

Participants were randomized 2:1 to receive ruxolitinib 1.5% cream BID or vehicle cream BID during the 24-week, DB, vehicle-controlled period. Participants were stratified by region (North America or Europe) and skin type (Fitzpatrick scale Type I and II vs Type III, IV, V, and VI). Areas on the face and body identified for treatment at baseline (up to 10% total body surface area [BSA]) were treated throughout the DB period even if the area fully repigmented. Participants who completed the Week 24 assessments with no safety concerns could continue into the 28-week, TE period. Participants initially randomized to vehicle cream were crossed over to active drug, and participants treated with ruxolitinib cream received an additional 28 weeks of treatment with ruxolitinib 1.5% cream BID. During the TE period, which was ongoing at the time of this interim report, participants are to continue to treat depigmented areas identified for treatment at baseline even if the area fully repigmented. Total treated areas (facial and non-facial areas) are not to exceed 10% BSA. PK samples were collected preapplication at Weeks 4 and 24 during the double-blind period and at Week 40 during the treatment extension period.

Results:

Study INCB 18424-306

Demographics:

Table 39 presents the descriptive summary of the PK-evaluable population's characteristics for participants initially enrolled in the study (double-blind period). There were no significant differences in T-BSA, %BSA treated, or lesion area treated between ruxolitinib treatment group and vehicle group during the double-blind period. The population for analysis was approximately 43% male. A total of 35 participants (11.3%) in the study were 12 to < 18 years of age, 247 participants (79.4%) were aged 18 to < 65 years, and 29 participants (9.3%) were aged ≥ 65 years.

Table 39. Participant Baseline Population Characteristics and Cream Application Parameters in Double-Blind Period

Parameters		Statistics	Vehicle Group	1.5% Ruxolitinib Cream Group	Overall
Age Group (years)	12 to < 18	N (%)	10 (10.3)	25 (11.7)	35 (11.3)
	18 to < 65	N (%)	74 (76.3)	173 (80.8)	247 (79.4)
	≥ 65	N (%)	13 (13.4)	16 (7.5)	29 (9.3)
Sex	Female	N (%)	44 (45.4)	133 (62.1)	177 (56.9)
	Male	N (%)	53 (54.6)	81 (37.9)	134 (43.1)
Region	Europe	N (%)	34 (35.1)	74 (34.6)	108 (34.7)
	North America	N (%)	63 (64.9)	140 (65.4)	203 (65.3)
Skin Type	Types I, and II	N (%)	38 (39.2)	80 (37.4)	118 (37.9)
	Types III, IV, V, and VI	N (%)	59 (60.8)	134 (62.6)	193 (62.1)
Total Body Surface Area (m^2)		Mean (SD)	1.93 (0.254)	1.86 (0.255)	1.88 (0.256)
		Median	1.92	1.84	1.86
		Min, Max	1.30, 2.50	1.20, 2.58	1.20, 2.58
		Geometric mean	1.91	1.84	1.86
		N	97	214	311
% BSA Treated (%)		Mean (SD)	7.12 (2.03)	7.21 (2.02)	7.19 (2.02)
		Median	7.3	7.7	7.4
		Min, Max	3.70, 10.0	3.20, 10.0	3.20, 10.0
		Geometric mean	6.81	6.90	6.87
		N	97	214	311
Total Body Lesion Area Treated (cm^2)		Mean (SD)	1380 (453)	1340 (436)	1360 (441)
		Median	1420	1310	1330
		Min, Max	603, 2350	543, 2530	543, 2530
		Geometric mean	1300	1270	1280
		N	97	214	311
Daily Ruxolitinib Dose (mg)		Mean (SD)	-	66.4 (36.4)	-
		Median	-	60.9	-
		Min, Max	-	5.55, 239	-
		Geometric mean	-	55.5	-
		N	97	214	311
Cream Application Rate (mg/cm^2)		Mean(SD)	1.37 (0.600)	1.65 (0.754)	1.57(0.720)
		Median	1.41	1.7	1.61
		Min, Max	0.123, 3.03	0.263, 3.84	0.123, 3.84
		Geometric mean	1.21	1.45	1.37
		N	97	214	311

Source: Table 6. DMB-21.52.1

Summary of PK:

Plasma ruxolitinib concentrations were similar at Week 4, Week 24, and Week 40 (**Table 40** and **Figure 18**) after treatment with 1.5% ruxolitinib cream BID, which indicates steady state was reached at or before Week 4. Application of 1.5% ruxolitinib cream BID resulted in mean (geometric mean, CV%) Css of 55.8 nM (28.4 nM, 247%; **Table 40**). Similar Css were observed for participants from Europe and North America. The Css were similar for participants with skin type of Fitzpatrick scale Types I and II and Types III, IV, V, and VI (**Table 41** and **Figure 19**). The Css for age group of 12-< 18 years, 18-< 65 years and > = 65 years are comparable although

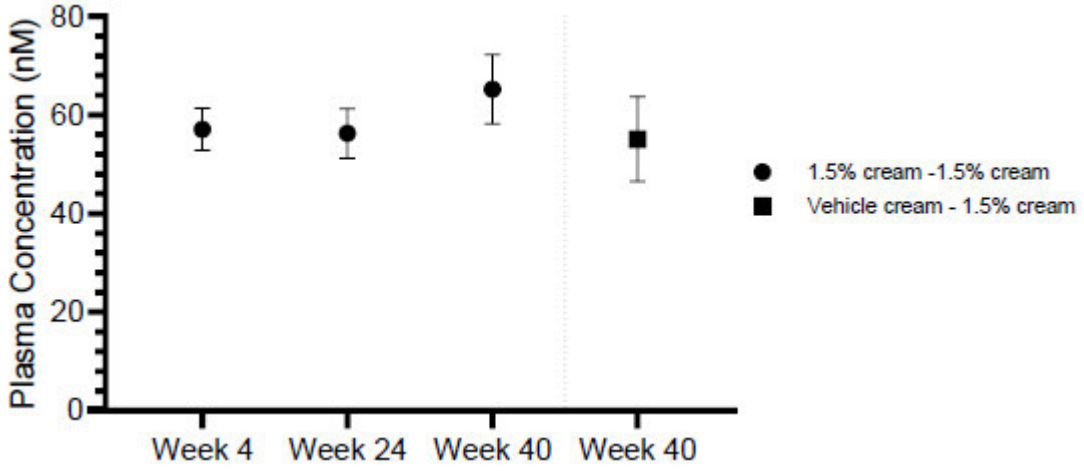
relatively low Css was observed for age group of 12-< 18 years. The mean (geometric mean) of Css for participants in age group of 12-< 18 years, 18-< 65 years and > = 65 years was 45.0 nM (16.5 nM), 57.5 nM (30.0 nM) and 54.6 nM (36.7 nM), respectively. The mean (geometric mean) topical bioavailability for ruxolitinib cream in vitiligo participants in this study was 9.62% (5.87%). The relationship of average daily dosage and ruxolitinib Css was demonstrated in **Figure 20**.

Table 40. Summary of Plasma Concentrations of Ruxolitinib (nM) Following Administration of 1.5% Ruxolitinib Cream BID

	Week 4	Week 24	Week 40	
			1.5% Cream -1.5% Cream[a]	Vehicle Cream-1.5% Cream[b]
Concentration (nM)	57.1 ± 61.4 (26.7, 300) N= 206	56.3 ± 69.4 (19.6, 551) N = 191	65.2 ± 69.8 (30.9, 323) N = 100	55.1 ± 59.3 (19.3, 723) N = 47

Note: Values are presented in the format of mean ± SD (geometric mean, CV%) and number of participants.
[a] 1.5% cream -1.5% cream: participants were initially randomized in 1.5% ruxolitinib cream treatment group and continued 1.5% ruxolitinib cream treatment at Week 24.
[b] Vehicle cream -1.5% cream: participants were initially randomized in vehicle treatment group and crossed over to 1.5% ruxolitinib cream treatment at Week 24.
Source: Table 2. DMB-21.52.1

Figure 18. Plasma Concentrations of Ruxolitinib (Mean ± SE) Following Topical Administration of 1.5% Ruxolitinib Cream BID



Source: Figure 1. DMB-21.52.1

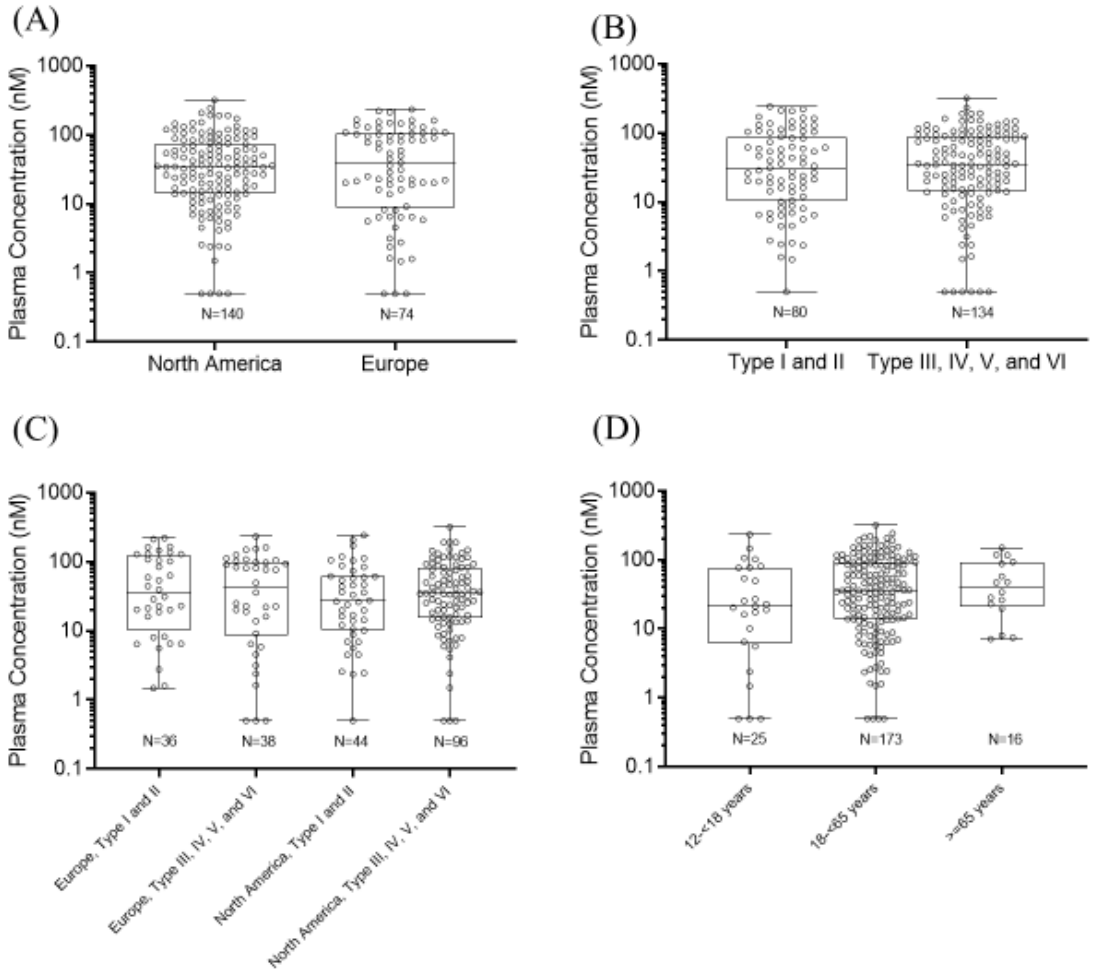
Table 41. Summary of Baseline Population Characteristics and Ruxolitinib Steady-State Pharmacokinetic Parameters by Geographical Region, Skin Type, and Age Group

Stratification		N	Age (year)	Total BSA (m^2)	%BSA Treated (%)	Lesion Area Treated (cm^2)	Application Rate (mg/cm2)	Daily Ruxolitinib Dose (mg)	C_{ss} (nM)[a]	Projected AUC_{0-24h} (h·nM)[b]	Bioavailability (%)
All Participants		214	40.5 ± 15.6 (37.0, 48.2)	1.86 ± 0.255 (1.84, 13.8)	7.21 ± 2.02 (6.90, 31.5)	1340 ± 436 (1270, 34.9)	1.65 ± 0.754 (1.45, 59.7)	66.4 ± 36.4 (55.5, 73.6)	55.8 ± 56.7 (28.4, 247)	1340 ± 1360 (682, 247)	9.62 ± 7.82 (5.87, 197)
Region	Europe	74	30.9 ± 13.9 (27.8, 50.5)	1.78 ± 0.271 (1.76, 15.2)	7.19 ± 1.94 (6.91, 29.6)	1270 ± 388 (1220, 31.4)	1.60 ± 0.728 (1.41, 59.9)	60.6 ± 30.6 (51.3, 70.9)	63.0 ± 60.6 (28.6, 336)	1510 ± 1460 (687, 336)	10.5 ± 8.49 (6.40, 199)
	North America	140	45.5 ± 13.9 (43.0, 37.9)	1.90 ± 0.236 (1.89, 12.4)	7.23 ± 2.07 (6.90, 32.6)	1380 ± 456 (1330, 36.5)	1.68 ± 0.768 (1.48, 59.7)	69.5 ± 38.8 (57.8, 74.8)	52.0 ± 54.3 (28.3, 210)	1250 ± 1300 (679, 210)	9.14 ± 7.43 (5.62, 196)
Skin Type	Types I and II	80	38.7 ± 15.5 (35.2, 48.4)	1.86 ± 0.260 (1.84, 14.1)	7.27 ± 2.06 (6.95, 31.5)	1360 ± 463 (1280, 36.6)	1.53 ± 0.790 (1.32, 64.2)	61.8 ± 36.1 (50.7, 77.4)	55.9 ± 59.6 (27.5, 238)	1340 ± 1430 (660, 238)	9.75 ± 7.23 (6.22, 182)
	Types III, IV, V and VI	134	41.6 ± 15.5 (38.0, 48.0)	1.86 ± 0.252 (1.84, 13.7)	7.18 ± 2.01 (6.87, 31.6)	1330 ± 420 (1270, 33.9)	1.72 ± 0.725 (1.54, 56.1)	69.2 ± 36.4 (58.5, 70.8)	55.7 ± 55.1 (28.9, 255)	1340 ± 1320 (695, 255)	9.53 ± 8.18 (5.68, 206)
Age Group	12- < 18 years	25	14.2 ± 1.87 (14.1, 13.1)	1.63 ± 0.235 (1.61, 14.7)	7.06 ± 2.21 (6.69, 35.3)	1130 ± 364 (1080, 33.4)	1.46 ± 0.845 (1.24, 67.9)	50.9 ± 33.5 (40.0, 87.5)	45.0 ± 55.8 (16.5, 495)	1080 ± 1340 (396, 495)	8.23 ± 6.91 (4.74, 230)
	18- < 65 years	173	41.6 ± 11.0 (40.1, 28.4)	1.89 ± 0.243 (1.87, 12.8)	7.20 ± 2.00 (6.90, 30.9)	1360 ± 438 (1290, 34.4)	1.69 ± 0.734 (1.50, 56.5)	68.4 ± 36.2 (58.0, 69.3)	57.5 ± 57.8 (30.0, 230)	1380 ± 1390 (720, 230)	9.71 ± 8.01 (5.93, 197)
	> = 65 years	16	68.9 ± 3.91 (68.8, 5.51)	1.94 ± 0.221 (1.93, 10.9)	7.64 ± 2.08 (7.31, 34.0)	1480 ± 435 (1410, 35.4)	1.59 ± 0.817 (1.33, 77.8)	69.0 ± 39.2 (56.4, 83.3)	54.6 ± 45.2 (36.7, 131)	1310 ± 1090 (881, 131)	10.8 ± 7.09 (7.47, 155)

Note: Values are presented in the format of mean ± SD (geometric mean, CV%).
[a] C_{ss} is the average concentration of Weeks 4 and 24 for individual participants.
[b] The projected AUC_{0-24h} values are calculated as steady-state concentration (C_{ss}) multiplying by 24.

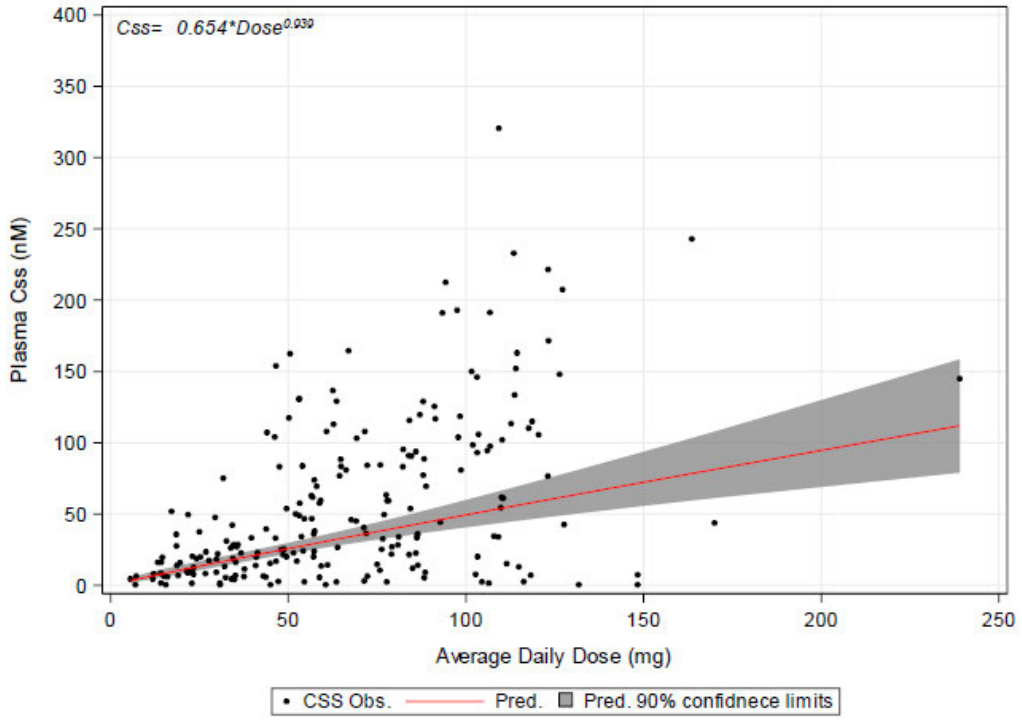
Source: Table 3. DMB-21.52.1

Figure 19. Comparison of Steady-State Ruxolitinib Css Following Topical Administration of 1.5% Ruxolitinib Cream Twice Daily by Geographical Region (A), Skin Type (B), Region and Skin Type (C), and Age (D) Group



Source: Figure 2. DMB-21.52.1

Figure 20. Relationship of Average Daily Dosage of Ruxolitinib and Css of Ruxolitinib



Source: Figure 3. DMB-21.52.1

Reviewer's comments:

1. *Following topical application of ruxolitinib cream (1.5% BID) in subjects with vitiligo in the Phase 3 study (INCB 18424-306), trough plasma ruxolitinib concentrations were similar at Weeks 4, 24, and 40, which indicates steady state was reached at or likely before Week 4.*

2. *The ruxolitinib plasma trough concentration exhibited large interparticipant variability (CV% > 100%, **Table 4**), which at least in part attributes to a broad range of % BSA treated and a wide span of application rate, ranging from 3.5% to 10% on %BSA treated and from 0.19 to 4.56 mg/cm^2 on application rate, respectively. Refer to the Pharmacometrics Review for more detailed investigation.*

Study INCB 18424-307

Demographics:

Table 42 presents the descriptive summary of the PK-evaluable population characteristics for participants initially enrolled in the study (double-blind period). There were no significant differences in total BSA, %BSA treated, or lesion area treated between the ruxolitinib treatment group and vehicle group during the double-blind period. The population for analysis was

approximately 49% male. A total of 35 participants (10.8%) in the study were 12 to < 18 years of age, 275 participants (84.6%) were aged 18 to < 65 years, and 15 participants (4.6%) were aged ≥ 65 years. The PK analysis population included 99 participants (30.5%) from Europe and 226 participants (69.5%) from North America, 87 participants (26.8%) with skin type of Fitzpatrick scale Type I and II and 238 participants (73.2%) with skin type of Fitzpatrick scale III, IV, V, and VI. The total BSA was ranged from 1.26 m^2 to 2.63 m^2, with a mean ± SD (median) of 1.91 ± 0.252 (1.91) m^2. The range of %BSA treated was from 3.50% to 10.1%, with an overall mean ± SD (median) of 7.51% ± 2.02% (8.0%). The overall range of the lesion areas treated was from 510 cm2 to 2490 cm2, with an overall mean ± SD (median) of 1440 ± 439 (1480) cm2. The calculated daily ruxolitinib dose for the ruxolitinib cream treatment group ranged from 5.40 mg to 253 mg with a mean ± SD (median) of 65.1 ± 37.4 (61.0) mg.

Summary of PK:

Plasma ruxolitinib concentrations were similar at Week 4, Week 24, and Week 40 (**Table 43** and **Figure 21**) after treatment with 1.5% ruxolitinib cream BID, which indicates steady state was reached at or before Week 4. Application of 1.5% ruxolitinib cream BID resulted in mean (geometric mean, CV%) Css of 58 nM (246.4 nM, 321%, **Table 44**).

Comparable Css were observed for participants from Europe and North America (see **Table 43** and **Figure 22**). The mean (geometric mean) Css for participants from Europe and North America was 63.4 nM (33.5 nM) and 55.5 nM (23.7 nM), respectively. The Css were comparable for participants with skin type of Fitzpatrick scale Type I and II and Type III, IV, V, and VI (see Table 3 and Figure 2). The mean (geometric mean) Css for participants with Fitzpatrick scale Type I and II and Type III, IV, V, and VI was 67.9 nM (33.3 nM) and 54.7 nM (24.5 nM), respectively. Ruxolitinib plasma concentrations were lower in the age-group of 12 to < 18 years and higher in the age group of ≥ 65 years compared to the age group of 18 to < 65 years. The mean (geometric mean) Css for participants in the age group of 12 to < 18 years, 18 to < 65 years, and ≥ 65 years was 21.5 nM (9.75 nM), 62.4 nM (29.4 nM), and 82.6 nM (63.0 nM), respectively. The mean (geometric mean) topical bioavailability for ruxolitinib cream in participants with vitiligo in this study was 9.83% (5.70%). The relationship of average daily dosage and ruxolitinib Css was demonstrated in **Figure 23**.

Table 42. Participant Baseline Population Characteristics and Ruxolitinib Cream Application Parameters in the Double-Blind Period

Parameters	Statistics	Vehicle Group	1.5% Ruxolitinib Cream Group	Overall
Age group (y)				
12 to < 18	N (%)	6 (5.5)	29 (13.5)	35 (10.8)
18 to < 65	N (%)	101 (91.8)	174 (80.9)	275 (84.6)
≥ 65	N (%)	3 (2.7)	12 (5.6)	15 (4.6)
Sex				
Female	N (%)	59 (53.6)	108 (50.2)	167 (51.4)
Male	N (%)	51 (46.4)	107 (49.8)	158 (48.6)
Region				
Europe	N (%)	31 (28.2)	68 (31.6)	99 (30.5)
North America	N (%)	79 (71.8)	147 (68.4)	226 (69.5)
Skin type				
Type I and II	N (%)	33 (30)	54 (25.1)	87 (26.8)
Type III, IV, V, and VI	N (%)	77 (70)	161 (74.9)	238 (73.2)
Total BSA (m^2)	Mean (SD)	1.94 (0.251)	1.90 (0.251)	1.91 (0.252)
	Median	1.95	1.89	1.91
	Min, max	1.35, 2.59	1.26, 2.63	1.26, 2.63
	Geometric mean	1.93	1.88	1.90
	N	110	215	325
% BSA treated (%)	Mean (SD)	7.71 (2.03)	7.40 (2.01)	7.51 (2.02)
	Median	8.35	7.7	8.0
	Min, max	3.60, 10.1	3.50, 10.0	3.50, 10.1
	Geometric mean	7.39	7.10	7.20
	N	110	215	325
Total body lesion area treated (cm^2)	Mean (SD)	1500 (455)	1410 (428)	1440 (439)
	Median	1540	1430	1480
	Min, max	652, 2490	510, 2430	510, 2490
	Geometric mean	1420	1330	1360
	N	110	215	325
Daily ruxolitinib dose (mg)	Mean (SD)	—	65.1 (37.4)	—
	Median	—	61.0	—
	Min, max	—	5.40, 253	—
	Geometric mean	—	53.2	—
	N	110	215	325
Cream application rate (mg/cm^2)	Mean(SD)	1.49 (0.701)	1.52 (0.701)	1.51 (0.700)
	Median	1.49	1.56	1.52
	Min, max	0.263, 4.01	0.186, 4.65	0.186, 4.65
	Geometric mean	1.30	1.33	1.32
	N	110	215	325

Source: Table 6. DMB-21.54.1

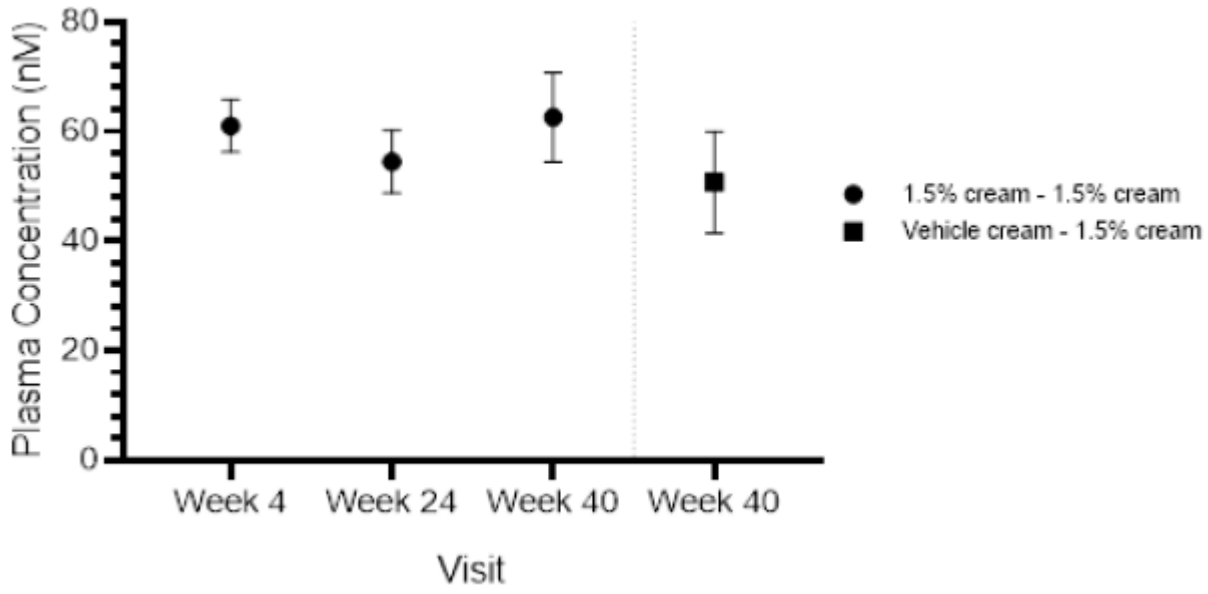
Table 43. Summary of Plasma Concentrations of Ruxolitinib Following Administration of 1.5% Ruxolitinib Cream Twice Daily

	Week 4	Week 24	Week 40	
			1.5% Cream - 1.5% Cream	Vehicle Cream - 1.5% Cream
Concentration (nM)	61.0 ± 68.6 (26.6, 346) N = 208	54.5 ± 79.1 (17.0, 654) N = 189	62.6 ± 79.5 (21.1, 596) N = 95	50.6 ± 62.2 (18.8, 552) N = 48

Note: Values are presented in the format of mean ± SD (geometric mean, CV%) and number of participants.
1.5% cream - 1.5% cream = participants were initially randomized to the 1.5% ruxolitinib cream treatment group and continued 1.5% ruxolitinib cream treatment at Week 24.
Vehicle cream - 1.5% cream = participants were initially randomized to the vehicle treatment group and crossed over to 1.5% ruxolitinib cream treatment at Week 24.

Source: Table 2. DMB-21.54.1

Figure 21. Plasma Concentrations of Ruxolitinib (Mean ± SE) Following Topical Administration of 1.5% Ruxolitinib Cream BID



Source: Figure 1. DMB-21.54.1

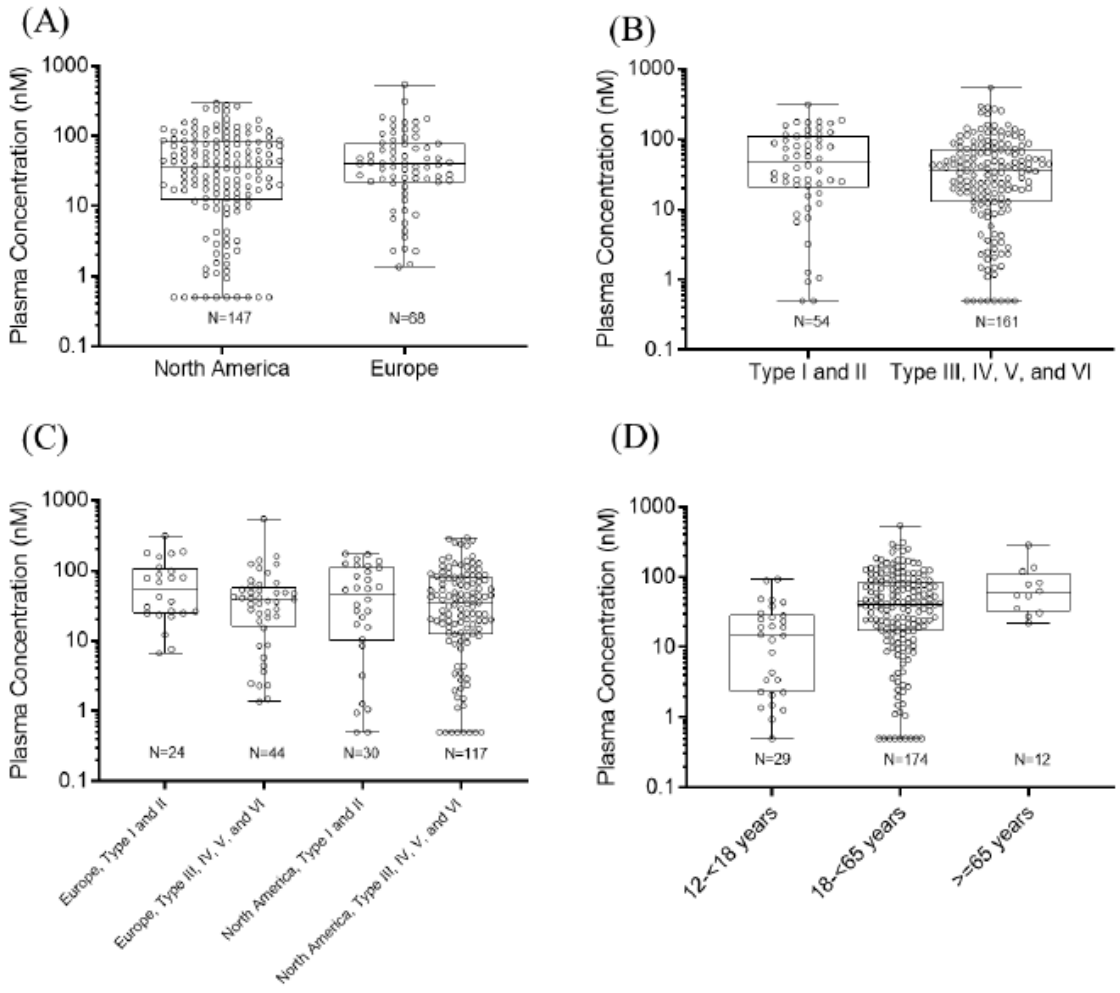
Table 44. Summary of Baseline Population Characteristics and Steady-State Pharmacokinetic Parameters by Geographical Region, Skin Type, and Age Group

Stratification	N	Age (y)	Total BSA (m^2)	%BSA Treated (%)	Lesion Area Treated (cm^2)	Application Rate (mg/cm^2)	Daily Ruxolitinib Dose (mg)	C_{ss} (nM)	Projected $AUC_{ss,\ 0\text{-}24h}$ (h*nM)[a]	Bioavailability (%)
All participants	215	38.1 ± 15.3 (34.6, 48.5)	1.90 ± 0.251 (1.88, 13.3)	7.40 ± 2.01 (7.10, 31.0)	1410 ± 428 (1330, 34.5)	1.52 ± 0.701 (1.33, 61.0)	65.1 ± 37.4 (53.2, 78.8)	58.0 ± 68.1 (26.4, 321)	1390 ± 1640 (634, 321)	9.83 ± 8.46 (5.70, 215)
Geographical region										
Europe	68	36.5 ± 15.1 (33.2, 47.5)	1.86 ± 0.244 (1.85, 13.1)	7.37 ± 1.88 (7.11, 28.5)	1370 ± 375 (1310, 29.4)	1.45 ± 0.672 (1.27, 59.7)	60.8 ± 33.8 (50.2, 75.2)	63.4 ± 81.8 (33.5, 201)	1520 ± 1960 (805, 201)	11.1 ± 8.68 (7.66, 135)
North America	147	38.8 ± 15.4 (35.3, 49.1)	1.91 ± 0.254 (1.90, 13.4)	7.42 ± 2.08 (7.09, 32.1)	1420 ± 450 (1340, 36.8)	1.55 ± 0.714 (1.36, 61.7)	67.1 ± 38.9 (54.7, 80.5)	55.5 ± 60.9 (23.7, 388)	1330 ± 1460 (568, 388)	9.25 ± 8.32 (4.97, 252)
Skin type										
Type I and II	54	40.4 ± 16.2 (36.7, 48.6)	1.90 ± 0.245 (1.89, 12.8)	7.20 ± 2.21 (6.83, 35.1)	1360 ± 445 (1290, 35.8)	1.51 ± 0.640 (1.36, 50.9)	64.2 ± 36.6 (52.6, 77.0)	67.9 ± 64.9 (33.3, 322)	1630 ± 1560 (799, 322)	11.4 ± 7.66 (7.25, 229)
Type III, IV, V and VI	161	37.3 ± 15.0 (34.0, 48.5)	1.90 ± 0.254 (1.88, 13.5)	7.47 ± 1.94 (7.19, 29.5)	1420 ± 422 (1350, 34.1)	1.52 ± 0.723 (1.32, 64.3)	65.4 ± 37.8 (53.4, 79.7)	54.7 ± 69.1 (24.5, 319)	1310 ± 1660 (587, 319)	9.28 ± 8.67 (5.25, 209)
Age group										
12 to <18 y	29	14.6 ± 1.82 (14.5, 12.6)	1.71 ± 0.288 (1.69, 16.4)	7.51 ± 2.21 (7.14, 34.9)	1300 ± 455 (1210, 41.9)	1.31 ± 0.751 (1.07, 79.1)	50.0 ± 34.3 (39.0, 90.7)	21.5 ± 24.2 (9.75, 282)	517 ± 581 (234, 282)	7.26 ± 8.92 (2.87, 375)
18 to < 65 y	174	39.9 ± 11.4 (38.2, 30.6)	1.93 ± 0.239 (1.91, 12.3)	7.37 ± 1.97 (7.08, 30.0)	1420 ± 422 (1360, 32.8)	1.55 ± 0.704 (1.37, 58.9)	67.6 ± 38.1 (55.6, 77.2)	62.4 ± 70.9 (29.4, 313)	1500 ± 1700 (705, 313)	9.96 ± 8.25 (6.06, 194)
≥ 65 y	12	68.7 ± 3.20 (68.6, 4.54)	1.89 ± 0.129 (1.89, 6.95)	7.58 ± 2.29 (7.20, 37.0)	1430 ± 452 (1360, 38.0)	1.52 ± 0.442 (1.46, 31.3)	65.0 ± 27.3 (59.4, 48.0)	82.6 ± 72.5 (63.0, 85.7)	1980 ± 1740 (1510, 85.7)	14.0 ± 9.18 (12.2, 56.5)

Note: Values are presented in the format of mean ± SD (geometric mean, CV%).
[a] Calculated as steady-state concentration multiplied by 24.

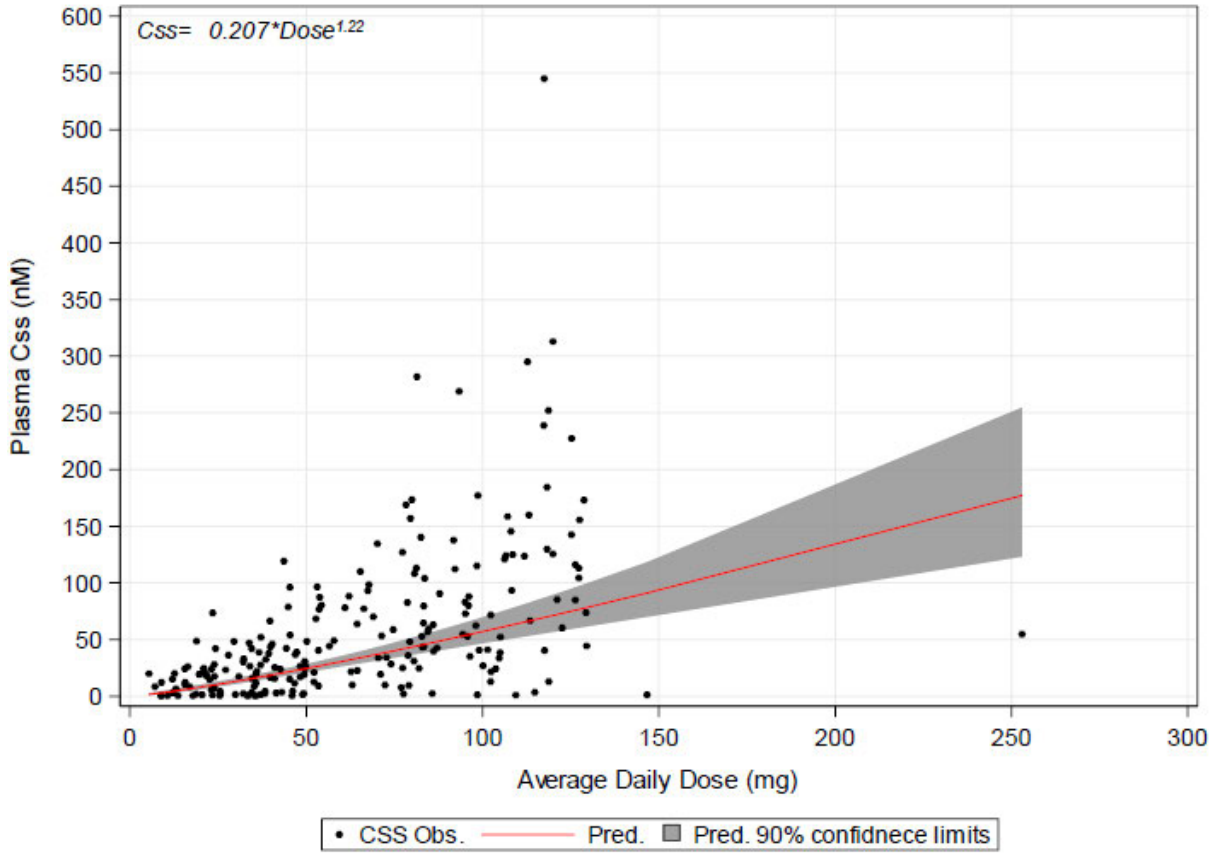
Source: Table 3. DMB-21.54.1

Figure 22. Comparison of Steady-State Ruxolitinib Plasma Concentration Following Topical Administration of 1.5% Ruxolitinib Cream Twice Daily by (A) Geographical Region, (B) Skin Type, (C) Region and Skin Type, and (D) Age Group



Source: Figure 2. DMB-21.54.1

Figure 23. Relationship of Average Daily Dose of Ruxolitinib and Steady-State Plasma Concentration of Ruxolitinib



Source: Figure 3. DMB-21.54.1

Reviewer's comments:

1. *Following topical application of ruxolitinib cream (1.5% BID) in subjects with vitiligo in the Phase 3 study (INCB 18424-307), trough plasma ruxolitinib concentrations were similar at Weeks 4, 24, and 40, which indicates steady state was reached at or likely before Week 4.*
2. *The ruxolitinib plasma trough concentration exhibited large interparticipant variability (CV% > 100%, **Table 44**), which at least in part attributes to a broad range of % BSA treated and a wide span of application rate, ranging from 3.5% to 10% on %BSA treated and from 0.19 to 4.56 mg/cm^2 on application rate, respectively. Refer to the Pharmacometrics Review for more detailed investigation.*

Bioanalytical Assay and Method Validation

Plasma samples for the determination of ruxolitinib concentrations were analyzed by (b) (6) by Incyte Corporation (Wilmington, DE) (**Table 45**). The bioanalytical assay and validation methods similar to the original approval (NDA 215309) were utilized in the vitiligo clinical development program. The plasma samples were assayed by a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method with a linear validated range of 1 nM to 1000 nM (Study 211) and 0.979 nM (0.3 ng/mL) to 979 nM (300 ng/mL) (studies 306 and 307) in human plasma. The lower limit of quantification (LLOQ) is referred as 1 nM throughout this report unless more specific detail is necessary. The performance characteristics of the bioanalytical assays are shown in **Table 46** summarizing the accuracy (%Bias) and precision (CV%) of the assay quality control samples during the analysis of the plasma samples and long-term stabilities.

Table 45. Summary of Analytical Methods Used for the Ruxolitinib Cream Clinical Studies

Clinical Study No.	Bioanalytical Site	Method Used (Validation Report No.)	Sample Analysis Report No.
INCB 18424-211	Incyte	GLP-015 (DMB-07.111)	DMB-20.36
INCB 18424-306	(b) (6)	(b) (6) (DMB-20.64)	DMB-21.61
INCB 18424-307		(DMB-20.64)	DMB-21.62

Source: Table 1. DMB-21.52.1

Table 46. Accuracy, Precision of the Plasma Assay Quality Control Samples and Long-term Stability

Study 211:

Analyte	Low QC			Middle QC			High QC		
	Theo[a]	Bias%	CV%	Theo[a]	Bias%	CV%	Theo[a]	Bias%	CV%
INCB018424	3	0.3	3.2	50	2.0	2.3	800	–0.1	4.9

[a] Theo = theoretical or nominal concentration of INCB018424 in nM.

Source: Table 1. DMB-20.34.2

The longest period of study sample storage time at −70°C from sample collection to analysis was 440 days in this study. The long-term stability of ruxolitinib in human plasma at −70°C was verified for at least 672 days.

Study 306:

Analyte	Low QC			Middle 1 QC			Middle QC			High QC		
	Theo[a]	Bias%	CV%	Theo[a]	Bias%	CV%	Theo[a]	Bias%	CV%	Theo[a]	Bias%	CV%
Ruxolitinib	0.9	-5.6	15.8	3.0	3.0	5.6	15	-1.3	5.7	225	-3.6	5.9

[a] Theo = theoretical or nominal concentration of ruxolitinib in ng/mL.

Source: Table 1. DMB-21.52.1

The ruxolitinib stock and spike solution stability was established at -20 °C for 104 days and long term matrix stability was established at -20 °C and -70 °C for 105 days. Extended long term stability at -70 °C to sufficiently cover the duration of the study will be reported in an addendum to the validation report.

Study 307:

	Low QC			Middle 1 QC			Middle QC			High QC		
Analyte	Theo	Bias%	CV%	Theo	Bias%	CV%	Theo	Bias%	CV%	Theo	Bias%	CV%
Ruxolitinib	0.9	−7.4	7.5	3	−0.7	8.2	15	1.3	7.0	225	−4.0	5.3

Theo = theoretical or nominal concentration of ruxolitinib in ng/mL.

Source: Table 1. DMB-20.54.1

The ruxolitinib stock and spike solution stability was established at -20 °C for 104 days and long term matrix stability was established at -20 °C and -70 °C for 105 days. Extended long term matrix stability was established at -20 °C and -70 °C for 991 days.

Incurred sample reanalysis:

Ten percent of total samples were selected for incurred sample reanalysis (IRS). This meets the criteria of at least two-thirds (67%) of the sample values need to be within 20% of the original concentration (**Table 47**).

Table 47. Incurred Sample Reanalysis

Study 211:

- A total of 104 samples were selected for ISR, representing 9.9% (104/1055) of study samples (Table 6). Overall, 100% of ISR results (104 out of 104) agree within 20% of the original results, demonstrating the reproducibility of ISR.

Source: Table 1. DMB-20.36.1

Studay 306:

- Ten percent total samples were selected for IRS and met the the criteria of at least two-thirds (67%) of the sample values need to be within 20% of the original concentration.

Source: Table 1. DMB-21.61.1

Studay 307:

- Ten percent total samples were selected for IRS and met the the criteria of at least two-thirds (67%) of the sample values need to be within 20% of the original concentration.

Source: Table 1. DMB-21.62.1

Pharmacometrics (PM) Review

The relationships between dose, plasma concentration, and clinical responses to ruxolitinib cream in participants with vitiligo were investigated as following:

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

1.1. Data Description:

Data from 3 studies of ruxolitinib cream in participants with vitiligo were included in the analyses: 2 identically designed, randomized, double-blind, global, Phase 3 studies (INCB 18424-306 and INCB 18424-307) composed of 24-week double-blind and 28-week treatment-extension periods in participants ≥ 12 years and a randomized, double-blind, dose-ranging, Phase 2 study in North America only in participants ≥ 18 years (INCB 18424-211). The relationship between plasma ruxolitinib Css and the average daily application dose of API during the double-blind, vehicle-controlled treatment period was analyzed using pooled data from Studies INCB 18424-211, -306, and -307. The relationships between the efficacy data (i.e., F-VASI75, F-VASI50, proportion of participants achieving VNS45, or percentage change from baseline in F-BSA) and plasma ruxolitinib Css were analyzed in the pooled data from Phase 3 studies. The exposure-response for efficacy is considered as exploratory as the drug is applied directly to the target site (skin) and the systemic exposure would inform systemic safety and may not be directly correlated with efficacy. The graphical analyses were performed on the relationships between clinical laboratory test results of select hematology endpoints such as platelet count, mean platelet volume, hemoglobin and neutrophil count, and plasma ruxolitinib Css using the combined Phase 3 data.

The overall population consisted of 785 participants with vitiligo from the 3 studies who were treated with vehicle or ruxolitinib cream. The population was approximately 53.8% female, mostly White (82.9%), and mostly non-Hispanic (73.0%). The age range was 18 to 73 years for the Phase 2 study and 12 to 79 years for the Phase 3 studies. The mean and median values of age were similar between the pooled vehicle groups and ruxolitinib within each of the Phase 2 and Phase 3 studies, with the mean (median) age at 48.4 (49) years and 39.4 (39) years, respectively. The overall mean (median) age was 41.1 (40.0) years across all 785 participants. All participants in Study INCB 18424-211 were in North America (the United States), whereas the Phase 3 studies were global studies in both North America and Europe with an approximate ratio of 2:1. Approximately 33% of the participants had Fitzpatrick scale Types I or II, and 67% of the participants had Fitzpatrick scale Types III, IV, V, or VI. The total BSA ranged from 1.20 to 2.84 m^2, with a mean ± STD (median) of 1.91 ± 0.257 (1.9) m^2. The range of %BSA treated involved with vitiligo at baseline was from 3.5% to 88%, with an overall mean ± STD (median) of 22.0% ± 18.7% (16.3%) for Study INCB 18424-211 and from 3.2% to 10.1%, with an overall mean ± STD (median) of 7.35% ± 2.03% (7.7%) for Studies INCB 18424-306/307. The overall median %BSA treated, F-VASI, and T-VASI scores at baseline in the pooled Phase 2 and Phase 3 PK population with vitiligo were 8.1% (range: 3.20%-88.0%), 0.7 (range: 0.130-3.00), and 7.2 (range: 2.28-70.3), respectively. Overall, a total of 8.9% of the participants were 12 to < 18 years of age, 83.2% of the participants were aged 18 to < 65 years, and 7.9% of the participants were aged ≥ 65 years.

A total of 1227 trough PK samples collected at Weeks 4 and 24 during the double-blind period from 548 participants with vitiligo treated with ruxolitinib enrolled in the Phase 2 (N = 119) and Phase 3 (N = 429) studies were included in the dose-concentration analysis. The Css of ruxolitinib was derived as the average of the Ctrough from Weeks 4 and 24 during the double-blind period per participant for all 3 studies.

1.2. Applications of Ruxolitinib Cream:

In the Phase 3 studies, ruxolitinib 1.5% cream was applied BID to depigmented vitiligo areas identified at baseline (including ≥ 0.5% BSA on the face and ≥ 3% BSA on nonfacial areas, up to a maximum total body involvement of 10% BSA) during the double-blind and treatment extension periods. In Study INCB 18424-211, 4 ruxolitinib cream strengths were applied QD or BID (0.15% QD, 0.5% QD, 1.5% QD, and 1.5% BID) onto skin area(s) affected by vitiligo at baseline (including ≥ 0.5% BSA on the face and ≥ 3% BSA on nonfacial areas, up to a maximum total body involvement of 20% BSA) during the double-blind and treatment-extension periods.

1.3. PK Sample Collection:

In the Phase 3 studies, preapplication PK samples were collected at Weeks 4 and 24 during the double-blind period and at Week 40 during the treatment extension period. In Study INCB 18424-211, preapplication and 2-hour post application samples were collected at Weeks 4 and 24 during the vehicle-controlled, double-blind period and at Weeks 28 and 52 during the double-blind, treatment-extension period.

1.4. Clinical Efficacy Assessment:

Assessment of total %BSA treated (including facial and nonfacial areas) depigmented by vitiligo were performed by the palmar method. The binary response endpoint of F-VASI75 is defined as 1 for percentage improvement from baseline in F-VASI score of 75% or greater and 0 otherwise. F-VASI50 is defined with the same pattern. The VNS is a participant-reported measure of vitiligo treatment success, which has a 5-point scale. A VNS score of 4 or 5 is interpreted as representing treatment success.

1.5. Clinical Hematology Laboratory Tests:

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

2. Dose-Concentration Analysis

2.1. Objectives:

• To characterize the relationship between ruxolitinib Css and the topical application dose of ruxolitinib free base equivalent (i.e., the API dose).
• To identify and evaluate the impacts of intrinsic and/or extrinsic factors such as age, sex, race, geographic region, Fitzpatrick scale type, treated vitiligo lesion region, baseline disease extent and/or severity such as %BSA treated with vitiligo at the baseline, T-VASI at the baseline on plasma ruxolitinib Css.

2.2. Methods:

The primary PK modeling was performed using the pooled Phase 3 data, with Study INCB 18424-211 data included in a sensitivity analysis. A linear regression framework was adopted on account that the ruxolitinib Css was 1 value per participant that was derived as the average of C_{trough} during the VC period. The concentration and API dose were log-transformed. Participants' demographic assessments (sex, age, race, ethnicity, total BSA), baseline disease extent and/or severity such as %BSA treated with vitiligo, T-VASI score, and F-VASI score, and clinical study design factors such as stratifications by region (North America vs Europe) and skin type (Fitzpatrick scale Types I, or II vs Types III, IV, V, or VI) were explored as potential covariate predictors of the ruxolitinib Css. The covariate search was performed in a stepwise univariate fashion during the forward selection process followed by a backward elimination process. The likelihood ratio test was used to evaluate the significance of the inclusion/dropping of covariates into/from the working model with p-values of 0.01 and 0.001 as thresholds for forward selection and backward elimination, respectively.

2.3. Results:

A dose-PK (Css) linear model (**Figure 24**) was developed to characterize the relationship between the plasma ruxolitinib Css during the double-blind, vehicle-controlled period (VC) period and the average application dose of API, both transformed into the logarithmic domain. The model was also used to assess the impacts of significant covariate predictors. Per the Applicant, the relationship between the API dose and the plasma ruxolitinib Css was quantified with an exponent of 0.986 (95% CI: 0.874, 1.10) on API dose, which includes 1; that is, the doubling of the API dose alone would result in doubling in Css. The final dose-PK model includes age (median age of 40 years) and total BSA (total body surface area; median BSA of 1.88 m^2) as significant covariates. The parameter estimates for these covariates are 0.561 (95% CI: 0.316, 0.806) and −1.66 (95% CI: −2.45, −0.869), respectively. The precision of parameter estimation was < 25% RSE except 36.3% RSE on the intercept (**Table 48**). The model diagnostic plots (**Figure 25**) of the standardized residuals versus fitted values, API dose, %BSA treated, age, and total BSA show that the standardized residuals are in general distributed around 0 with an approximately constant variance. There were only very few possible outliers observed outside ± 3 standard deviations (SDs). The magnitude of impact of age and total BSA on the Css of ruxolitinib is illustrated in a Forest plot (**Figure 26**).

Based on the final dose-PK model, plasma ruxolitinib Css increases as age increases and decreases as BSA increases. The Applicant estimated that the 80% range (ie, from 10th to 90th percentiles) of the impacts of age (18 and 62 years) and/or BSA (1.58 and 2.23 m^2) on plasma ruxolitinib Css were within 40% in either direction, which were considered clinically nonsignificant on account of the > 100% GCV interindividual variability in plasma ruxolitinib Css.

Figure 24. Final PK Model Equations (Upper equation: in log form; Lower equation: in multiplicative form)

$$\text{Log}(C_{ss}\ [\text{nM}]) = -0.626 + 0.986 \times \text{Log}(\text{API Dose [mg]}) + 0.561 \times \text{log}(\text{Age (year)} / 40) - 1.66 \times \text{Log}(\text{BSA } [\text{m}^2] / 1.88)$$

$$C_{ss}\ (\text{nM}) = 0.535\ (\text{nM}) \times [\text{API Dose (mg)}]^{0.986} \times (\text{Age (year)} / 40)^{0.561} \times (\text{BSA } (\text{m}^2) / 1.88)^{(-1.66)}$$

Note: In the final PK model, the median age was 40 years and median BSA was 1.88 m^2

Source: Pharmaceutical Development Report DMB-21.53.1

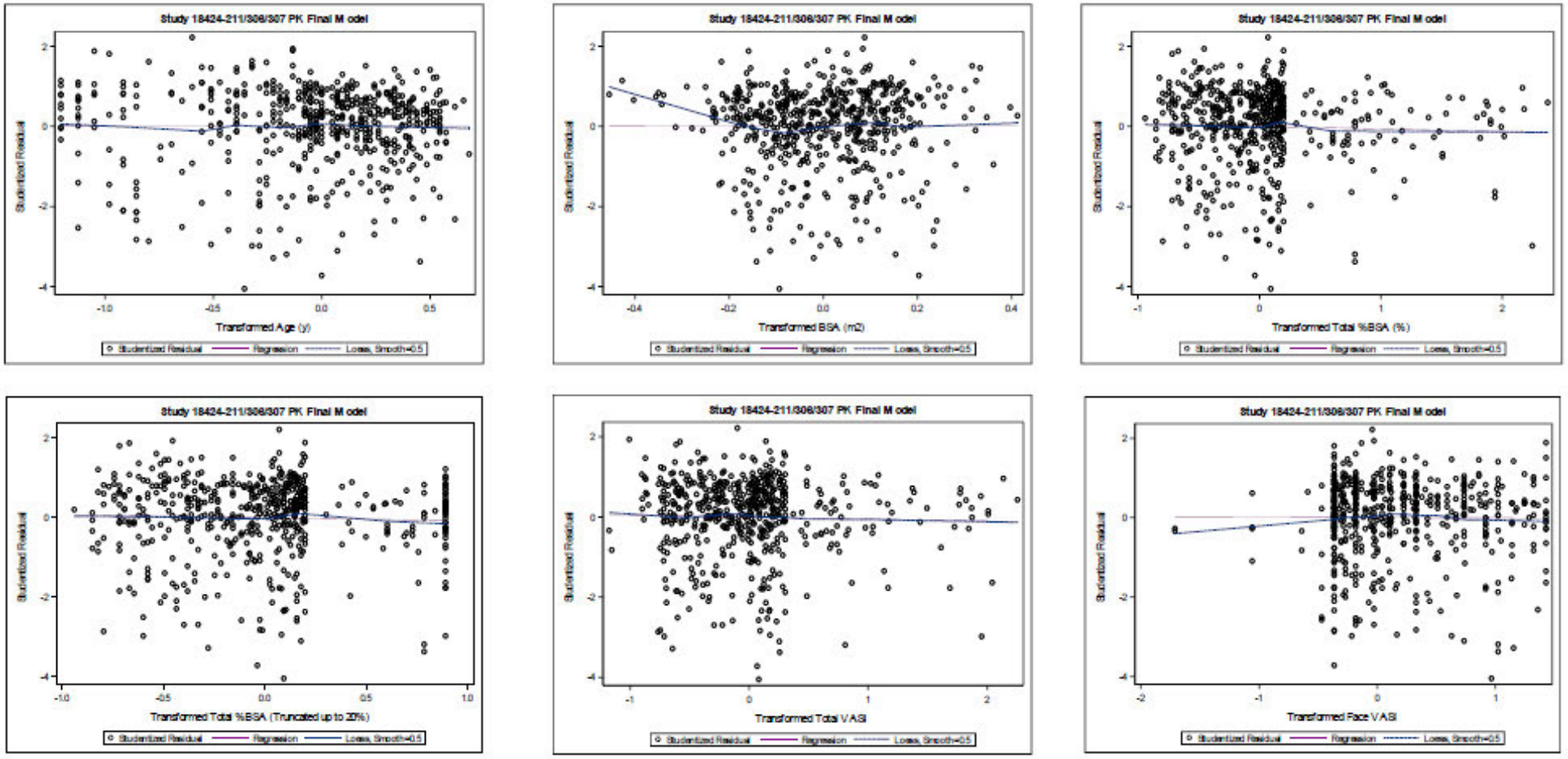
Table 48. Final PK Model Parameter Estimations

Effect	Estimate	RSE (%)[a]	p-value	95% CI	
				Lower	Upper
Linear model parameterization in the log-domain					
Intercept	−0.626	36.3	0.0061	−1.07	−0.179
Exponent on LnDose	0.986	5.76	< 0.0001	0.874	1.10
Exponent on age (years)	0.561	22.2	< 0.0001	0.316	0.806
Exponent on BSA (m^2)	−1.66	24.2	< 0.0001	−2.45	−0.869
In the multiplicative form of the model equation[b]					
Intercept (nM) in the multiplicative model equation	0.535	—	—	0.342	0.836

[a] RSE = standard error / estimate * 100 (%).
[b] The transformation into the multiplicative form was exp(x) for both the estimates and the lower/upper limits.

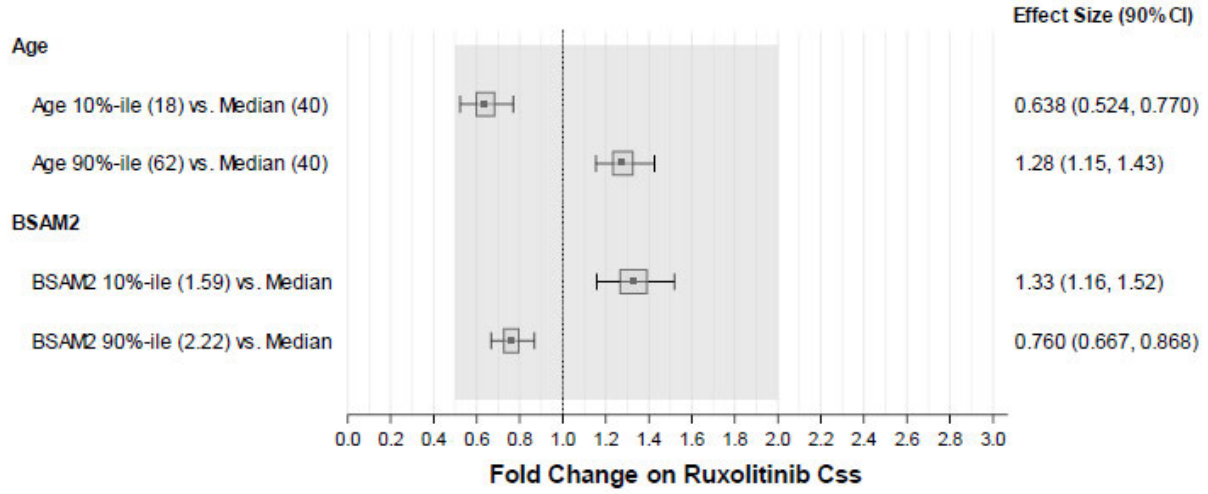
Source: Table 6. Pharmaceutical Development Report DMB-21.53.1

Figure 25. Diagnostic Plots the Final PK Model



Source: Figures 5. Pharmaceutical Development Report DMB-21.53.1

Figure 26. Forest Plot of Impacts of Covariates on Ruxolitinib Steady-State Concentration



Source: Figures 7. Pharmaceutical Development Report DMB-21.53.1

2.4. Discussion

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

- Average API dose:
  Average API dose (mg) = Average application weight of drug product [g] * Strength of Cream Formulation (%) / 100 * 1000 (mg/g);
  - Strength of Cream Formulation = 1.5 (%)
- Application Rate:
  Application Rate (mg/cm^2) = (Average daily application weight of ruxolitinib cream [g]) × 1000 (mg/g) / Total Area of Treated Lesion(s) (cm^2)

The API dose equation term in the dose-PK model contains components including total BSA, %BSA, application rate as well as formulation strength. Among these components, only formulation strength (strength = 1.5%) is a constant for the pooled Phase 3 studies. Hence, it is challenging to straightforwardly interpret the dose-PK model. Independent analysis was conducted by the reviewer to expand the API dose term and combining the BSA into a single parameter, which enables a better interpretation for the four independent parameters, which are % BSA, Application rate, Age, and BSA (**Table 49**):

Table 49. PK-Model Deformation	
Original dose-PK model	C_{ss} (nM) = 0.535 (nM) × [API Dose (mg)]^0.986 × (Age (year) / 40)^0.561 × (BSA (m^2) / 1.88)^(-1.66)
Model rearrangement_1	Css (nM) = 0.535 (nM) × [%BSA/100 × BSA (m^2) × Application Rate (mg/cm^2) × Strength]$^{0.986}$ × (Age (year) / 40)$^{0.561}$ × (BSA (m^2) /1.88)$^{-1.66}$
Model rearrangement_2	Css (nM) = 0.535 (nM) × [%BSA/100 × Application Rate (mg/cm^2) × Strength]$^{0.986}$ × (Age (year) / 40)$^{0.561}$ × BSA (m^2)$^{0.986}$× (BSA (m^2) /1.88)$^{-1.66}$
Model rearrangement_3	Css (nM) = 0.535 (nM) × [**%BSA**/100 × **Application Rate** (mg/cm^2)]$^{0.986}$ × (0.015) $^{0.986}$ × (**Age** (year) / 40)$^{0.561}$ × (**BSA** (m^2))$^{-0.674}$ x (1 /1.88)$^{-1.66}$
Model rearrangement_4	Css (nM) = 0.535 (nM) × (**%BSA**/100) $^{0.986}$ × (**Application Rate** (mg/cm^2)$^{0.986}$ × (0.015) $^{0.986}$ × (**Age** (year) / 40)$^{0.561}$ × (**BSA** (m^2))$^{-0.674}$ x (1 /1.88)$^{-1.66}$
Source: Reviewer's independent analysis	

In the rearranged dose-PK model, the exponents on both %BSA and application rate are equal (0.986) and it's approximately equal to 1, which indicates plasma ruxolitinib Css is linearly correlated to both %BSA and application rate. Of note, the %BSA investiaged in the Phase 3 studies (306 and 307 pooled) ranged from 3.2 % to 10%. In addition, the application rate measured in the Phase 3 studies (306 and 307 pooled) ranged from 0.186 to 4.65 mg/cm^2.

Plasma ruxolitinib Css increases with age, %BSA and application rate and decreases with BSA. The range of 10th to 90th percentiles of each parameter was used to quantatively demonstrate its relative impact on the plasma ruxolitinib Css assuming all other parameters remain the same (**Table 50)**. Among them, application rate has the largest impact on Css with ↓ 60.9% and ↑ 48.8% when comparing 10th percentile and 90th percentile to median, respectively.

Table 50. Percent and fold of Impacts of Variables on Ruxolitinib Css

Impact of Age on Css:

	Trial Measurement (Years)	Percent of Impact on Css vs. Median	Fold of Css (10^{th} vs. 90^{th} percentile)
Age 10^{th} Percentile	16	↓ 40.1%	2.1
Age 50^{th} Percentile (median)	40	--	
Age 90^{th} Percentile	61	↑ 26.7%	

Impact of Total BSA on Css:

	Trial Measurement (m^2)	Percent of Impact on Css vs. Median	Fold of Css (10^{th} vs. 90^{th} percentile)
BSA 10^{th} Percentile	1.57	↑ 12.3%	1.3
BSA 50^{th} Percentile (median)	1.87	--	
BSA 90^{th} Percentile	2.20	↓ 10.6%	

Impact of %BSA Treated on Css:

	Trial Measurement (%)	Percent of Impact on Css vs. Median	Fold of Css (10^{th} vs. 90^{th} percentile)
%BSA 10^{th} Percentile	4.3	↓ 43.7%	2.3
%BSA 50^{th} Percentile (median)	7.7	--	
%BSA 90^{th} Percentile	9.8	↑ 26.8%	

Impact of Application Rate (AppR) on Css:

	Trial Measurement (mg/m^2)	Percent of Impact on Css vs. Median	Fold of Css (10^{th} vs. 90^{th} percentile)
AppR 10^{th} Percentile	0.63	↓ 60.9%	3.8
AppR 50^{th} Percentile (median)	1.62	--	
AppR 90^{th} Percentile	2.42	↑ 48.8%	

Source: Reviewer's independent analysis

Considering the extreme situations on the lower end, a subject with total body BSA at 2.20 m^2 (90^{th} percentile is used, since BSA is raised to a negative power in the dose-PK model), %BSA at 4.3% (10^{th} percentile), application rate at 0.63 mg/cm^2 (10^{th} percentile) and age of 16 years (10^{th} percentile) is expected to have a Css at 2.12 nM. On the other hand, considering the extreme situations on the higher end, a subject with total body BSA at 1.57 m^2 (10^{th} percentile), %BSA at 9.8% (90^{th} percentile), application rate at 2.42 mg/cm^2 (90^{th} percentile) and age of 61 years (90^{th} percentile) is expected to have a Css at 48.4 nM. The differennce in Css between these two subjects was about 22.8 fold (**Table 51**).

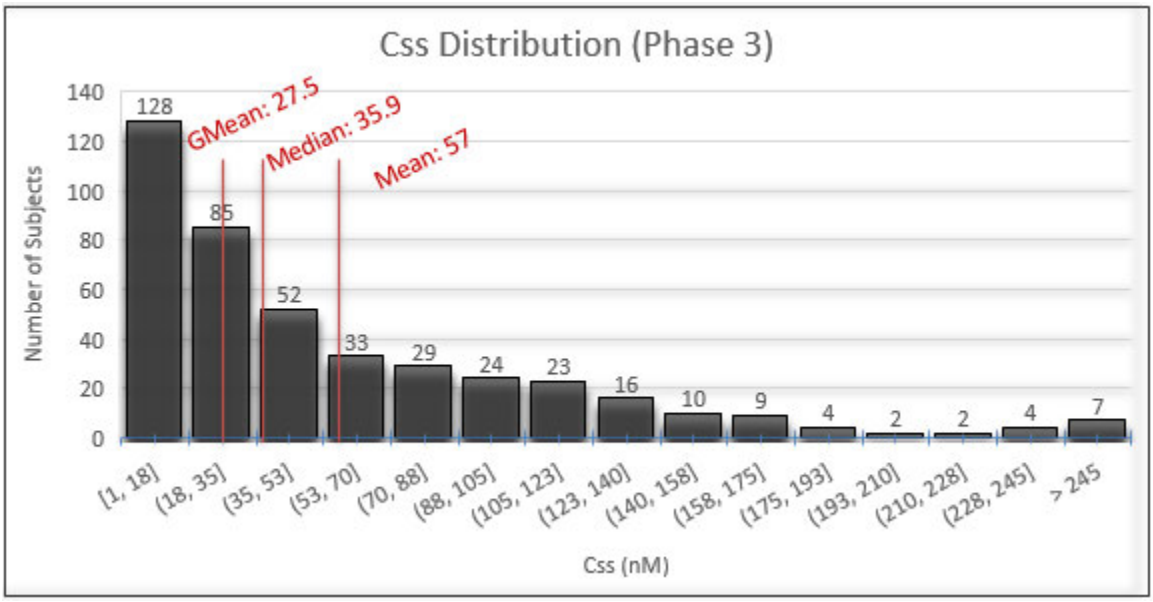
Based on the final model, the subject at the 90^{th} percentiles for each parameter is predicted to have a concentration around 48.4 nM, while actual data observed in the pooled Phase 3 trails having a median Css at 35.9 nM and containing many concentrations as high as 545 nM (**Figure 27**). This discrepency indicates that the dose-PK model was inadequte in capturing the extreme high concentrations as observed.

Table 51. Ruxolitinib Css Prediction in Participants with Extreme Variables

	Total BSA (m^2)	**%BSA Treated (%)**	**AppR (mg/m^2)**	**Age (years)**	**Predicted Css (nM)**	**Fold of Difference**
Participant_1	2.20	4.3	0.63	16	2.12	22.8
Participant_2	1.57	9.8	2.42	61	48.4	

Note: AppR, application rate
Source: Reviewer's independent analysis

Figure 27. Plasma Ruxolitinib Css Distribution in Phase 3 Studies (306 and 307 pooled)



Note: GMean: geometric mean
Source: Reviewer's independent analysis

Reviewer's Comments:

1. *Ruxolitinib Css exhibits a linear relationship with respect to %BSA treated as well as the application rate. Based on the rearranged dose-PK model, plasma ruxolitinib Css generally increases with age, %BSA and application rate and decreases with total BSA (body size).*
2. *Based on the rearranged dose-PK model, subjects with extreme parameters (10^{th} and 90^{th} percentiles) on BSA, %BSA, application rate and age are expected to have up to 22.8-fold difference in ruxolitinib Css.*
3. *While the dose-concentration model was able to describe the central tendency, it as inadequate in capturing the extreme high Css concentrations as observed.*

3. Systemic Ruxolitinib Concentration-Efficacy Response Analyses

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

3.1. Objectives

• To characterize the relationship between plasma ruxolitinib Css and the primary efficacy response rates in F-VASI75 at Week 24.
• To characterize the relationship between plasma ruxolitinib Css and the efficacy response rates in F-VASI50 at Week 24.
• To characterize the relationship between plasma ruxolitinib Css and proportion of VNS45 responders at Week 24.
• To characterize the relationship between plasma ruxolitinib Css and the efficacy response of percentage change from baseline in F-BSA at Week 24.

3.2. Methods

The plasma ruxolitinib Css during the double-blind, vehicle-controlled period paired with the efficacy responses at Week 24 for each participant were analyzed. A nonlinear, generalized model with a logit link function was evaluated to characterize the primary efficacy endpoint, F-VASI75 binary responses (responder or not) at Week 24, as a function of plasma ruxolitinib Css. The structural model was parameterized in terms of the maximum effect attributed to the plasma ruxolitinib Css (Emax), and the plasma ruxolitinib EC50, all in the logit domain of the probability of the F-VASI75 response. Participants' demographic assessments (e.g., sex, age, race, ethnicity, BSA), baseline disease severity and extent such as %BSA treated with vitiligo, T-VASI score, and F-VASI score, and clinical study design factors such as stratifications by region (North America vs Europe) and skin type (Fitzpatrick scale Types I, or II vs Types III, IV, V, or VI) were explored as potential covariate predictors. The same modeling framework and the development process were applied to the other 2 efficacy endpoints: F-VASI50 and VNS45 response.

3.3. Results

Treatment-dependent and concentration-dependent efficacy was observed in the Phase 3 studies, and correlation analyses of treatment with ruxolitinib cream and the plasma ruxolitinib Css were performed with the efficacy parameters: F-VASI75 (primary) (**Figure 28**), F-VASI50 (key secondary) (**Figure 29)**, and VNS45 (key secondary) (**Figure 30**) using a nonlinear generalized logit-Emax model. However, no statistically significant association between plasma ruxolitinib Css and changes (from baseline) in F-BSA at Week 24 (key secondary) was detected.

For all the binary efficacy endpoints, the probabilities of achieving a response were sigmoidally associated with Css, and the estimated EC50 values were all low, in the range of 6 to 10 nM (7.70 nM for F-VASI75, 6.14 nM for F-VASI50, and 9.27 nM for VNS45), which are approximately between the 15^{th} and 20^{th} percentiles of the distribution of the observed plasma ruxolitinib Css in Phase 3 studies.

Race (others vs white) were identified as the only significant predictor of F-VASI75 response. The odds for non-White participants to achieve F-VASI75 responses were 128% higher than for White participants. Race and ethnicity were identified as significant covariate predictors of F-VASI50 response. But the joint distribution of race and ethnicity was not statistically significantly more predictive than the separate distributions of race and ethnicity. In addition,

Baseline T-VASI score was identified as the only significant covariate predictor of VNS45 response. The odds of VNS45 response decrease by 13.3% for a 1-unit increase in the baseline T-VASI score. The similar model framework and the model development process from Phase 3 data were applied to the Phase 2 data, and similar concentration-response relationships between responses and plasma ruxolitinib Css held true.

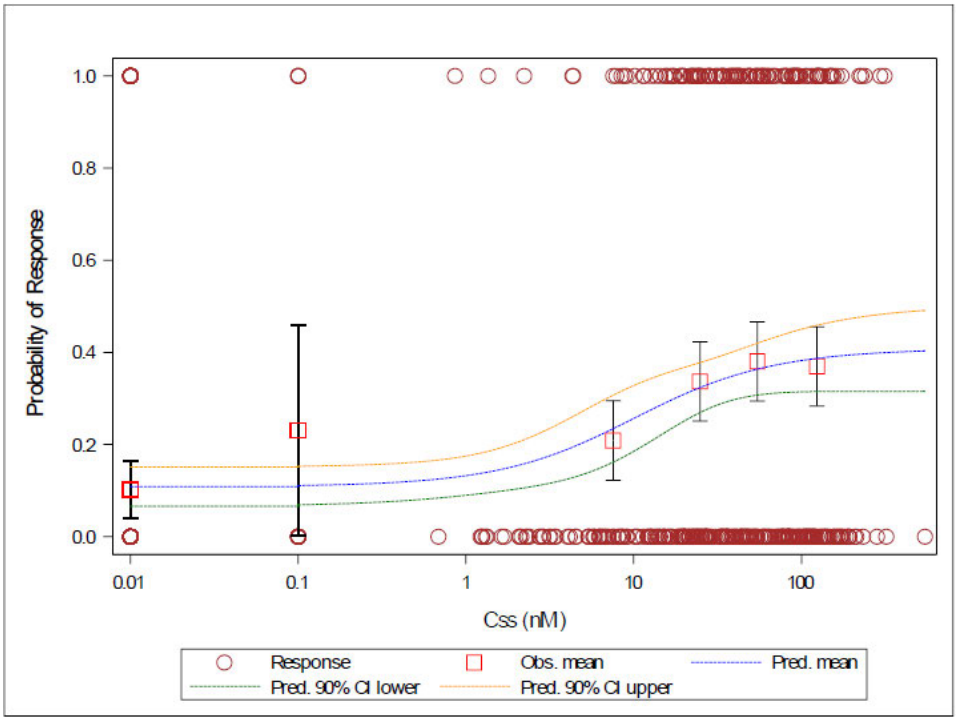
Dose-dependent efficacy was observed in the Phase 2 and Phase 3 studies, and correlation analyses of treatment with ruxolitinib cream and the plasma concentration of ruxolitinib were performed with the efficacy parameters: IGA-TS (primary) (**Figure 19**), EASI75 (key secondary) (**Figure 20**), and ITCH4 (key secondary) (**Figure 21** using a nonlinear generalized logit-Emax model.

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

Another common feature of these logit-Emax models is that the estimated EC50 values were all very low, in the range of 1 to 4 nM (1.43 nM for IGA-TS, 3.69 nM for EASI75, and 1.13 nM for ITCH4), which are approximately between the 10th and the 20th percentiles of the distribution of the observed Css among all ruxolitinib cream–treated participants. Further, the imputed EC90 values (ie, 9-fold of EC50) were 12.9 nM for IGA-TS, 33.2 nM for EASI75, and 10.2 nM for ITCH4, which are lower than the observed 50th, 75th, and 50th percentiles of Css, respectively; that is, > 50% of ruxolitinib cream–treated participants had achieved the EC90 for IGA-TS and ITCH4 and > 25% for EASI75.

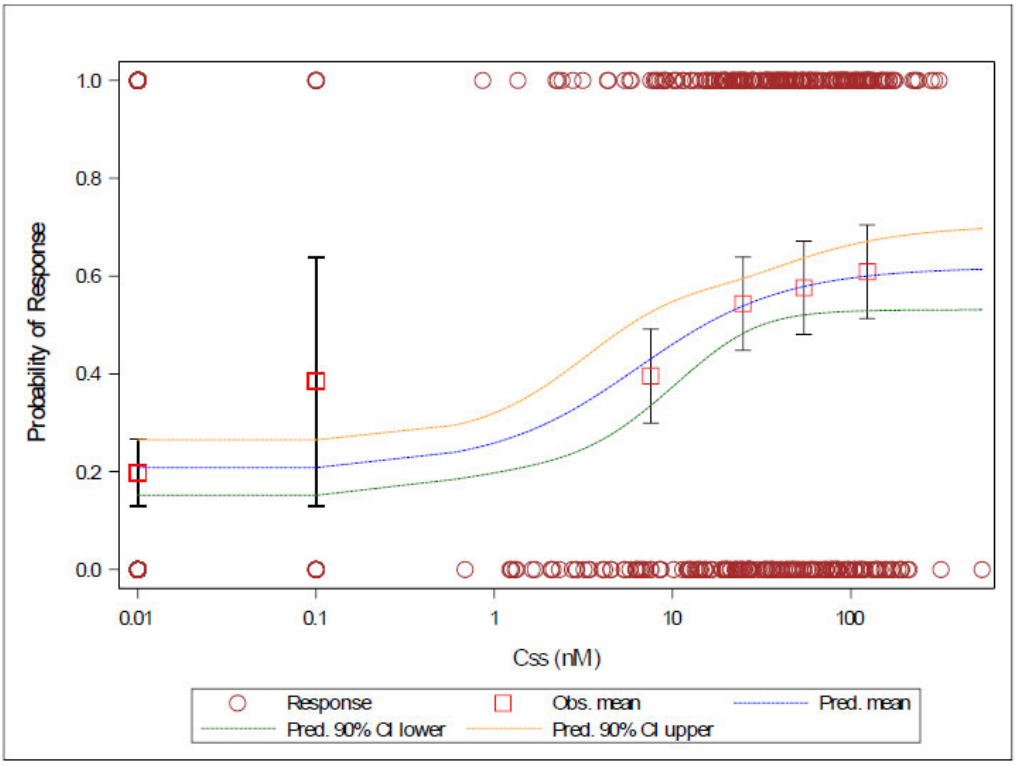
Baseline IGA score and geographic region were identified as significant predictors of IGA-TS response, in addition to the ruxolitinib cream treatment indicator variable (vs vehicle cream treatment) and the ruxolitinib Css. Geographic region was identified as the only significant covariate predictor of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

Figure 28. Exploratory Graphical Analysis of Responses at Week 24 Versus Css During the Double-Blind, Vehicle-Controlled Period in Pooled Phase 3 Css — PK/PD Population of F-VASI75



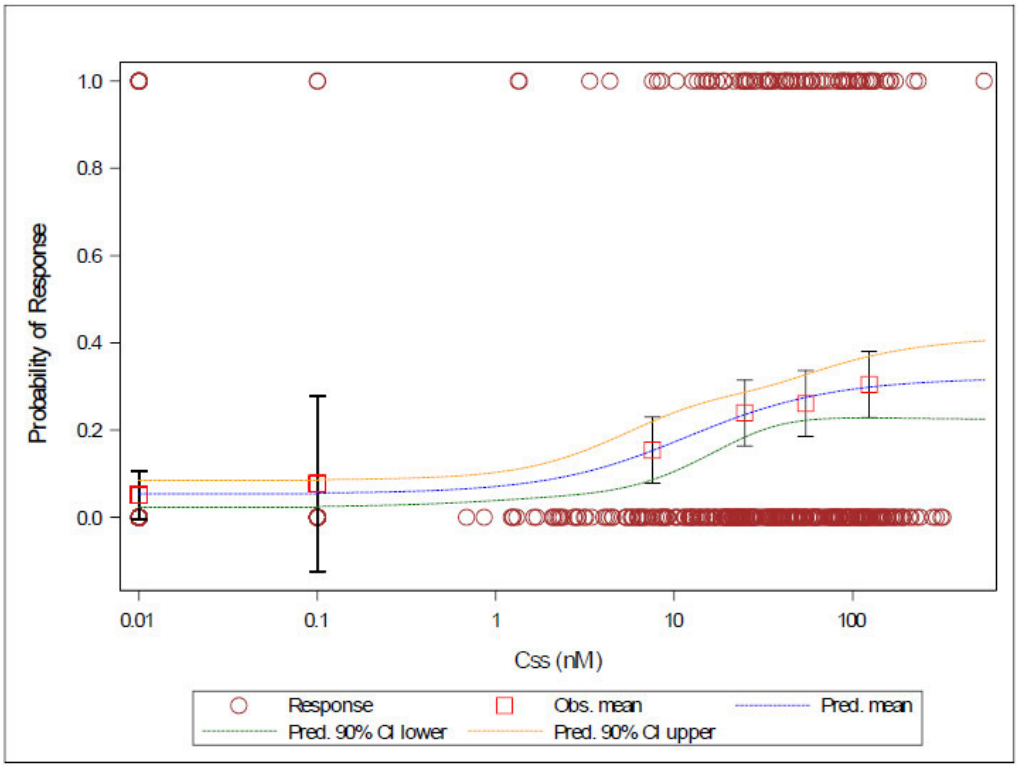
Source: Figures 9. Pharmaceutical Development Report DMB-21.53.1

Figure 29. Exploratory Graphical Analysis of Responses at Week 24 Versus Css During the Double-Blind, Vehicle-Controlled Period in Pooled Phase 3 Css — PK/PD Population of F-VASI50



Source: Figures 9. Pharmaceutical Development Report DMB-21.53.1

Figure 30. Exploratory Graphical Analysis of Responses at Week 24 Versus Css During the Double-Blind, Vehicle-Controlled Period in Pooled Phase 3 Css — PK/PD Population of VNS45



Source: Figures 9. Pharmaceutical Development Report DMB-21.53.1

Reviewer's Comments:

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

4. Systemic ruxolitinib concentration-hematology analyses

4.1. Objectives

To explore and summarize the relationships between plasma ruxolitinib Css after topical ruxolitinib application and the clinical laboratory test results of platelet indices such as platelet count and mean platelet volume, hemoglobin, and neutrophil count by visit during the double-blind period.

4.2. Methods

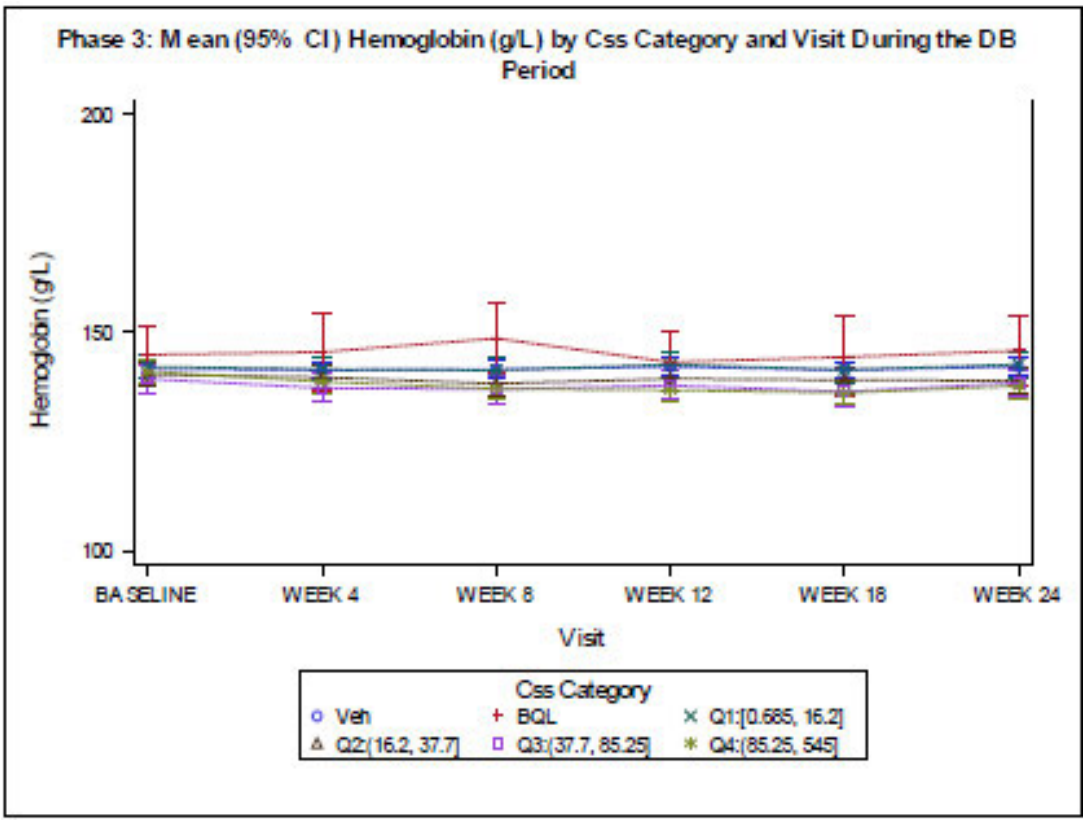
Descriptive graphical analyses of clinical laboratory tests of hemoglobin, absolute neutrophil count (ANC), and platelet indices (platelet count and MPV) by visit through the double-blind,

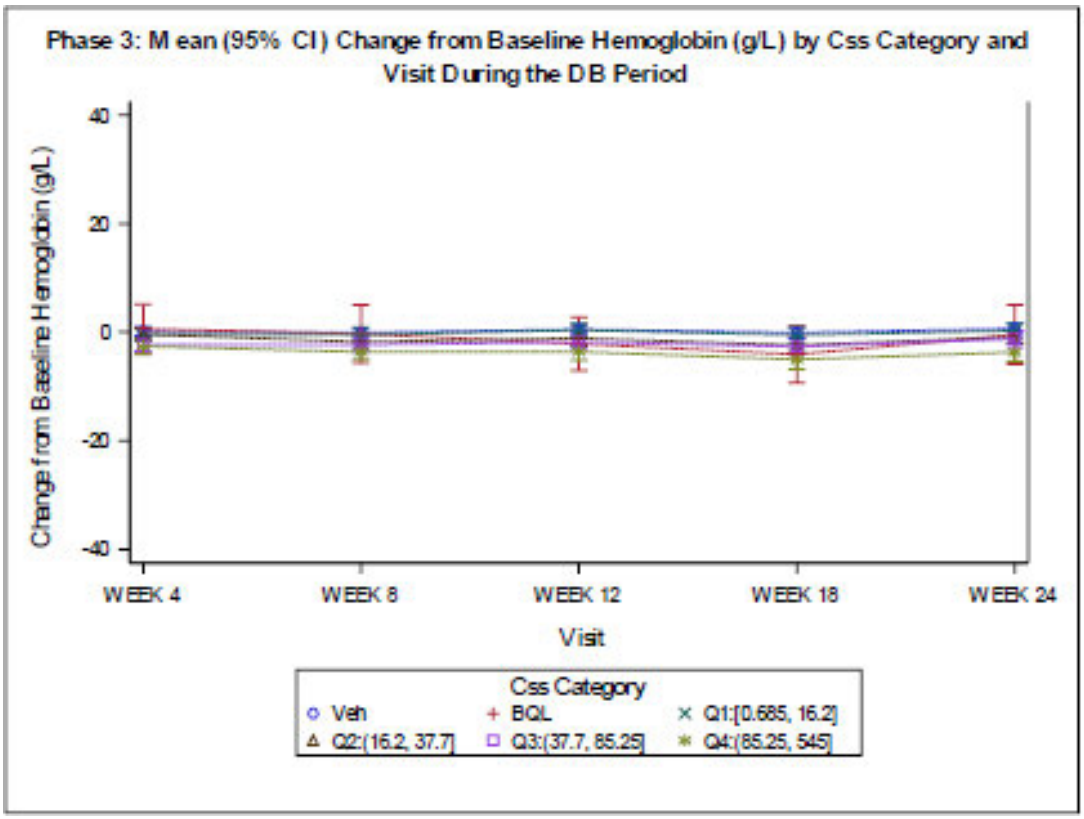
vehicle-controlled period were performed with respect to treatment groups or ordered categorical groups of plasma ruxolitinib Css. Incidences (frequencies) of increased platelet counts > 450 Gi/L or 600 Gi/L based on the clinical laboratory test data were tabulated with respect to treatment groups or ordered categories of plasma ruxolitinib Css. Box plots of plasma ruxolitinib Css in participants with any CTC grade events in these hematology parameters were generated.

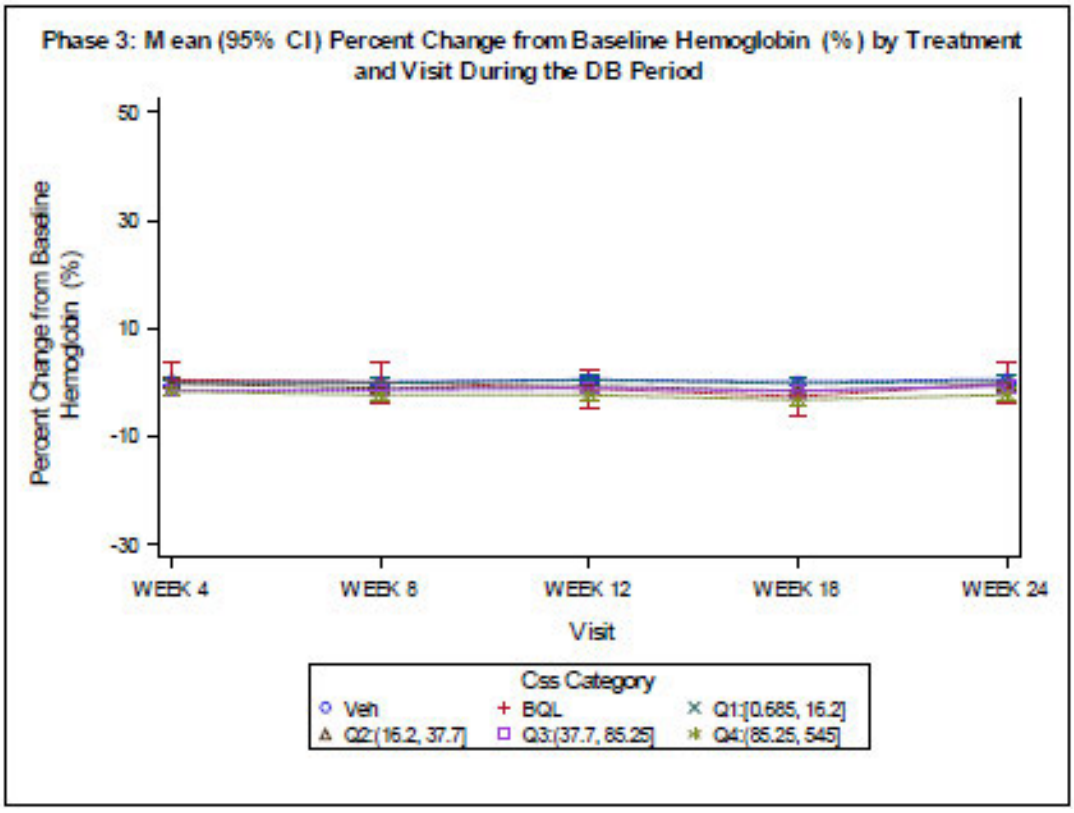
4.3. Results

No clinically meaningful trends in hematologic parameters were observed in any of the Phase 3 and Phase 2 studies in participants with vitiligo. Among the parameters examined in this report (hemoglobin level (**Figure 31**), ANC (**Figure 32**), platelet count (**Figure 33**), and mean platelet volume (MPV)), no patterns of decreases were observed. A discernible phenomenon in the hematologic parameters observed in these 3 vitiligo studies was a mild increase (~20 Gi/L or ~10%) in the mean platelet count by Week 12 in participants treated with ruxolitinib cream in the Phase 3 studies, which remained at a level higher than baseline through Week 24.

Figure 31. Exploratory Mean (95% CI) of Measured Values, Change-From-Baseline, and Percent Change-From-Baseline Hemoglobin by Css Category and Visit During the Double-Blind, Vehicle-Controlled Period

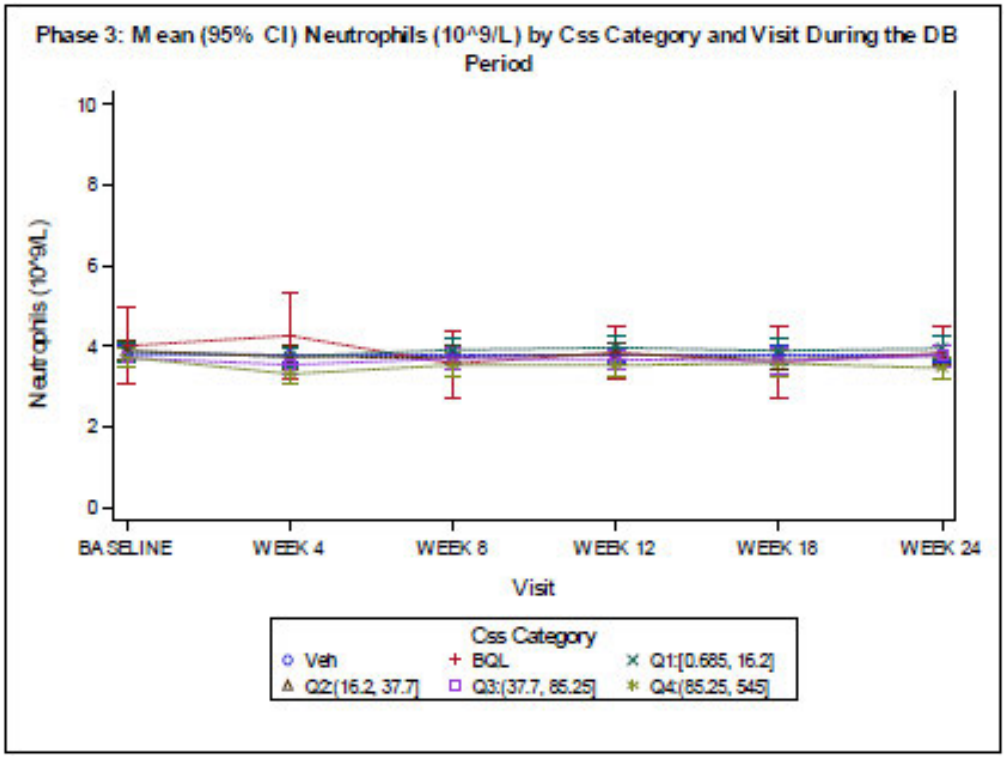


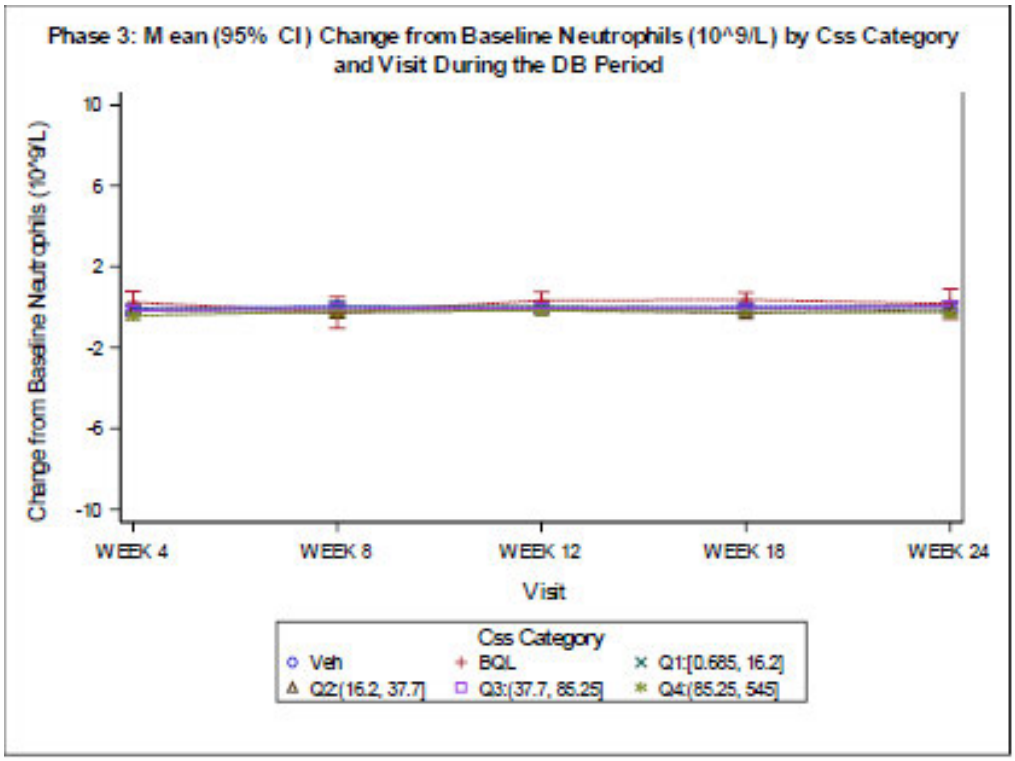

Phase 3: Mean (95% CI) Change from Baseline Hemoglobin (g/L) by Css Category and Visit During the DB Period
Change from Baseline Hemoglobin (g/L)
40
20
0
-20
-40
WEEK 4
WEEK 8
WEEK 12
WEEK 18
WEEK 24
Visit
Css Category
Veh
BQL
Q1:[0.685, 16.2]
Q2:(16.2, 37.7]
Q3:(37.7, 85.25]
Q4:(85.25, 545]

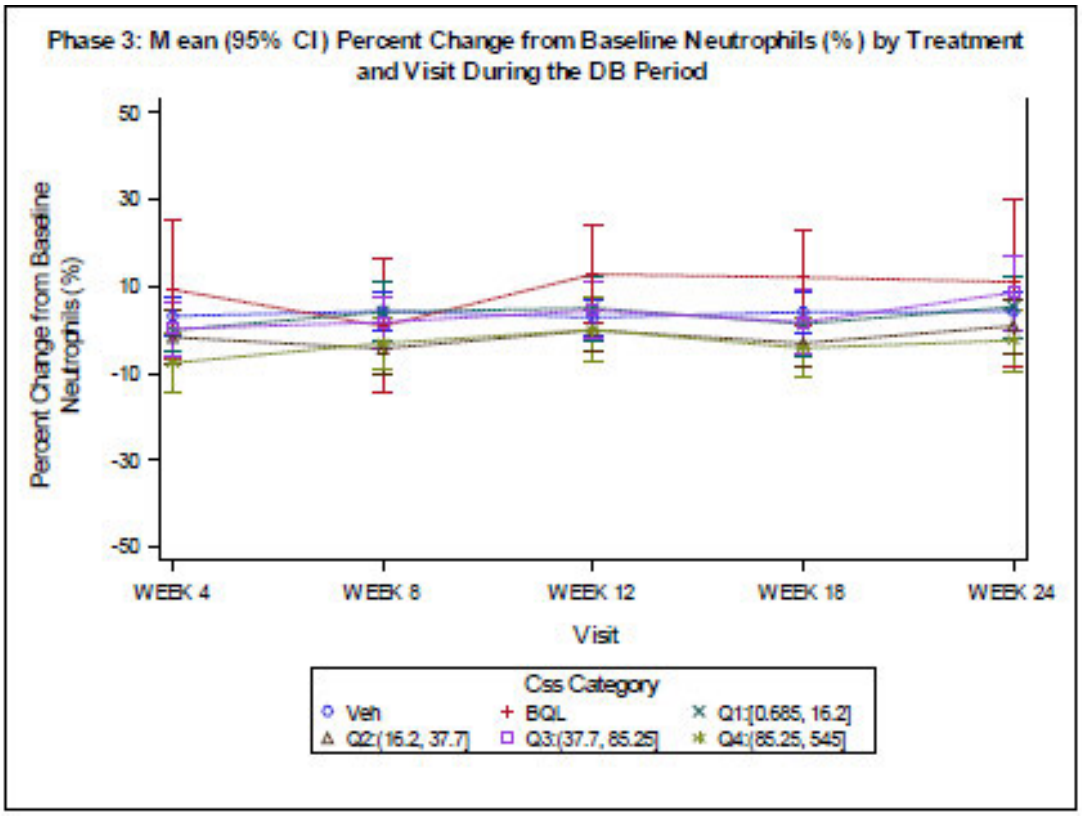

Phase 3: Mean (95% CI) Percent Change from Baseline Hemoglobin (%) by Treatment and Visit During the DB Period
Percent Change from Baseline Hemoglobin (%)
50
30
10
-10
-30
WEEK 4
WEEK 8
WEEK 12
WEEK 18
WEEK 24
Visit
Css Category
Veh
BQL
Q1:[0.685, 16.2]
Q2:(16.2, 37.7]
Q3:(37.7, 85.25]
Q4:(85.25, 545]

Source: Figures 22. Pharmaceutical Development Report DMB-21.53.1

Figure 32. Mean (95% CI) of Measured Values, Change-From-Baseline, and Percent Change-From-Baseline Absolute Neutrophil Count by Css Category and Visit During the Double-Blind, Vehicle-Controlled Period

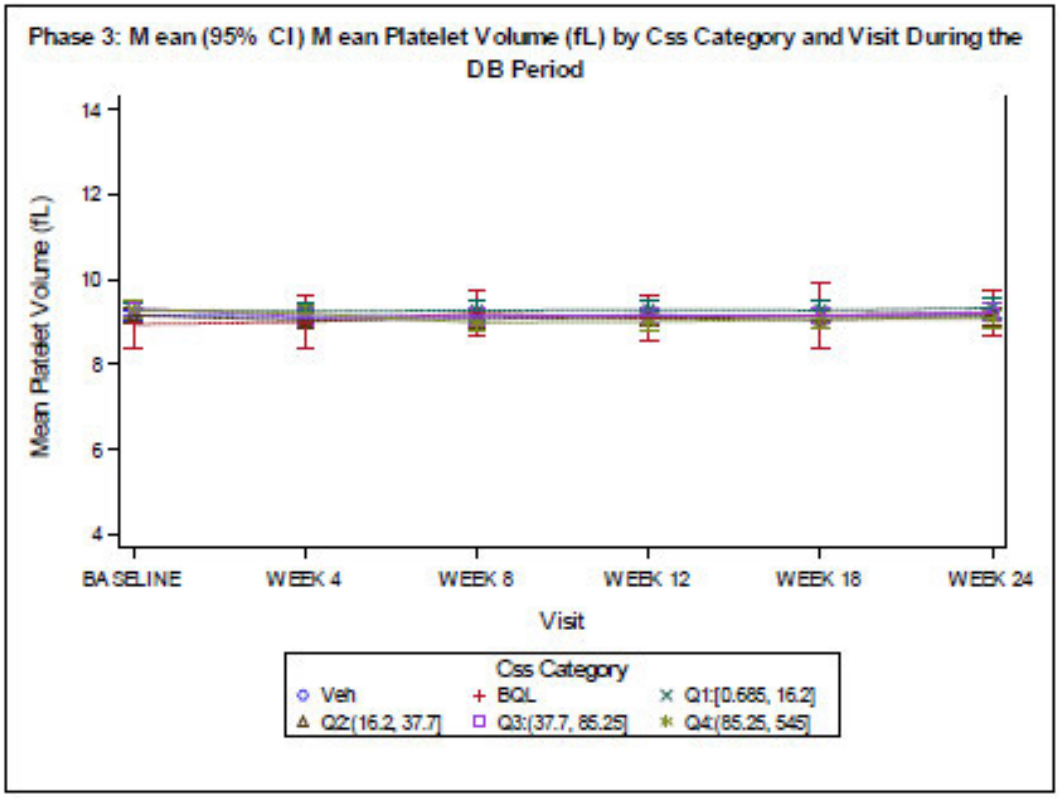


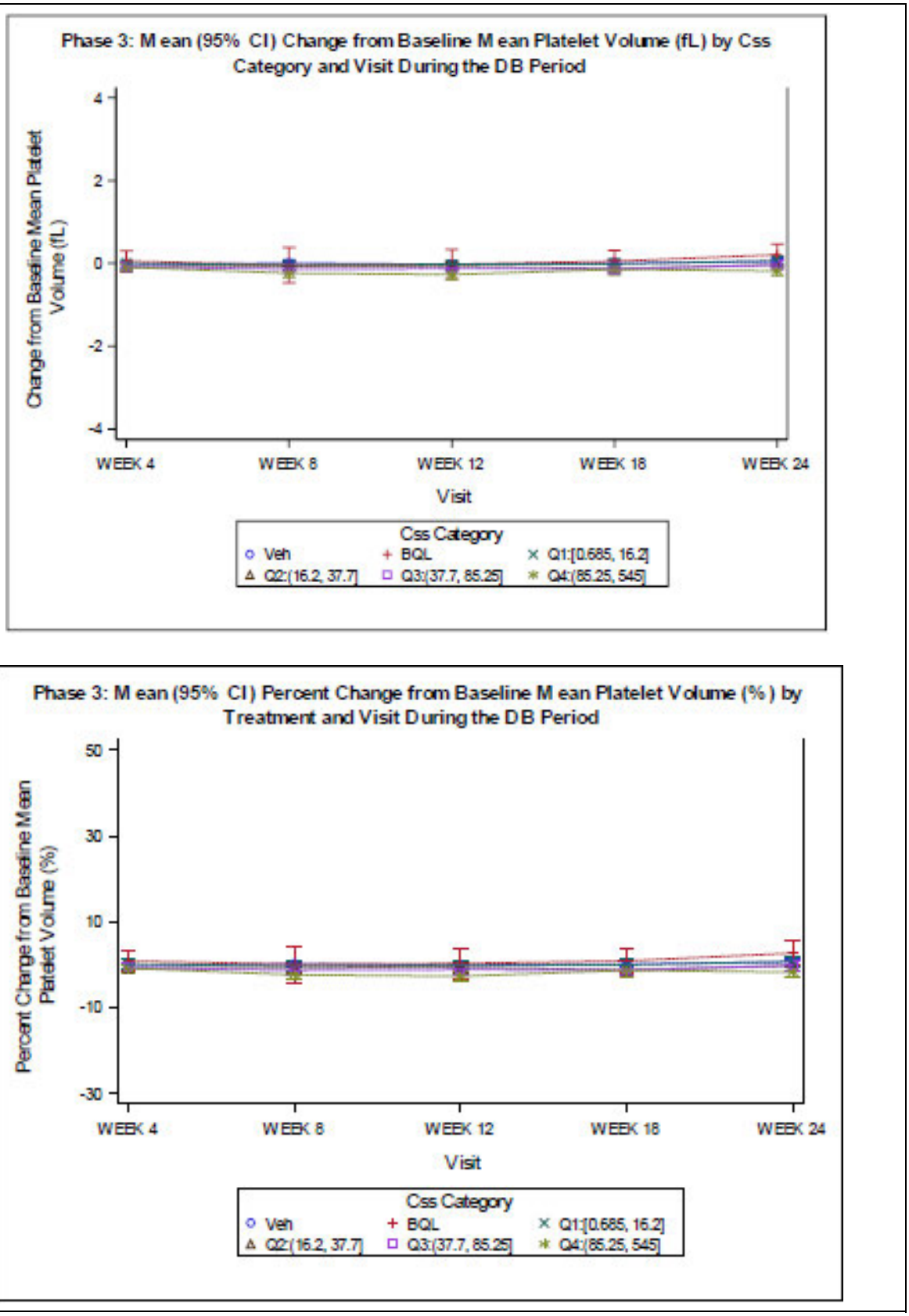




Source: Figures 24. Pharmaceutical Development Report DMB-21.53.1

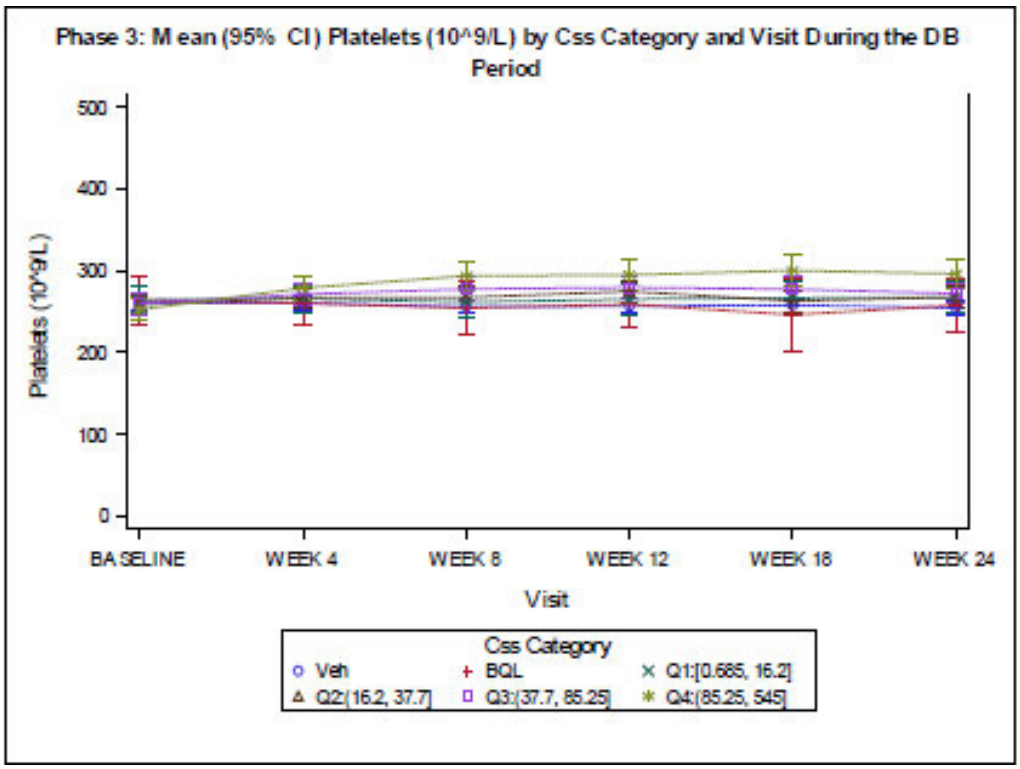
Figure 33. Mean (95% CI) of Measured Values, Change-From-Baseline, and Percent Change-From-Baseline Mean Platelet Volume by Css Category and Visit During the Double-Blind, Vehicle-Controlled Period

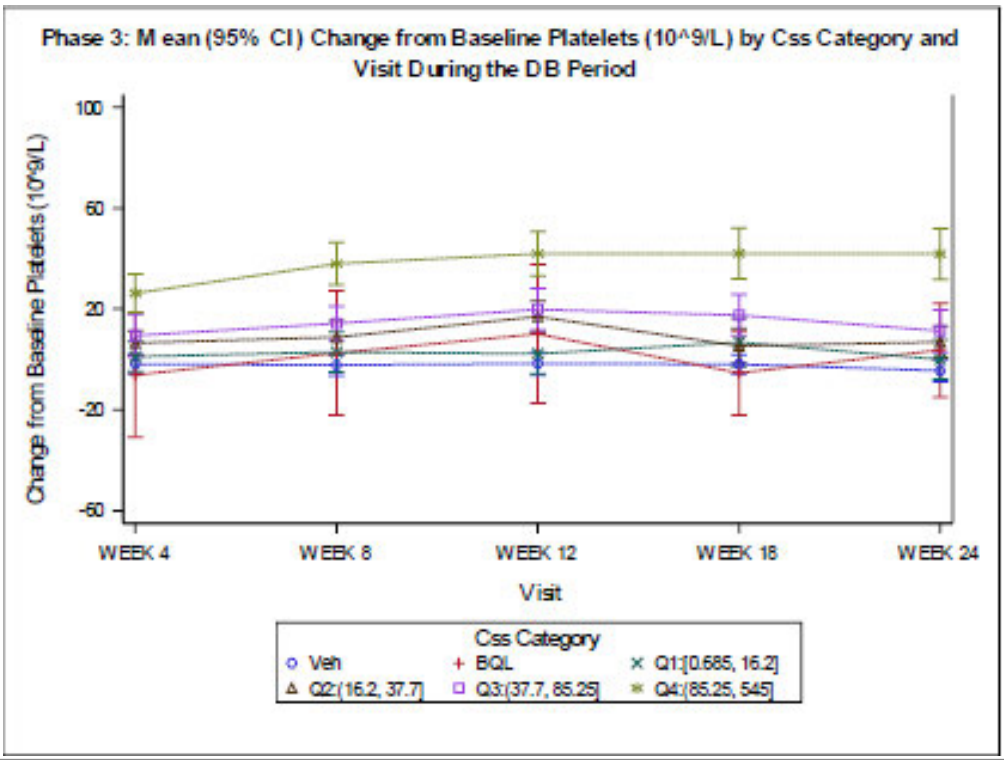


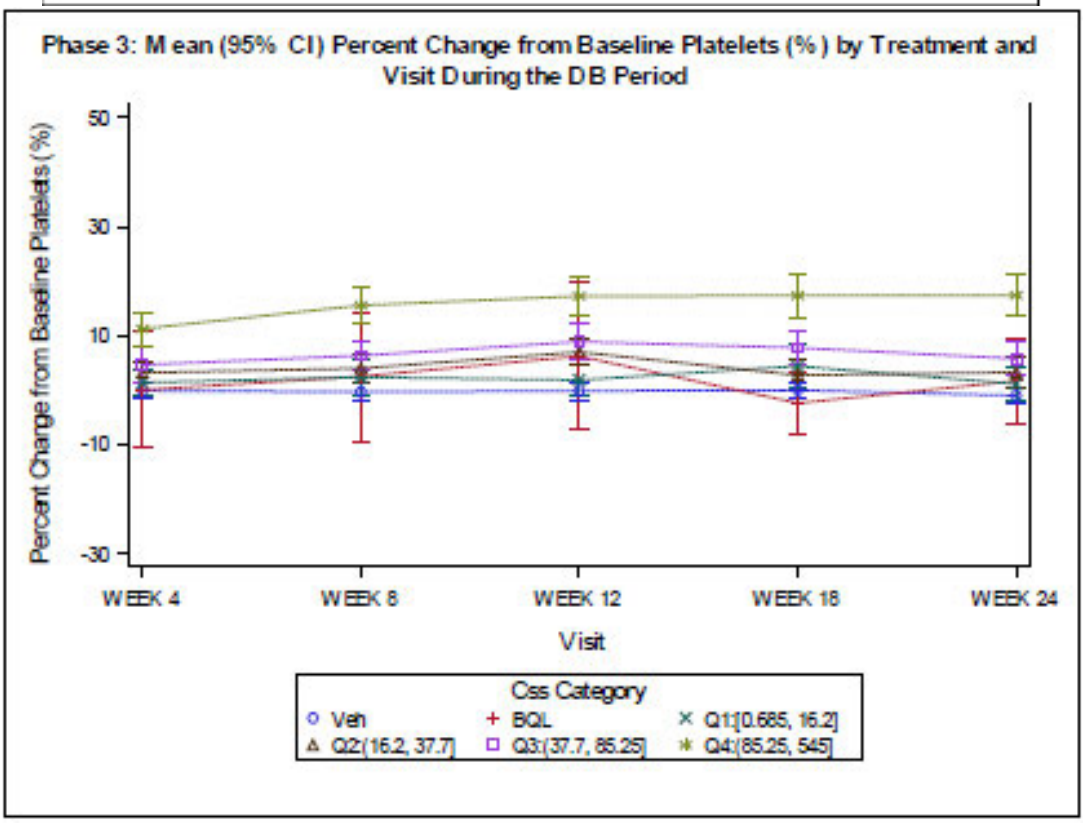

Phase 3: Mean (95% CI) Change from Baseline Mean Platelet Volume (fL) by Css Category and Visit During the DB Period
Change from Baseline Mean Platelet Volume (fL)
4
2
0
-2
-4
WEEK 4
WEEK 8
WEEK 12
WEEK 16
WEEK 24
Visit
Css Category
Veh
BQL
Q1:[0.685, 16.2]
Q2:(16.2, 37.7]
Q3:(37.7, 85.25]
Q4:(85.25, 545]
Phase 3: Mean (95% CI) Percent Change from Baseline Mean Platelet Volume (%) by Treatment and Visit During the DB Period
Percent Change from Baseline Mean Platelet Volume (%)
50
30
10
-10
-30
WEEK 4
WEEK 8
WEEK 12
WEEK 16
WEEK 24
Visit
Css Category
Veh
BQL
Q1:[0.685, 16.2]
Q2:(16.2, 37.7]
Q3:(37.7, 85.25]
Q4:(85.25, 545]

Source: Figures 26. Pharmaceutical Development Report DMB-21.53.1

Figure 34. Phase 3: Mean (95% CI) of Measured Values, Change-From-Baseline, and Percent Change-From-Baseline Platelet Count by Css Category and Visit During the Double-Blind, Vehicle-Controlled Period







Source: Figures 28. Pharmaceutical Development Report DMB-21.53.1

Reviewer's Comments:

1. *No clinically meaningful trends in hematology parameters, including hemoglobin level, ANC, and MPV, were observed in any of the 3 studies in vitiligo.*
2. *A discernible phenomenon in the hematologic parameters observed in these 3 vitiligo studies was a mild increase (~20 Gi/L or ~10%) in the mean platelet count by Week 12 in participants treated with ruxolitinib cream in the Phase 3 studies, which remained at a level higher than baseline through Week 24. Although such increases were treatment- and concentration-dependent, they were small in scale (< 20% mean increase from baseline at Week 12 among participants in the highest Css quartile [Q4; 85.25 to 545 nM]) in Phase 3 studies. The Mean platelet counts (250-325 Gi/L) remained well within the normal range at all visits during the double-blind, vehicle-controlled period.*

15.4. Additional Clinical Outcome Assessment Analyses

15.4.1. Anchor-Based Analyses: Clinical Meaningfulness of T-VASI50

For development programs utilizing COA-based endpoints, it is important to evaluate how well results of a COA-based endpoint correspond to a treatment benefit that is meaningful to patients. When a COA-based endpoint is proposed as a binary responder, a single responder threshold should be prespecified to define the endpoint. The clinically meaningful within-patient change threshold identified by anchor-based methods (if a single threshold can be clearly determined) is often used as the responder threshold. The anchor scale(s) are used as external criteria to define patients who have or have not experienced a meaningful change in their condition, with the change in COA score evaluated in these sets of patients.

The Applicant conducted anchor-based analyses using absolute change[‡‡‡‡] in the T-VASI score and determined that an improvement range between 1.69 and 3.88 is clinically meaningful to patients. However, given that T-VASI50 is defined based on percent change from baseline, FDA issued an information request (IR) on February 24, 2022 to request additional empirical cumulative distribution function (eCDF) and probability density function (PDF) plots based on percent change in T-VASI score. The Applicant provided a written response to the IR on March 4, 2022. PFSS replicated the Applicant's analyses based on percent change and conducted additional analyses to evaluate the clinically meaningful within-patient (percent) change threshold in the T-VASI score, i.e., whether the pre-specified ≥50% reduction in T-VASI score responder threshold is representative of a clinically meaningful improvement for patients with total body vitiligo at Week 24. Refer to Section 8.1.1 for more discussion on the T-VASI and the anchor scales (i.e., T-PhGVA and T-PaGIC-V) used in the anchor-based analyses.

[‡‡‡‡] The use of "absolute change" refers to the exact numerical difference between baseline and Week 24 T-VASI scores.

Based on findings from the quantitative anchor-based analyses, the Applicant's pre-specified ≥50% reduction in T-VASI score responder threshold is representative of a clinically meaningful improvement for patients with total body vitiligo at Week 24. Compared to the FDA-determined meaningful threshold range, the ≥50% improvement appears to be a more stringent threshold. In addition, findings from qualitative methods (refer to Section 15.4.2) appear to complement the quantitative results reported in this review. Refer to the full review by PFSS (dated July 6, 2022) for detailed discussion of the quantitative anchor-based analyses for the evaluation of clinically meaningfulness of the T-VASI50.

15.4.2. Evaluation of Exit Interviews

In addition to anchor-based analyses, the Applicant conducted exit interviews (n=36) to help inform the meaningful change threshold for the T-VASI at Week 24. These exit interviews were aligned with the study completion of Studies MVT-601-3101 and MVT-601-3102 and were administered via telephone. The eligibility criteria for the exit interviews were based on completion of the 24-week double-blind controlled period of Studies 306 and 307.[§§§§] Refer to the full COA review by the DCOA (dated June 23, 2022) for additional details regarding the methodology of these exit interviews.

The following parameters were queried in the exit interviews:

- Importance of improvement: Participants were asked to rate the importance of vitiligo improvement. This was assessed on a scale from 0-10, where 0 is "not at all important" and 10 is "extremely important."
- Treatment satisfaction: Participants were asked to rate their treatment satisfaction. This was assessed on a scale from 0 – 10, where 0 is "not at all satisfied" and 10 is "extremely satisfied." If participants provided a rating for a variety of body parts, the highest rating was taken as the 'total body' rating.
- Meaningful change: Participants were directly asked if their observed changes were meaningful and then asked to elaborate upon their responses. Responses were used to categorize whether observed changes in vitiligo were meaningful. "Treatment satisfaction" was also used to assess the meaningfulness of T-VASI reduction from baseline. Observable differences among subgroups were used to define a threshold for meaningful VASI reduction from baseline

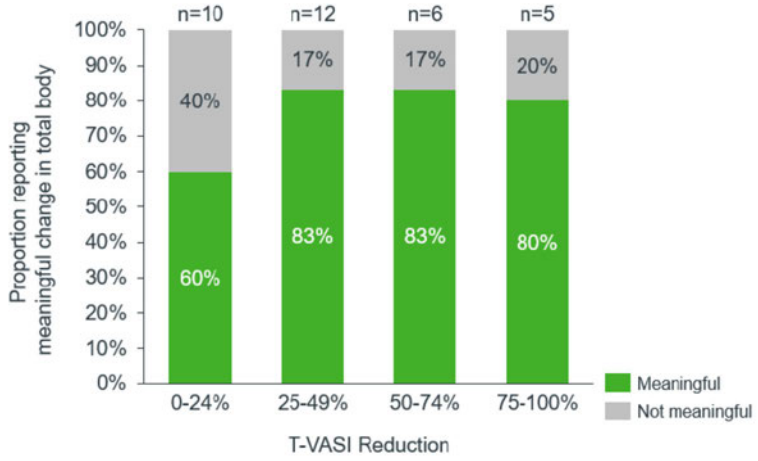
[§§§§] Inclusion criteria: • Patient has recently completed the 24-week double-blind treatment period of the ruxolitinib cream Phase III clinical trial INCB18424-306 or INCB18424-307, • Patient is available to be interviewed within approximately 10-15 weeks of completion of each respective trial time point (24- and 52-week time points), • Patient is willing and able to sign an informed consent addendum, • Patient has access to a telephone or cell phone, • Able to participate in a 60-minute interview to discuss impacts related to vitiligo and treatment experience in INCB 18424-306/307, and • Reside in any state in the United States or Canada
Exclusion Criterion: • history of either significant neurological events (such as major stroke) or a mental condition rendering him/her unable to understand the nature, scope, and possible consequences of the sub-study. [Source: Study report PIR-21-01-1 "Vitiligo Phase 3 Patient Exit Interviews in study INCB18424-306/307: Summary of Week 24 Findings" Section 4.1: *Study inclusion and exclusion criteria.]*

Participants were equally distributed across males and females with a mean age of 38.2 years (range: 12-80 years). The majority of participants had Fitzpatrick skin type III-VI (n= 22, 61.1%). The mean time since diagnosis was 13.8 years.

A summary of the findings is presented below:

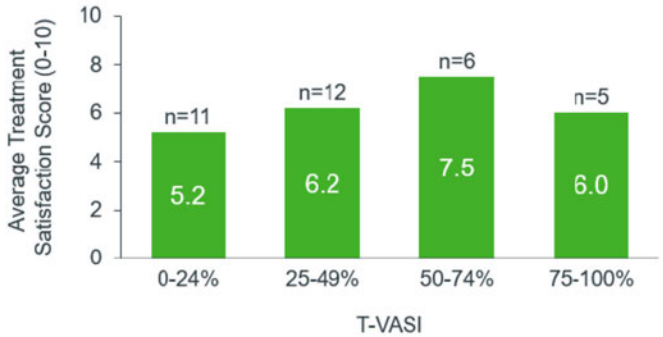
- 33 participants (91.7%) were asked about meaningful change
- 6/33 participants (18.2%) who achieved 50-74% reduction in T-VASI perceived their change as meaningful (Figure 35)
- 8/33 participants (24.2%) achieved 50% reduction (+/- 5) reduction in T-VASI; and of those all perceived their change as meaningful
- The highest average satisfaction rating was identified for participants who achieved 50-74% reduction in T-VASI (Figure 36)

Figure 35. Percent of Patients Reporting Meaningful Change in Total Body Vitiligo at Week 24



Source: Figure 8 of Vitiligo Phase 3 Patient Exit Interviews in study INCB18424-306/307: Summary of Week 24 Findings Report (internal report number PIR-21.01.1) dated June 23, 2021

Figure 36. Average total body treatment satisfaction by T-VASI reduction by sub-group



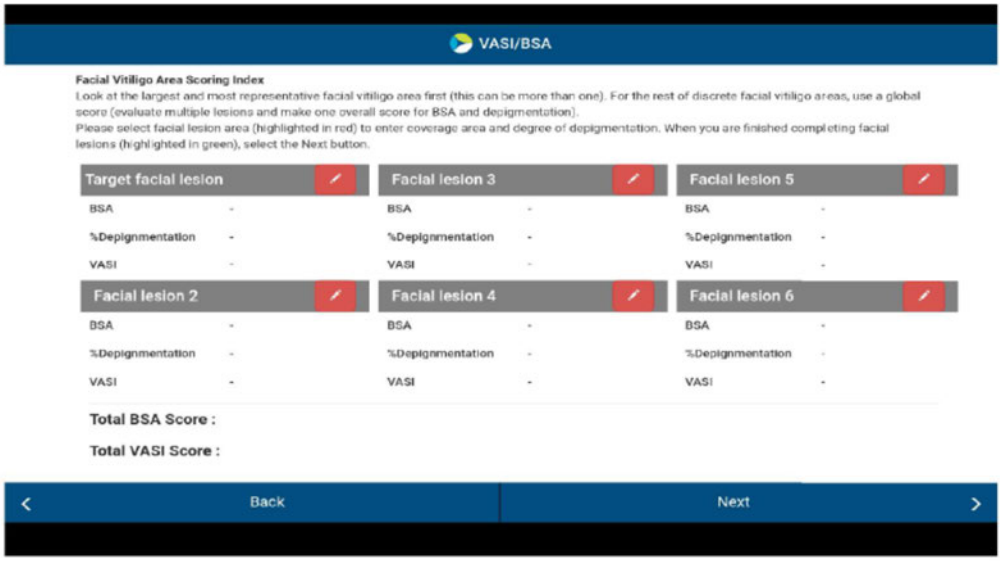
Satisfaction measured on a 0-10 scale, where 0 is “not at all satisfied” and 10 is “extremely satisfied.”

Source: Figure 6 of Vitiligo Phase 3 Patient Exit Interviews in study INCB18424-306/307: Summary of Week 24 Findings Report (internal report number PIR-21.01.1) dated June 23, 2021

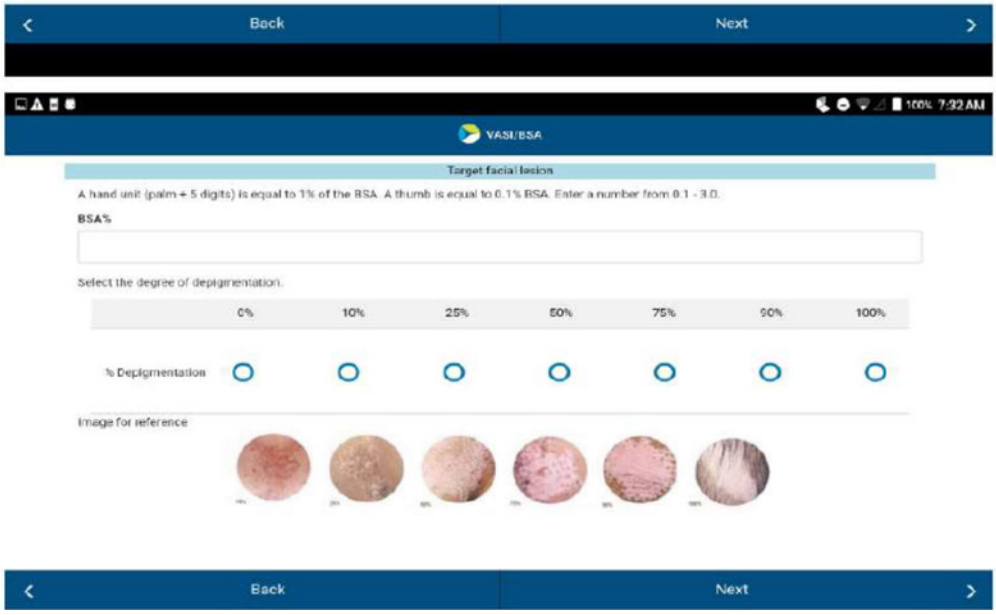
Overall, the qualitative methods appear to complement the findings from the anchor-based analyses providing support that the 50% threshold at Week 24 used by the Applicant is reasonable. Similar to the findings reported by PFSS, the threshold for meaningful within-patient score change in the T-VASI may be even less than 50% as participants also reported that a range of 25-49% was a meaningful change (reduction in T-VASI); participants were also satisfied with this range.

15.5. Clinical Outcome Assessment Instruments

Figure 37. F-VASI/BSA

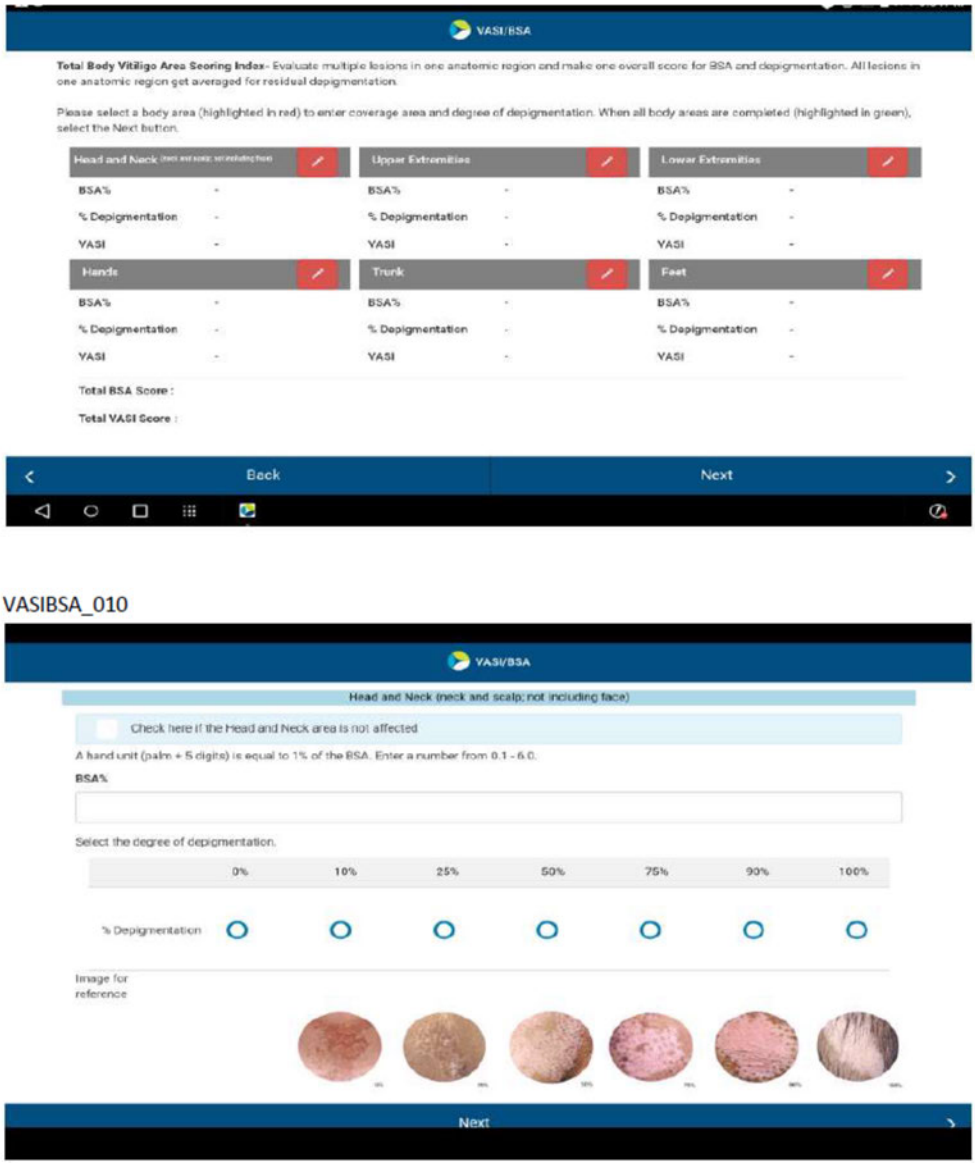


VASIBSA_003



Source: Appendix C of Applicant's Response to 24 February 2022 FDA Request for Clinical Information

Figure 38. T-VASI/BSA



VASIBSA_010

Source: Appendix C of Applicant's Response to 24 February 2022 FDA Request for Clinical Information

Figure 39. F-PhGVA

Facial Physician's Global Vitiligo Assessment Scale

Score	Severity	Description
0	Clear	No signs of vitiligo or complete/near complete repigmentation
1	Almost Clear	Mostly pigmented areas with small depigmented or difficult to repigment areas (eg, philtrum, nares, corners of eyes, perioral skin)
2	Mild Disease	Modest areas of depigmentation (not more than half of facial skin) with approximately 50% pigmentation within vitiligo areas or significant perifollicular pattern present
3	Moderate Disease	Large areas of depigmented vitiligo areas (more than half of facial skin); significant depigmentation within vitiligo areas
4	Severe Disease	Extensive areas of vitiligo to complete depigmentation on face

Source: Appendix D of Applicant's Response to 24 February 2022 FDA Request for Clinical Information

Figure 40. T-PhGVA

Total Body Physician's Global Vitiligo Assessment Scale

Score	Severity	Description
0	Clear	No signs of vitiligo or complete/near complete repigmentation
1	Almost Clear	Mostly pigmented areas with small depigmented or difficult to repigment areas (eg, hands, feet, philtrum, nares, corners of eyes, perioral skin)
2	Mild Disease	Modest areas of depigmentation with approximately 50% pigmentation within vitiligo areas or significant perifollicular pattern present
3	Moderate Disease	Large areas of depigmented vitiligo areas; significant depigmentation within vitiligo areas
4	Severe Disease	Extensive areas of vitiligo with complete depigmentation

Source: Appendix D of Applicant's Response to 24 February 2022 FDA Request for Clinical Information

Figure 41. VNS

Vitiligo Noticeability Scale

Compared with before treatment, how noticeable is the vitiligo now?
☐(1) More noticeable
☐(2) As noticeable
☐(3) Slightly less noticeable
☐(4) A lot less noticeable
☐(5) No longer noticeable

Source: Appendix D of Applicant's Response to 24 February 2022 FDA Request for Clinical Information

Figure 42. F-PaGIC-V

Patient Global Impression of Change-Vitiligo (Facial)

Since the start of the treatment you've received in this study, your vitiligo on your face treated with the study drug is:

- ☐ (1) Very much improved
- ☐ (2) Much improved
- ☐ (3) Minimally improved
- ☐ (4) No change
- ☐ (5) Minimally worse
- ☐ (6) Much worse
- ☐ (7) Very much worse

Source: Appendix D of Applicant's Response to 24 February 2022 FDA Request for Clinical Information

Figure 43. T-PaGIC-V

Patient Global Impression of Change-Vitiligo (Total Body)

Since the start of the treatment you've received in this study, your vitiligo on your total body treated with the study drug is:

- ☐ (1) Very much improved
- ☐ (2) Much improved
- ☐ (3) Minimally improved
- ☐ (4) No change
- ☐ (5) Minimally worse
- ☐ (6) Much worse
- ☐ (7) Very much worse

Source: Appendix D of Applicant's Response to 24 February 2022 FDA Request for Clinical Information

---

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

/s/

HON SUM KO
07/18/2022 12:53:59 PM

DA ZHANG
07/18/2022 12:55:19 PM

CHINMAY SHUKLA
07/18/2022 01:04:39 PM

YOUWEI N BI
07/18/2022 01:29:30 PM

WEIMENG WANG
07/18/2022 01:33:24 PM

LILI GARRARD
07/18/2022 01:42:33 PM

WEI TAN
07/18/2022 01:54:01 PM

KATHLEEN S FRITSCH
07/18/2022 01:56:38 PM

MOHAMED A ALOSH
07/18/2022 03:06:21 PM

SELENA R DANIELS
07/18/2022 03:08:33 PM

DAVID S REASNER
07/18/2022 08:15:36 PM

BRENDA CARR
07/18/2022 08:17:27 PM

SHARI L TARGUM
07/18/2022 08:19:29 PM

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

NEW DRUG APPLICATION

NDA #:	NDA 215309/S-001
Drug Name:	Opzelura (ruxolitinib) Cream, 1.5%
Indication(s):	Nonsegmental Vitiligo in adult and pediatric patients 12 years of age and older
Applicant:	Incyte Corporation
Measure(s):	Total Body Vitiligo Area Scoring Index (T-VASI)
Clinical Outcome Assessment (COA) Type:	Clinician-reported Outcome (ClinRO)
Date(s):	Date Submitted: October 18, 2021 PDUFA Due Date: July 9, 2022 Review Completion Date: July 6, 2022
Review Priority:	Priority
Biometrics Division:	DBIII
Patient-Focused Statistical Support (PFSS) Team:	Weimeng Wang, MA, MEd, Lili Garrard, PhD (Team Leader)
Statistical Team:	Kathleen Fritsch, PhD, Mohamed Alosh, PhD (Team Leader)
Division of Clinical Outcome Assessment (DCOA):	Mira Patel, PhD, Selena Daniels, PharmD, PhD (Team Leader), David Reasner, PhD (Division Director)
Medical Division:	Division of Dermatology and Dentistry (DDD)
Clinical Team:	Brenda Carr, MD, Hon Sum Ko, MD (Team Leader)
Project Manager:	Matthew White

Keywords: NDA Review, Clinician-reported Outcome (ClinRO), Meaningful Change

Contents

Tables

Figures

1 Background

On October 18, 2021, the Applicant (Incyte Corporation) submitted a sNDA for ruxolitinib 1.5% cream for the treatment of nonsegmental vitiligo in adult and pediatric patients who are 12 years of age and older. The Applicant submitted data from two identical, randomized, double-blind, vehicle-controlled phase 3 studies (INCB 18424-306 and INCB 18424-307; hereafter Study 306 and Study 307) to support the determination of safety and efficacy of ruxolitinib 1.5% cream. In both Study 306 and Study 307, the severity of vitiligo was assessed using the Face Vitiligo Area Scoring Index (F-VASI) and the Total Body Vitiligo Area Scoring Index (T-VASI). The primary efficacy endpoint is the proportion of patients achieving F-VASI75 at Week 24 (≥75% reduction from baseline to Week 24). The proportion of patients achieving T-VASI50 at Week 24 (≥50% reduction from baseline to Week 24) is included as one of the key secondary endpoints.

Of note, for development programs utilizing COA-based endpoints, it is important to evaluate how well results of a COA-based endpoint correspond to a treatment benefit that is meaningful to patients. When a COA-based endpoint is proposed as a binary responder, a single responder threshold should be prespecified to define the endpoint. The clinically meaningful within-patient change threshold identified by anchor-based methods (if a single threshold can be clearly determined) is often used as the responder threshold. The anchor scale(s) are used as external criteria to define patients who have or have not experienced a meaningful change in their condition, with the change in COA score evaluated in these sets of patients.

This statistical review is provided in response to a PFSS consult received from the Clinical and DCOA teams regarding the clinical meaningfulness of the T-VASI50 key secondary endpoint in Studies 306 and 307. According to the Applicant's Psychometrics Analysis Report submitted as part of the sNDA, the Applicant's anchor-based analyses using absolute change[1] in the T-VASI score determined that an improvement range between 1.69 and 3.88 is clinically meaningful to patients. However, given that T-VASI50 is defined based on percent change from baseline, FDA issued an information request (IR) on February 24, 2022 to request additional empirical cumulative distribution function (eCDF) and probability density function (PDF) plots based on percent change in T-VASI. The Applicant provided a written response to the IR on March 4, 2022. PFSS reviewed the Applicant's anchor-based analyses based on absolute change and the response to the IR. We replicated the Applicant's analyses based on percent change and conducted additional analyses to evaluate whether ≥50% reduction in the T-VASI score responder threshold is representative of a clinically meaningful improvement for patients with total body vitiligo at Week 24. Please refer to the multidisciplinary review and evaluation document for detailed discussion on the study designs and efficacy review issues. Please refer to the DCOA review for detailed discussion on the F-VASI, T-VASI, and the anchor scales used in the anchor-based analyses.

[1] The use of "absolute change" in this document refers to the exact numerical difference between baseline and Week 24 T-VASI scores.

2 Clinical Meaningfulness of T-VASI50 in Studies 306 and 307

2.1 Anchor Assessment

Two anchor scales were used in the Applicant's anchor-based analyses. The DCOA review recommends the use of both a current state (non-comparative) patient global impression of severity scale and a patient global impression of change scale as external anchors. Studies 306 and 307 included a clinician impression of severity scale (see Section 2.1.1) and a patient global impression of change scale (see Section 2.1.2), but not a current state patient global impression of severity scale. However, based on DCOA's assessment from a qualitative perspective, the two anchor scales used by the Applicant "appear to be adequate external anchors for the corresponding COA endpoints". Please refer to the DCOA review for more discussion on the anchors.

2.1.1 Total Body Physician Global Vitiligo Assessment (T-PhGVA)

The T-PhGVA is a single-item ClinRO assessing the severity of a patient's total body vitiligo using a 5-category response scale, as shown in Table 1 below. The T-PhGVA was assessed at day 1, Week 12, Week 24, Week 40, and Week 52.

Table 1. Total Body Physician Global Vitiligo Assessment (T-PhGVA) Item and Scoring

Question	Response option	Score
How severe is the vitiligo on the subject's total body?	Clear: no signs of vitiligo or complete/near complete repigmentation	0
	Almost clear: mostly pigmented areas with small depigmented or difficult to repigment areas (e.g., hands, feet, philtrum, nares, corners of eyes, perioral skin)	1
	Mild Disease: modest areas of depigmentation with approximately 50% pigmentation within vitiligo areas or significant perifollicular pattern present	2
	Moderate Disease: large areas of depigmented vitiligo areas; significant depigmentation within vitiligo areas	3
	Severe Disease: extensive areas of vitiligo with complete depigmentation	4

Source: Reviewer's table, adapted from page 50/443 of the Appendix C INCB 18424-306/307 COA screenshots in the Applicant's IR response dated March 4, 2022.

2.1.2 Total Body Patient Global Impression of Change-Vitiligo (T-PaGIC-V)

The T-PaGIC-V is a single-item patient-reported outcome (PRO) assessing a patient's global impression of change in his/her total body vitiligo "since the start of the treatment you've received in this study" using a 7-category response scale, as shown in Table 2 below. The T-PaGIC-V was assessed on Week 12, Week 24, Week 40, and Week 52.

Table 2. Total Body Patient Global Impression of Change-Vitiligo (T-PaGIC-V) Item and Scoring

Question	Response option	Score
Since the start of the treatment that you received in this study, the vitiligo on the areas treated with the study drug is	Very much improved	1
	Much improved	2
	Minimally improved	3
	No change	4
	Minimally worse	5
	Much improved	6
	Very much improved	7

Source: Reviewer's table, adapted from page 33/443 of the Appendix C INCB 18424-306/307 COA screenshots in the Applicant's IR response dated March 4, 2022.

2.1.3 Correlations Between Percent Change from Baseline in T-VASI Score and Anchors

As part of the sensitivity to change (a longitudinal measurement property of a COA) analyses, the Applicant reported the Spearman correlation between the absolute change from baseline in T-VASI to Week 24 and the two anchors. Because T-VASI50 is defined using percent change, PFSS conducted Spearman correlation analyses to investigate the strength and magnitude of the relationship between percent change from baseline to Week 24 in T-VASI and the T-PhGVA and the T-PaGIC-V (Table 3). T-PaGIC-V at Week 24 correlates higher with the percent change from baseline to Week 24 in the T-VASI score. Of note, the overall relatively modest correlation results were expected as the recall period of the anchors ("previous 4 weeks" for T-PhGVA and "since taking study medication" for T-PaGIC-V) differed from the assessment time frame of the T-VASI endpoint (momentary). Please refer to the DCOA review for more discussion on the measurement properties of the T-VASI.

Table 3. Spearman Correlations Between Percent Change From Baseline to Week 24 in T-VASI Score and Anchor Scores

Anchor Scores	**Percent Change from Baseline to Week 24 in T-VASI Score**	
	Study 306 (N=330)	**Study 307 (N=344)**
Change from Baseline to Week 24 in T-PhGVA	0.38	0.35
T-PaGIC-V at Week 24	0.50	0.50

Source: PFSS reviewer generated table.
Abbreviations: T-PhGVA = Total Body Physician Global Vitiligo Assessment, T-PaGIV-V = Total Body Patient Global Impression of Change-Vitiligo, T-VASI = Total Body Vitiligo Area Scoring Index

2.2 Anchor-Based Analyses

Anchor-based methods supplemented with eCDF curves were used to assess whether the pre-specified ≥50% reduction in T-VASI score is representative of a clinically meaningful within-

patient improvement. The anchor-based analyses, that leveraged both patients' and clinicians' perspectives, were conducted separately using pooled data (across arms) in Studies 306 and 307 and by both the Applicant and PFSS.

2.2.1 Distribution of Baseline and Percent Change from Baseline to Week 24 in T-VASI Score

In order to understand the percent change in T-VASI score that is considered meaningful to patients, PFSS examined the distribution of baseline T-VASI score and the percent change from baseline to Week 24 in T-VASI score by treatment arm and by study (Table 4). The T-VASI score has a theoretical range of 0-100 (refer to the scoring algorithm in the DCOA review). T-VASI score at baseline ranges from 3.01 to 10 (treatment: 3.01 to 10; vehicle: 3.06 to 10) and 2.65 to 10.00 (treatment: 2.65 to 10; vehicle: 3.10 to 10) for patients in Studies 306 and 307, respectively. Both mean and median T-VASI score at baseline were around 6 for Study 306 and around 7 for Study 307. The mean and median percent change from baseline to Week 24 in T-VASI are -28.19% and -24.02% and -9.92% and -7.61% for patients in the treatment and vehicle, respectively, in Study 306; and -30.50% and -26.07% and -11.71% and -2.86% for patients in the treatment and vehicle arm, respectively, for Study 307.

Table 4. Distribution of Baseline T-VASI Score and Percent Change From Baseline to Week 24 in T-VASI Score by Study and Treatment Arm

	Statistics	Study 306 (N=330)		Study 307 (N=344)	
		1.5% BID	Vehicle BID	1.5% BID	Vehicle BID
Baseline	Min / Max	3.01 / 10.00	3.06 / 10.00	2.65 / 10.00	3.10 / 10.00
	Median	6.38	6.25	7.28	7.30
	[IQR]	[4.72;8.20]	[4.83;7.90]	[5.00;8.64]	[4.83;9.07]
	Mean (SD)	6.49 (2.02)	6.42 (1.92)	6.83 (2.06)	7.02 (2.20)
	N	221	109	229	115
	Missing	0	0	0	0
Percent (%) Change from Baseline	Min / Max	-91.87 / 62.55	-89.32 / 132.04	-94.89 / 72.27	-92.63 / 50.11
	Median	-24.02	-7.61	-26.07	-2.86
	[IQR]	[-46.78; -7.29]	[-21.89;0.66]	[-51.99; -5.63]	[-21.43;0]
	Mean (SD)	-28.19 (26.25)	-9.92 (26.35)	-30.50 (30.84)	-11.71 (28.01)
	N	195	90	206	101
	MISSING	26	19	23	14

Source: PFSS reviewer generated table.
Abbreviations: IQR =interquartile range, SD = standard deviation, N =sample size, Min = minimum, Max = maximum

2.2.2 Target Anchor Change Category

Ideally, a target anchor change category should be pre-specified by the Applicant and agreed upon by FDA during the IND phase. However, the Applicant did not pre-specify a target change category in the T-PhGVA nor the T-PaGIC-V. Based on discussions among the DCOA and PFSS teams, a 1-category improvement on the 5-category T-PhGVA and "much improved" on the T-PaGIC-V were determined to be reasonable to support further anchor-based meaningful change analyses. Refer to the sections below for more discussion on PFSS's assessment.

Total Body Physician Global Vitiligo Assessment (T-PhGVA)

What patients consider to be clinically meaningful improvement may be impacted by their baseline symptom severity. Patients' baseline symptom severity should be considered when determining clinically meaningful within-patient improvement thresholds. Because Studies 306 and 307 did not include a PRO measure that directly assesses symptom severity from the patients' perspectives, the T-PhGVA (based on clinician reporting) was used as a way to classify a patient's total body vitiligo severity. A 1-category improvement on the 5-category T-PhGVA could occur in the following ways:

- Change from "Severe disease" to "Moderate disease"
- Change from "Moderate disease" to "Mild disease"
- Change from "Mild disease" to "Almost clear"
- Change from "Almost clear" to "Clear"

During internal discussion with the Statistical and Clinical review teams, there was concern that a 1-category improvement may not be adequate to represent a meaningful improvement for patients and a 2-category improvement may be needed. PFSS examined the distribution of change patterns in T-PhGVA between baseline and Week 24 for Studies 306 (Table 5) and 307 (Table 6), using data pooled across arms. Both studies showed similar change patterns in T-PhGVA. The majority of patients were rated by their clinician as having mild to moderate disease severity at baseline; and the majority of these patients remained no change at Week 24, followed by a 1-category improvement for patients who started with "Moderate disease" at baseline and a 1-category worsening for patients who started with "Mild disease" at baseline. Very few patients (6 out of 281 patients and 8 out of 300 patients in Studies 306 and 307, respectively) were rated by their clinician as experiencing a 2-category improvement at Week 24. While post-hoc analyses are not recommended to determine the target anchor change category, to facilitate review of the Applicant's anchor-based analyses, DCOA and PFSS teams determined that a 1-category improvement on the T-PhGVA was reasonable for the evaluation of meaningful change in total body vitiligo.

Table 5. Category Change (n (%)) in T-PhGVA From Baseline to Week 24 by Baseline T-PhGVA (Study 306)

	Change from Baseline to Week 24 in T-PhGVA					
Baseline T-PhGVA	**Improved 3 Categories (N=0)**	**Improved 2 Categories (N=6)**	**Improved 1 Category (N=64)**	**No Change (N=198)**	**Worsened 1 Category (N=12)**	**Worsened 2 Category (N=1)**
Clear (N=1)	0	0	0	0	0	1 (100%)
Almost clear (N=6)	0	0	0	6 (100%)	0	0
Mild disease (N=103)	0	0	6 (5.83%)	85 (82.52%)	12 (11.65%)	0
Moderate disease (N=157)	0	4 (2.55%)	47 (29.94%)	106 (67.52%)	0	0
Severe disease (N=14)	0	2 (14.29%)	11 (78.57%)	1 (7.14%)	0	0
Missing (N=49)	-	-	-	-	-	-

Source: PFSS reviewer generated table.
Abbreviation: T-PhGVA = Total Physician Global Vitiligo Assessment

Table 6. Category Change (n (%)) in T-PhGVA From Baseline to Week 24 by Baseline T-PhGVA (Study 307)

	Change from Baseline in T-PhGVA at Week 24					
T-PhGVA at Baseline	**Improved 3 Categories (N=2)**	**Improved 2 Categories (N=8)**	**Improved 1 Category (N=82)**	**No Change (N=186)**	**Worsened 1 Category (N=22)**	**Worsened 2 Category (N=0)**
Clear (N=0)	0	0	0	0	0	0
Almost clear (N=8)	0	0	0	4 (50.00%)	4 (50.00%)	0
Mild disease (N=87)	0	0	5 (5.75%)	66 (75.86%)	16 (18.39%)	0
Moderate disease (N=196)	1 (0.51%)	7 (3.57%)	72 (36.73%)	114 (58.16%)	2 (1.02%)	0
Severe disease (N=9)	1 (11.11%)	1 (11.11%)	5 (55.56%)	2 (22.22%)	0	0
Missing (N=44)	-		-	-	-	-

Source: PFSS reviewer generated table.
Abbreviation: T-PhGVA = Total Physician Global Vitiligo Assessment

Total Body Patient Global Impression of Change-Vitiligo (T-PaGIC-V)

DCOA and PFSS teams consider "Much improved" on the T-PaGIC-V as an appropriate target anchor category. To support this decision, PFSS examined the crosstabulations of patient-reported T-PaGIC-V at Week 24 by the clinician-reported T-PhGVA at baseline for Studies 306 (Table 7) and 307 (Table 8), using data pooled across arms. Both studies showed similar results that the majority of patients self-reported on the T-PaGIC-V as "Minimally improved" followed by "No Change" at Week 24. When taking into account the baseline T-PhGVA score, patients' impression of change at Week 24 measured by the T-PaGIC-V varied among patients with different baseline disease severity. For patients who were rated by their clinician as "Mild disease" at baseline, most patients reported "Minimally improved" (42.31%) followed by "No change" (28.85%) in Study 306; and equal proportion of patients reported "Minimally improved" (35.96%) and "No change" (35.96%) in Study 307. For patients who were rated by their clinician as "Moderate disease" at baseline, most patients reported "Minimally improved" (48.73%) followed by "Much improved" (21.52%) in Study 306; and "Minimally improved" (41.50%) followed by "No change" (28.50%) in Study 307. For the few patients who were rated by their clinician as "Severe disease" at baseline (21 patients and 10 patients in Studies 306 and 307, respectively), most patients reported "Minimally improved" (57.14%) followed by "Much improved" (21.43%) in Study 306; and "No change" (44.44%) followed by "Very much improved" (33.33%) in Study 307.

Overall, it appears that a minimal improvement on the T-PaGIC represented most patients' impression of change in total body vitiligo at Week 24, in both Studies 306 and 307. However, DCOA and PFSS teams concluded that a more stringent target anchor category of "Much improved" on the T-PaGIC would be needed to demonstrate that the treatment benefit is meaningful to patients.

Table 7. Crosstabulation (n (%)) of T-PaGIC-V at Week 24 By Baseline T-PhGVA (Study 306)

Baseline T-PhGVA	T-PaGIC-V at Week 24							
	Very much improved (N=3)	Much improved (N=59)	Minimally improved (N=132)	No change (N=67)	Minimally worse (N=18)	Much worse (N=4)	Very much worse (N=2)	Missing
Clear (N=1)	0	0	0	1 (100.00%)	0	0	0	0
Almost clear (N=6)	0	1 (16.67%)	3 (50.00%)	2 (33.33%)	0	0	0	0
Mild disease (N=122)	1 (0.96%)	21 (20.19%)	44 (42.31%)	30 (28.85%)	8 (7.69%)	0	0	18
Moderate disease (N=178)	2 (1.27%)	34 (21.52%)	77 (48.73%)	31 (19.62%)	9 (5.70%)	4 (2.53%)	1 (0.63%)	20
Severe disease (N=21)	0	3 (21.43%)	8 (57.14%)	1 (7.14%)	1 (7.14%)	0	1 (7.14%)	7
Missing (N=2)	0	0	0	2	0	0	0	0

Source: PFSS reviewer generated table.
Abbreviation: T-PaGIC-V = Total Patient Global Impression of Change-Vitiligo

Table 8. Crosstabulation (n (%)) of T-PaGIC-V at Week 24 By Baseline T-PhGVA (Study 307)

T-PhGVA at baseline	T-PaGIC-V at Week 24							
	Very much improved (N=15)	Much improved (N=52)	Minimally improved (N=122)	No change (N=95)	Minimally worse (N=18)	Much worse (N=3)	Very much worse (N=3)	Missing
Clear (N=0)	0	0	0	0	0	0	0	0
Almost clear (N=8)	1 (12.50%)	0	5 (62.50%)	1 (12.50%)	1 (12.50%)	0	0	0
Mild disease (N=101)	4 (4.49%)	14 (15.73%)	32 (35.96%)	32 (35.96%)	4 (4.49%)	3 (3.37%)	0	12
Moderate disease (N=232)	7 (3.50%)	37 (18.50%)	83 (41.50%)	57 (28.50%)	13 (6.50%)	0	3 (1.50%)	23
Severe disease (N=10)	3 (33.33%)	1 (11.11%)	1 (11.11%)	4 (44.44%)	0	0	0	1
Missing (N=2)	0	0	1	1	0	0	0	0

Source: PFSS reviewer generated table.
Abbreviation: T-PaGIC-V = Total Patient Global Impression of Change-Vitiligo

2.3 Results

2.3.1 Results Using T-PhGVA as the Anchor

The eCDF plots of percent change from baseline to Week 24 in T-VASI score by T-PhGVA category of change from baseline for Studies 306 and 307 are shown in Figure 1 and Figure 2, respectively. In general, the eCDF plots of both studies show clear and consistent separation between "1-category improvement" and "no change" curves. For Study 306, the median percent change in the T-VASI score for patients who were rated as experiencing a 1-category improvement on T-PhGVA is -34.20%. In order to minimize misclassifying patients who were rated as not experiencing a meaningful improvement (e.g., no change on the T-PhGVA) as experiencing a meaningful improvement, a threshold of at least 37.60% improvement should be considered. For Study 307, the median percent change in the T-VASI score for patients who were rated as experiencing a 1-category improvement on T-PhGVA is -41.30%. Furthermore, to minimize misclassifying patients who were rated as not experiencing a meaningful improvement as experiencing a meaningful improvement, a threshold of at least 44.33% improvement should be considered.

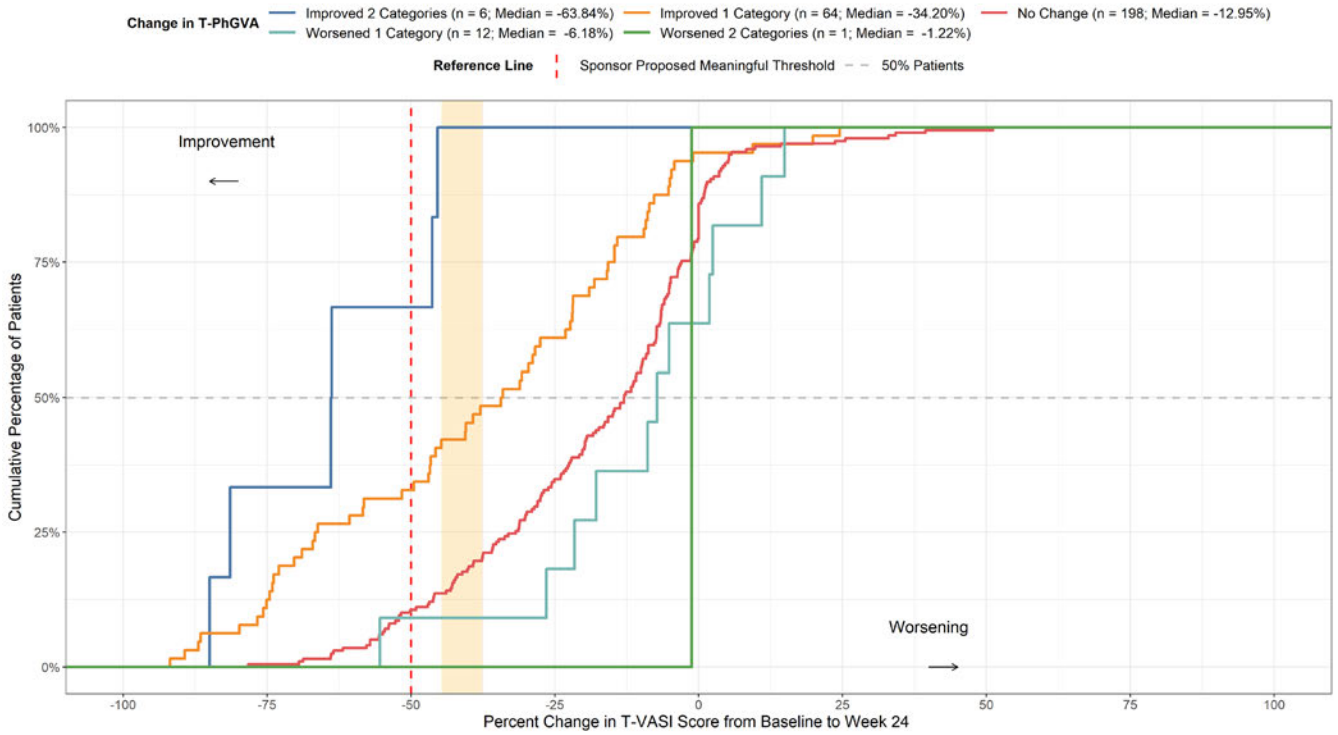
When patients' baseline T-PhGVA score was taken into account, the median percent change from baseline to Week 24 in T-VASI score for different baseline total body vitiligo severity varied (see Table 9 below). The majority of patients were rated as moderate disease severity at baseline by their clinicians. A 44.74% improvement and a 45.98% improvement would be needed to ensure that at least 50% of patients who were rated as moderate disease at baseline experience a meaningful change of 1-category improvement on the T-PhGVA, in Studies 306 and 307, respectively. Therefore, PFSS determined that a meaningful within-patient improvement range should be between 37.6% and 45.98% improvement across the two studies (Study 306: 37.60% to 44.74%; Study 307: 44.33% 45.98%).

Table 9. Percent Change From Baseline to Week 24 in T-VASI Score by Baseline T-PhGVA for Patients Who Achieved a 1-Category Improvement on T-PhGVA (Studies 306 and 307)

Study ID	Baseline T-PhGVA	N	Percent change from baseline to Week 24 in T-VASI Score				
			10th percentile	25th percentile	50th percentile	75th percentile	90th percentile
Study 306	Mild disease	6	-90.60	-88.73	-83.39	-65.46	-41.50
	Moderate disease	51	-75.07	-66.87	-44.74	-15.19	-5.00
	Severe disease	13	-58.84	-34.02	-23.14	-18.12	-10.25
Study 307	Mild disease	5	-73.43	-68.50	-57.36	0.00	3.90
	Moderate disease	80	-88.45	-75.37	-45.98	-17.40	0.00
	Severe disease	7	-54.98	-40.19	-39.31	-0.76	4.87

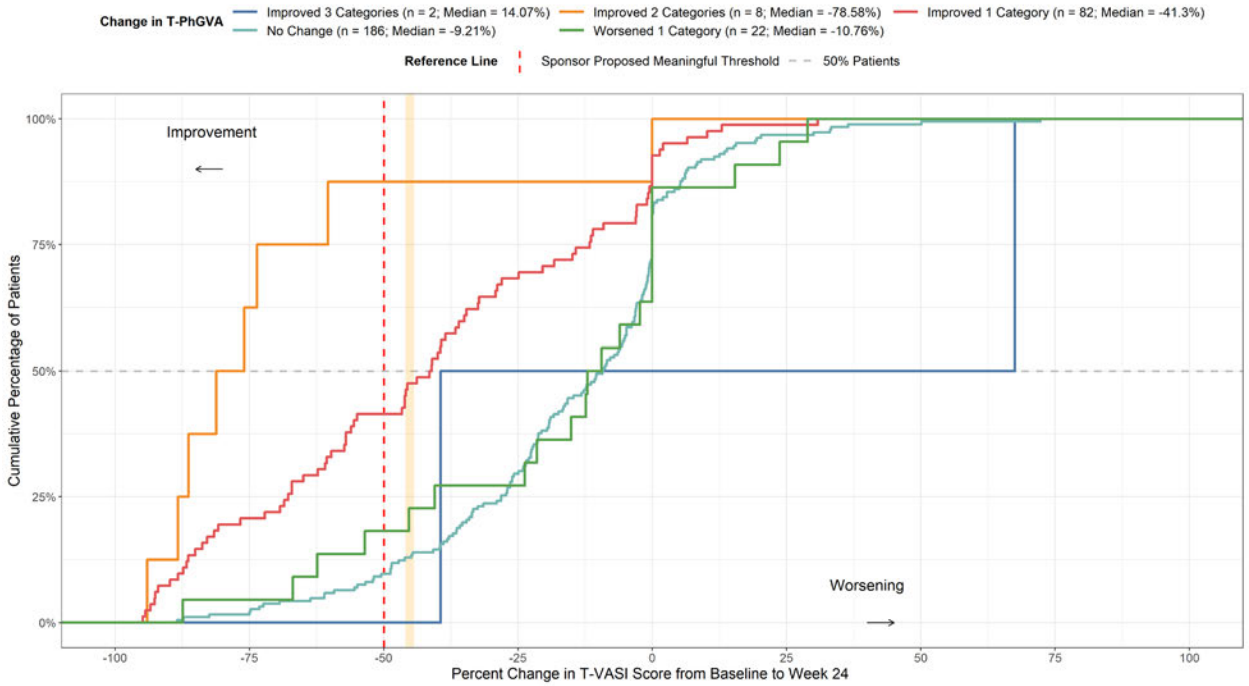
Source: PFSS reviewer generated table.
Abbreviation: T-PhGVA = Total Physician Global Vitiligo Assessment

Figure 1. eCDF, Percent Change From Baseline to Week 24 in T-VASI Score by T-PhGVA Category of Change From Baseline (Study 306)



Source: PFSS reviewer generated figure.
Note: Orange area denotes the PFSS-derived clinically meaningful within-patient change range (-44.74% to -37.60%)

Figure 2. eCDF, Percent Change From Baseline to Week 24 in T-VASI Score by T-PhGVA Category of Change From Baseline (Study 307)



Source: PFSS reviewer generated figure.
Note. Orange area denotes the PFSS-derived clinically meaningful within-patient change range (-45.98% to -44.33%).

2.3.2 Results Using T-PaGIC-V as the Anchor

Table 10 shows the distribution of the percent change in T-VASI score from baseline to Week 24 by each T-PaGIC-V response category at Week 24 for Study 306 and Study 307. For Study 306, the median percent change in the T-VASI score for patients who self-reported as "Much improved" on the T-PaGIC-V is -42.89%, which minimizes the misclassification rate to 14.35% (i.e., 14.35% of patients who experienced minimally improved, no change, or less in the T-PaGIC-V are incorrectly classified as experiencing meaningful change). For Study 307, the median percent change in the T-VASI score for patients who self-reported as "Much improved" is -46.07%, which minimizes the false classification rate to 16.25%. Therefore, a meaningful within-patient improvement range should be between 42.89% and 46.07% improvement across the two studies.

Table 10. Percent Change From Baseline to Week 24 in T-VASI Score by Baseline T-PaGIC-V Category (Studies 306 and 307)

Study ID	T-PaGIC at Week 24	N	Percent change in T-VASI from baseline to Week 24				
			10th percentile	25th percentile	50th percentile	75th percentile	90th percentile
Study 306	Very much improved	3	-79.42	-71.05	-57.10	-51.70	-48.46
	Much improved	59	-67.41	-56.36	-42.89	-22.19	-10.90
	Minimally improved	132	-55.49	-39.32	-20.50	-7.27	0.00
	No change	67	-28.85	-12.68	-4.84	1.65	10.24
	Minimally worse	18	-39.20	-17.40	-5.77	1.61	7.19
	Much worse	4	-56.29	-25.7	-6.17	-2.36	-0.07
	Very much worse	2	-30.09	-24.2	-14.38	-4.56	1.34
Study 307	Very much improved	15	-88.02	-83.16	-44.61	-32.50	-19.06
	Much improved	52	-87.23	-68.70	-46.07	-26.03	-10.80
	Minimally improved	122	-60.60	-40.75	-22.43	-3.46	0.00
	No change	95	-52.49	-12.59	-0.83	3.45	13.51
	Minimally worse	18	-43.79	-26.43	-0.82	0	7.78
	Much worse	3	-36.23	-22.64	0	3.25	5.19
	Very much worse	3	-5.22	-3.96	-1.87	6.78	11.97

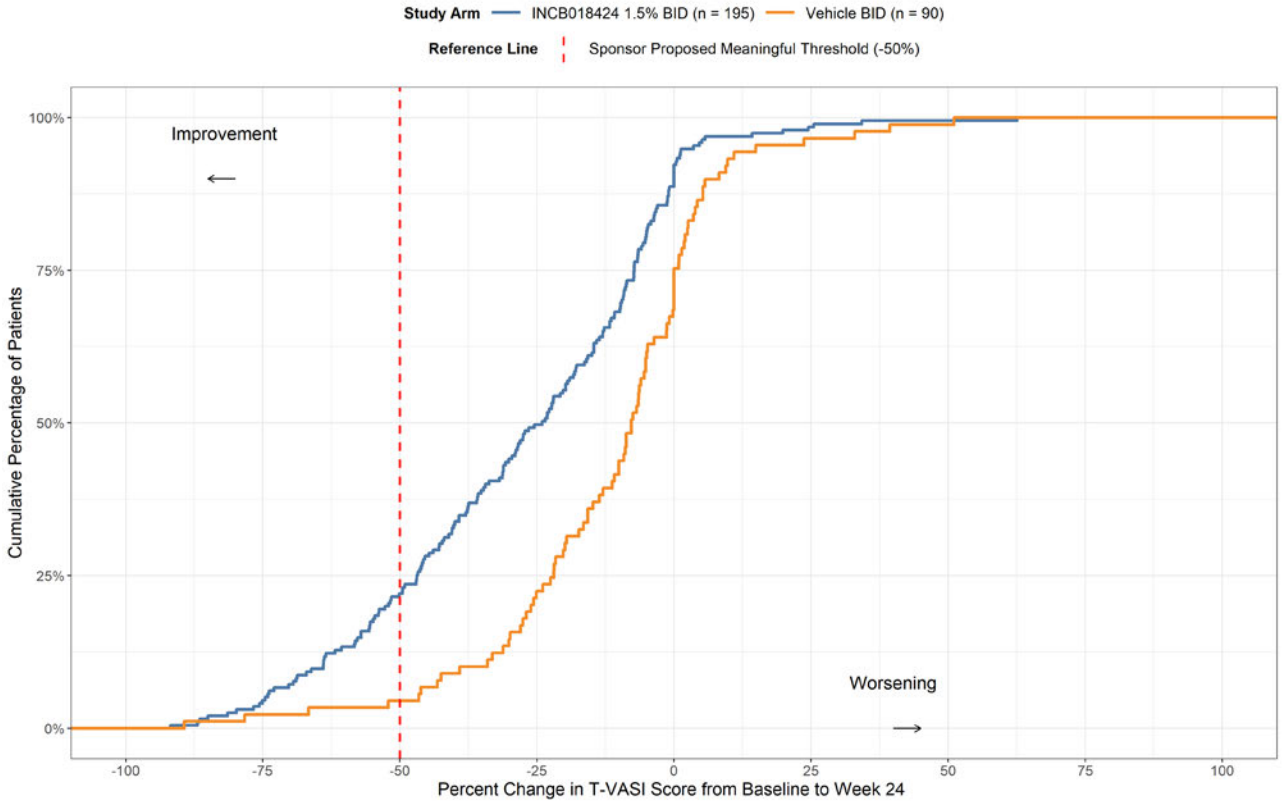
Source: PFSS reviewer generated table.

3 Conclusion

Based on findings from the quantitative anchor-based analyses, the Applicant's pre-specified ≥50% reduction in T-VASI score responder threshold is representative of a clinically meaningful improvement for patients with total body vitiligo at Week 24. Compared to the PFSS-determined meaningful threshold range, the ≥50% improvement appears to be a more stringent threshold. In addition, the findings from qualitative methods appear to complement the quantitative results reported in this review. Please refer to the DCOA review for detailed discussion on qualitative findings.

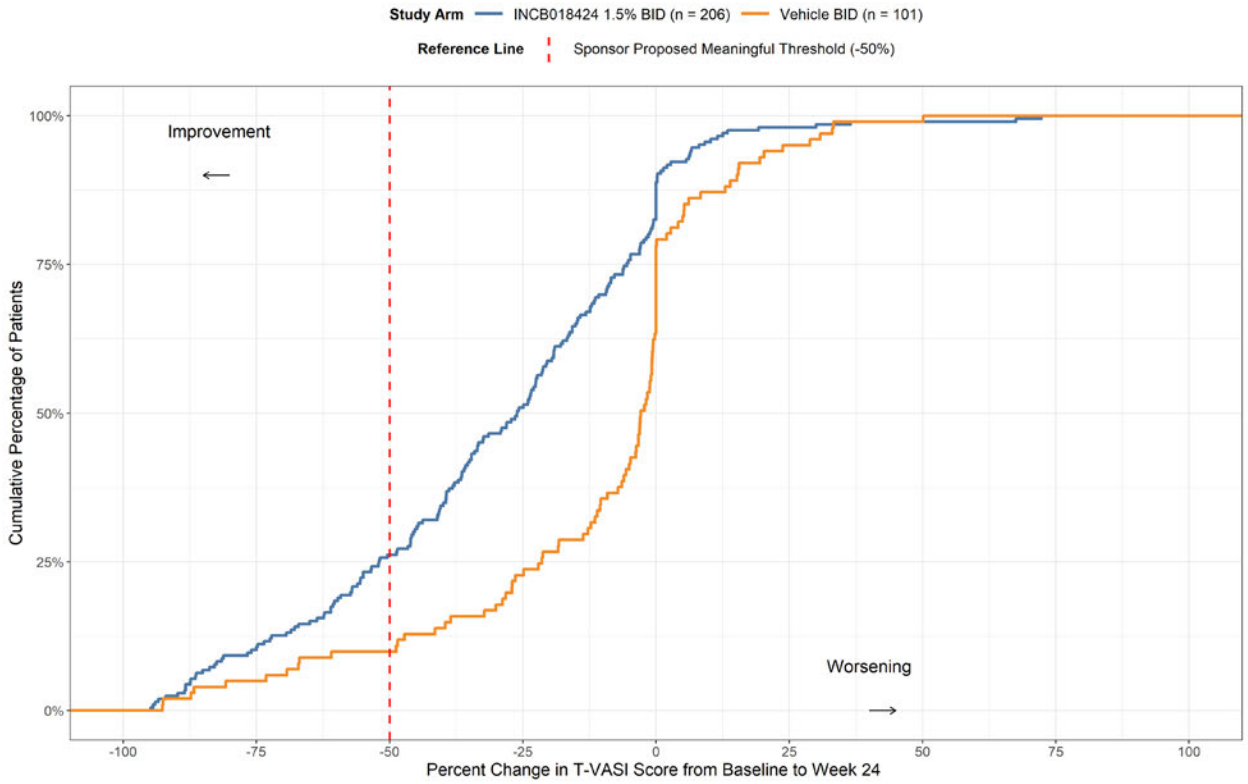
Furthermore, the eCDF plots of within-patient changes in the T-VASI score from baseline to Week 24 by treatment arm for Studies 306 and 307 are shown in Figures 3 and 4, respectively. Based on visual examination, there is a clear separation between treatment arms at the Sponsor's pre-specified ≥50% responder threshold in both studies.

Figure 3. eCDF, Percent Change From Baseline to Week 24 in T-VASI Score by Treatment Arm (Study 306)



Source: PFSS reviewer generated figure.

Figure 4. eCDF, Percent Change From Baseline to Week 24 in T-VASI Score by Treatment Arm (Study 307)



Source: PFSS reviewer generated figure.

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

/s/

WEIMENG WANG
07/06/2022 03:54:55 PM

LILI GARRARD
07/06/2022 03:55:28 PM

STATISTICAL REVIEW AND EVALUATION
FILING REVIEW OF AN NDA/BLA

NDA/BLA #:	NDA 215309
Supplement #:	Efficacy Supplement 1
Related IND #:	77101
Product Name:	Ruxolitinib cream, 1.5%
Indication(s):	Vitiligo
Applicant:	Incyte
Dates:	Stamp Date: 10/18/2021 PDUFA Date: 8/18/2022
Review Priority:	Standard
Biometrics Division:	Division of Biometrics III
Statistical Reviewer:	Kathleen Fritsch, Ph.D.
Concurring Reviewers:	Mohamed Alosh, Ph.D.
Medical Division:	Dermatology and Dentistry
Clinical Team:	Brenda Carr, M.D. / Hon-Sum Ko, M.D.
Project Manager:	Matthew White

1. Summary of Efficacy/Safety Clinical Trials to be Reviewed

Table 1: Summary of Trials to be Assessed in the Statistical Review

Trial ID	Sample Size	Study Design	Primary Endpoint or Objective
INCB 18424-306	Rux. 1.5% - 221 Veh. - 109	Randomized, double-blind, vehicle-controlled; 24-week treatment period with 28-week long-term extension	Primary – F-VASI-75 at Week 24 Secondary – F-VASI-50, F-VASI-90, T-VASI-50, VNS 4 or 5, percent change in F-BSA
INCB 18424-307	Rux. 1.5% - 228 Veh. - 115		
INCB 18424-211	Rux. 1.5% (BID) – 33 Rux. 1.5% (QD) – 30 Rux. 0.5% (QD) – 31 Rux 0.15% (QD) – 31 Veh. (BID) - 32	24-week randomized, double-blind, vehicle-controlled; (plus 18-week double-blind period (no vehicle) and 104-week open-label period)	Primary – F-VASI-50 at Week 24 Secondary –F-PhGVA, T-VASI-50

Studies 306 and 307 enrolled subjects age 12 and older with a clinical diagnosis of nonsegmental vitiligo with depigmented areas including ≥ 0.5% BSA on the face, ≥ 0.5 F-VASI, ≥ 3% BSA on non-facial areas, ≥ 3 T-VASI, and total body vitiligo area (facial and non- facial) not exceeding 10% BSA. The initial randomized treatment period was 24 weeks. Subjects who completed the initial treatment period with no additional safety concerns continued into the 28-week treatment extension. Subjects originally randomized to ruxolitinib 1.5% continued ruxolitinib 1.5% treatment and subjects originally randomized to vehicle were crossed over to the active treatment.

Facial Vitiligo Area Scoring Index (F-VASI) is measured by percentage of vitiligo involvement (% of BSA) and the degree of depigmentation. The percentage of BSA (hand unit) vitiligo involvement is estimated by the investigator using the Palmar Method, based on subject's hand size. The degree of depigmentation for each vitiligo involvement site is determined and estimated as: 0, 10%, 25%, 50%, 75%, 90%, or 100%. The F-VASI is then derived by multiplying the values assessed for the vitiligo involvement by the percentage of affected skin for each site on the face and summing the values of all sites together (possible range 0-3). Total body VASI (T-VASI) is calculated similarly as the sum of the number of hand units times the residual depigmentation across all body sites, where the body sites include head/neck, hands, upper extremities (excluding hands), trunk, lower extremities (excluding feet), and feet. For the Vitiligo Noticeability Scale (VNS), subjects compare a photo of their baseline status to their mirror reflection and provide one of the following responses regarding the status of their vitiligo compared to baseline: (1) more noticeable, (2) as noticeable, (3) slightly less noticeable, (4) a lot less noticeable, and (5) no longer noticeable.

The primary and key secondary efficacy endpoints were statistically significant in both studies. Note, there is a question about how the applicant conducted their multiple imputation for missing data, as their statistical programs lead to slightly different estimates from the study report for the primary endpoint in Study 306 (7.4% rather than 7.5% for the estimated vehicle response rate); however this does not impact the conclusions.

Table 2 –Efficacy Results

	INCB 18424-306		INCB 18424-307	
	Vehicle N=109	Ruxolitinib 1.5% N=221	Vehicle N=115	Ruxolitinib 1.5% N=229
F-VASI-75 (Study Report)	7.5%	29.9%	12.9%	29.9%
p-value		<0.0001		0.0021
F-VASI-50	17.2%	51.5%	23.4%	51.4%
p-value		<0.0001		<0.0001
F-VASI-90	2.2%	15.5%	1.9%	15.4%
p-value		0.0035		0.0159
T-VASI-50	4.9%	20.6%	11.3%	26.1%
p-value		0.0015		0.0038
VNS 4 or 5	3.3%	24.5%	6.6%	21.9%

p-value		0.0002		0.0015
Percent change in F-BSA (LSMean)	-9.5	-28.8	2.3	-16.3
p-value		<0.0001		0.0221

2. Assessment of Protocols and Study Reports

Table 3: Summary of Information Based Upon Review of the Protocol(s) and the Study Report(s)

Content Parameter	Response/Comments
Designs utilized are appropriate for the indications requested.	Yes
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	Yes
Interim analyses (if present) were pre-specified in the protocol with appropriate adjustments in significance level. DSMB meeting minutes and data are available.	NA
Appropriate details and/or references for novel statistical methodology (if present) are included (e.g., codes for simulations).	Yes
Investigation of effect of missing data and discontinued follow-up on statistical analyses appears to be adequate.	Yes

3. Electronic Data Assessment

Table 4: Information Regarding the Data

Content Parameter	Response/Comments
Dataset location	\\CDSESUB1\evsprod\nda215309\0021\m5\datasets\
Were analysis datasets provided?	Yes
Dataset structure (e.g., SDTM or ADaM)	SDTM and ADaM
Are the define files sufficiently detailed?	Yes
List the dataset(s) that contains the primary endpoint(s)	adqs.xpt

Content Parameter	Response/Comments
Are the *analysis datasets* sufficiently structured and defined to permit analysis of the primary endpoint(s) without excess data manipulation? *	Yes
Are there any initial concerns about site(s) that could lead to inspection? If so, list the site(s) that you request to be inspected and the rationale.	See OSI consult for selected sites
Safety data are organized to permit analyses across clinical trials in the NDA/BLA.	Yes

* This might lead to the need for an information request or be a refuse to file issue depending on the ability to review the data.

4. Filing Issues

Table 5: Initial Overview of the NDA/BLA for Refuse-to-file (RTF):

Content Parameter	Yes	No	NA	Comments
Index is sufficient to locate necessary reports, tables, data, etc.	X			
ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	X			
Data sets are accessible, sufficiently documented, and of sufficient quality (e.g., no meaningful data errors).	X			
Application is free from any other deficiency that render the application unreviewable, administratively incomplete, or inconsistent with regulatory requirements	X			

IS THE APPLICATION FILEABLE FROM A STATISTICAL PERSPECTIVE? Yes

5. Comments to be Conveyed to the Applicant

5.1. Refuse-to-File Issues

None.

5.2. Information Requests/Review Issues

1. The submitted annotated CRFs for Studies INCB 18424-306 and INCB 18424-307 do not include the forms on which the data for key efficacy assessments such F-VASI, T-VASI, VNS, or F-BSA was collected. Thus, the SDTM datasets include data that does not map back to the submitted annotated CRF. Submit annotated copies of the blank forms on which the data elements used to calculate efficacy endpoints were collected so that the annotated case report form is complete and maps to all collected efficacy data.
2. The submitted statistical program for analyses for the primary and key secondary endpoints which use multiple imputation for handling missing data (t_vasi.sas) appears to use different inputs than those described in the Statistical Analysis Plans for Studies INCB 18424-306 and INCB 18424-307, such as the number of imputations used in the analysis (30 vs. 10). Clarify all of the differences between the analyses described in the Statistical Analysis Plans and the submitted programs, including justification for each discrepancy.
3. In addition, the output for the primary endpoint multiple imputation analysis from program t_vasi.sas differs slightly from the results presented in the Clinical Study Report for Study INCB 18424-306. Clarify the discrepancy between the output of the statistical programs and the study report and submit either corrected programs or corrected result tables. Note also that when submitting programs to ensure that they include all necessary information to run the programs, such as custom formats.

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

/s/

KATHLEEN S FRITSCH
12/03/2021 08:29:28 AM

MOHAMED A ALOSH
12/03/2021 12:51:29 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA215309Orig1s001

OTHER REVIEW(s)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Templates
Version: 2018-01-24

Date:	September 15, 2021
Reviewer:	Joel L. Wessfeld, MD MPH Division of Epidemiology I
Deputy Director:	Sukhminder K. Sandhu, PhD MPH MS Division of Epidemiology I
Subject:	ARIA Sufficiency Memo
Drug Name(s):	ruxolitinib cream (OPZELURA)
Application Type/Number:	NDA 215309
Submission Number:	eCTD 0001
Applicant/sponsor:	Incyte Corporation
OSE RCM #:	2021-1039

Expedited ARIA Sufficiency Template for Pregnancy Safety Concerns

1. BACKGROUND INFORMATION

1.1. Medical Product

NDA 215309 seeks FDA approval for OPZELURA™ (ruxolitinib cream) as a JAK kinase (JAK) inhibitor for the topical treatment of atopic dermatitis. OPZELURA™ (ruxolitinib cream) and JAKAFI™ (ruxolitinib tablet; NDA 202192) contain the same active ingredient (ruxolitinib phosphate, molecular weight 404.36), a selective inhibitor of JAK1 and JAK2 (intracellular mediators of cytokine signaling). FDA-approved treatment indications for JAKAFI™ include (1) myelofibrosis, (2) polycythemia vera, and (3) steroid-refractory acute graft-versus-host disease.

The OPZELURA™ label drafted by Incyte (b) (4) (b) (4)

1.2. Describe the Safety Concern

Atopic dermatitis (a chronic inflammatory skin disease) occurs in children and adults, including women in reproductive age groups. JAK molecular pathways regulate cell adhesion and cell polarity, biologic processes important to embryonic development.[b] A maximal use pharmacokinetic study demonstrated potential for systemic absorption from topical application.[c] Taken together, these factors establish a potential for serious risk for adverse pregnancy, fetal, or infant outcomes from use of ruxolitinib cream during pregnancy.

APPENDIX 1 summarizes results from studies in pregnant animals.

- One study showed 9% lower fetal weights in pregnant rats treated with ruxolitinib at 22 times the maximum recommended human dose (MRHD).
- A second study showed 8% lower fetal weights in pregnant rabbits treated with ruxolitinib at 0.7 times MRHD.
- A third study in rats showed no adverse effects from ruxolitinib treatment at 3.1 times MRHD on embryofetal survival or postnatal growth.

For labeling purposes, clinical studies of ruxolitinib cream provide insufficient information about safety during pregnancy. The clinical safety database for ruxolitinib cream (as of April 30, 2021) contains nine instances of pregnancy exposure with outcomes described as (1) full-

[a] Prescribing Information for OPZELURA™ (ruxolitinib) cream, for topical use, submitted to NDA 215309 (eCTD 001) on December 21, 2020.

[b] Limpert JL, MC Dinatale, and LP Yao, Division of Pediatric and Maternal Health Review, OPZELURA (ruxolitinib) 1.5% cream, filed under NDA 215309 on May 24, 2021 (DARRTS Reference ID: 4799814), p 14.

[c] Limpert JL, *op. cit.*, p 14.

term birth without congenital malformation (n=2), (2) termination because of molar pregnancy (n=1), (3) spontaneous abortion (n=2), (4) induced abortion (n=1), and (5) outcome unknown (n=3).[d] The sponsor's pharmacovigilance database for oral ruxolitinib contains (as of February 22, 2021) 36 instances of pregnancy exposure with outcomes described as (1) livebirth (N=4) including one livebirth with a congenital malformation (ambiguous genitalia), (2) fetal death (n=1), (3) spontaneous abortion (n=4), (4) induced abortion (n=7), and (5) outcome unknown (n=20).[e]

Citing "anticipated use of ruxolitinib in females of reproductive potential who may become pregnant" in combination with "the limited information to date," the Division of Pediatric and Maternal Health (DPMH) recommended a pregnancy registry and a complementary study as separate Post-Marketing Requirements (PMRs).[f] DPMH presented the registry PMR as a means for assessing "major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to ruxolitinib during pregnancy."[g,h] Citing typically slow accrual to pregnancy registries, DPMH presented earlier availability of information as a rationale for a complementary study.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ Specific FDA-approved indication in pregnant women exists and exposure is expected

☐ No approved indication, but practitioners may use product off-label in pregnant women

☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized

☒ No approved indication, but use in women of child bearing age is a general concern

2.2. Regulatory Goal

☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision

[d] Limpert, *op. cit.*, pp 5-6.

[e] Limpert, *op. cit.*, pp 6-9.

[f] Limpert, *op. cit.*, pp 14-15.

[g] Limpert, *op. cit.*, p 15.

[h] PMR scope clarified as "ruxolitinib cream for the atopic dermatitis population." Email communication from J Limpert to J Weissfeld on May 24, 2021, 3:47 PM.

and certainty

☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty.

☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review).

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

☒ Pregnancy registry with internal comparison group

☐ Pregnancy registry with external comparison group

☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)

☐ Electronic database study with chart review

☒ Electronic database study without chart review (*e.g.*, retrospective cohort study using claims or electronic medical record data)

☒ Other, please specify: additional pregnancy study using a different design (*e.g.*, case-control study in a pre-existing pregnancy or birth defect registry)

2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

☐ Study Population

☐ Exposures

☒ Outcomes (pregnancy registry)

☒ Covariates (pregnancy registry)

☒ Analytical Tools (additional pregnancy study)

For any checked boxes above, please describe briefly:

Outcomes: ARIA lacks access to medical records. A pregnancy registry entails collection of detailed patient information. A requirement for detailed patient information necessitates data collection not possible in the Sentinel Distributed Database (SDD). The patient information requirement covers both details about (1) drug and concomitant exposures (e.g., precise timing of specific exposures in relation to days before or after pregnancy onset) and (2) outcomes of interest (e.g., specific type of congenital malformation). Pregnancy registry requirements for accurate classification of congenital malformation outcomes necessitate independent review of primary source documents by physicians with special training or expertise in clinical genetics or birth defects.

Covariates: Unlike a pregnancy registry, SDD provides incomplete information about critical covariates (*e.g.*, smoking, folate supplementation, and family history of birth defects).

Analytical tools: The requested PMRs target more than one outcome, including major congenital malformations (MCM), spontaneous abortions, stillbirths, small for gestational age, and preterm birth. Moreover, the MCM outcome covers several subclasses of potential interest (e.g., congenital malformation of the circulatory system, congenital malformation of the nervous system, or cleft lip and cleft palate). ARIA might address the complexity presented by multiple discrete outcomes by means of an appropriate data mining approach. However, a suitable data

mining approach (e.g., TreeScan) is not yet available for signal detection of birth defects and other pregnancy outcomes in ARIA.

2.5. Please include the proposed PMR language in the approval letter.

(b) (4)

APPENDIX 1: Section 8.1 text recommended by DPMH for OPZELURA™ (ruxolitinib cream)

8.1 Pregnancy

Pregnancy Exposure Registry

There will be a pregnancy registry that monitors pregnancy outcomes in pregnant persons exposed to OPZELURA during pregnancy. Pregnant persons exposed to OPZELURA and healthcare providers should report OPZELURA exposure by calling XXX-XXX-XXXX.

Risk Summary

Available data from pregnancies reported in clinical trials with OPZELURA are not sufficient to evaluate a drug-associated risk for major birth defects, miscarriage, or other adverse maternal or fetal outcomes. In animal reproduction studies, oral administration of ruxolitinib to pregnant rats and rabbits during the period of organogenesis resulted in adverse developmental outcomes at doses associated with maternal toxicity (see Data).

The background risks of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies carry some risk of birth defects, loss, or other adverse outcomes. The background risks in the U.S. general population of major birth defects and miscarriage is 2-4% and 15-20%, respectively.

Data

Animal Data

Ruxolitinib was administered orally to pregnant rats or rabbits during the period of organogenesis, at doses of 15, 30 or 60 mg/kg/day in rats and 10, 30 or 60 mg/kg/day in rabbits. There were no treatment-related malformations at any dose. A decrease in fetal weight of approximately 9% was noted in rats at the highest and maternally toxic dose of 60 mg/kg/day. This dose resulted in systemic exposure approximately 22 times the clinical systemic exposure at the maximum recommended human dose (MRHD; the clinical systemic exposure from ruxolitinib cream, 1.5% applied twice daily to 25-40% body surface area is used for calculation of multiples of human exposure). In rabbits, lower fetal weights of approximately 8% and increased late resorptions were noted at the highest and maternally toxic dose of 60 mg/kg/day. This dose resulted in systemic exposure approximately 70% the MRHD clinical systemic exposure.

In a pre- and post-natal development study in rats, pregnant animals were dosed with ruxolitinib from implantation through lactation at doses up to 30 mg/kg/day. There were no drug-related adverse effects on embryofetal survival, postnatal growth, development parameters or offspring reproductive function at the highest dose evaluated (3.1 times the MRHD clinical systemic exposure).

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

/s/

JOEL L WEISSFELD
09/15/2021 04:28:33 PM

SUKHMINDER K SANDHU
09/15/2021 04:33:25 PM

JUDITH W ZANDER
09/15/2021 04:58:25 PM

SARAH K DUTCHER
09/15/2021 09:42:41 PM

ROBERT BALL
09/16/2021 08:41:28 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	May 26, 2022
To:	Matthew White Senior Regulatory Project Manager **Division of Dermatology and Dentistry (DDD)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Ruth Mayrosh, PharmD Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Jessica Chung, PharmD, MS Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Laurie Buonaccorsi, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	OPZELURA (ruxolitinib)
Dosage Form and Route:	cream, for topical use
Application Type/Number:	NDA 215309
Supplement Number:	S-001
Applicant:	Incyte Corporation

1 INTRODUCTION

On October 18, 2021, Incyte Corporation submitted for the Agency's review a Prior Approval Supplement (PAS) – Efficacy to their approved New Drug Application (NDA) 215309/S-001 for OPZELURA (ruxolitinib) cream. With this submission, the Applicant proposes the addition of a new indication for the topical treatment of vitiligo in patients 12 years of age and older.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Dermatology and Dentistry (DDD) on November 17, 2021 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for OPZELURA (ruxolitinib) cream.

2 MATERIAL REVIEWED

- Draft OPZELURA (ruxolitinib) cream MG received on October 18, 2021, and received by DMPP and OPDP on May 18, 2022.
- Draft OPZELURA (ruxolitinib) cream Prescribing Information (PI) received on October 18, 2021 and April 29, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 18, 2022.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

(b) (4)

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

/s/

JESSICA M CHUNG
05/26/2022 11:46:28 AM

LAURIE J BUONACCORSI
05/26/2022 11:58:56 AM

RUTH I MAYROSH
05/26/2022 12:02:33 PM

SHARON R MILLS
05/26/2022 12:06:51 PM

Office of Lifecycle Drug Products
Division of Post-Marketing Activities I, Branch II
Review of Chemistry, Manufacturing, and Controls

1. **NDA Supplement Number: NDA-215309-SUPPL-1**

2. **Submission(s) Being Reviewed**: SDN 45

Submission	Type	Submission Date	CDER Stamp Date	Assigned Date	PDUFA Goal Date	Review Date
Original Supplement	PA	18-OCT-2021	18-OCT-2021	18-OCT-2021	18-APR-2022	10-MAR-2022

3. **Proposed Changes**: Efficacy supplement providing for a new indication: the topical treatment of vitiligo in patients 12 years of age and older.

4. **Review #**: 1

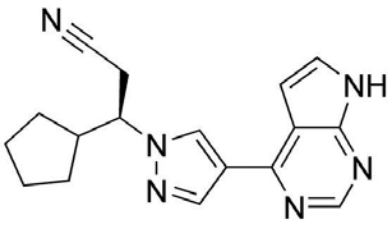
5. **Clinical Review Division**: Division of Dermatology and Dentistry (DDD)

6. **Name and Address of Applicant**: Incyte Corp.
1801 Augustine Cut-Off
Wilmington, DE 19803

7. **Drug Product**:

Drug Name	Dosage Form	Strength	Route of Administration	Rx or OTC	Special Product
Opzelura® (ruxolitinib)	Cream	1.5%	Topical	℞	No

8. **Chemical Name and Structure of Drug Substance**:



USAN: Ruxolitinib (IUPAC)
Chemical name: (3*R*)-3-cyclopentyl-3-[4-(7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)pyrazol-1-yl]propanenitrile
Molecular formula: $C_{17}H_{18}N_6$
MW: 306.4
CAS No.: [941678-49-5]

9. **Indication**: 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. PROPOSED: For the topical treatment of vitiligo in patients 12 years of age and older.

10. **Supporting/Relating Documents**: None.

11. **Consults**: None.

12. Executive Summary: This Efficacy supplement was submitted to NDA 215309 for Opzelura® (ruxolitinib) Cream, 1.5%, to provide for a new indication: the topical treatment of vitiligo in patients 12 years of age and older.

No changes were proposed to the CMC-related sections of the labeling (Sections 3 Dosage Forms and Strengths, 11 Description, 16 How Supplied/Storage and Handling) or to the carton and container labels.

The Applicant has requested a Categorical Exclusion from the requirement for preparation of an Environmental Assessment for the proposed change, which would result in increased usage of the active moiety upon approval. The claim included an estimate of total annual usage of the active ingredient from all products, and a calculation of the Estimated Introduction Concentration (EIC) therefrom; the estimate falls well below the (b) (4) action limit. The Categorical Exclusion request is therefore granted.

13. Conclusions & Recommendations:

This supplement is recommended for approval.

14. Comments/Deficiencies to be Conveyed to Applicant:

None. Approval is recommended.

15. Primary Reviewer:
Joel S. Hathaway, Ph.D., CMC reviewer, Branch II, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, Office of Pharmaceutical Quality (OPQ)
(see attached electronic signature)

16. Secondary Reviewer:
David B. Lewis, Ph.D., Branch Chief, Branch II, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, Office of Pharmaceutical Quality (OPQ)
(see attached electronic signature)

Joel Hathaway

Digitally signed by Joel Hathaway
Date: 3/10/2022 11:14:39AM
GUID: 508da72000029f70451ddd2b8b75a2fd

David Lewis

Digitally signed by David Lewis
Date: 3/10/2022 11:44:33AM
GUID: 508da72000029f287fa31e664741b577
Comments: concur; recommend approval from the standpoint of CMC

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	March 8, 2022
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	NDA 215309 /S-001 NDA 215309 /S-002
Product Name, Dosage Form, and Strength:	Opzelura (ruxolitinib) cream, 1.5%
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Incyte Corporation
FDA Received Date:	October 18, 2021 and December 17, 2021
OSE RCM #:	2021-2223 and 2022-47
DMEPA 1 Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA 1 Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

1 REASON FOR REVIEW

Incyte Corporation submitted two supplements for Opzelura (ruxolitinib) cream to provide for a new indication (NDA 215309/S-001): "topical treatment of vitiligo in patients 12 years of age and older" and to provide for the addition of a second package size of the already approved aluminum tube container closure system and manufacturing changes (NDA 215309/S-002). Subsequently, the Division of Dermatology and Dentistry (DDD) requested that we review the proposed Opzelura prescribing information (PI), container label, carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Supplement NDA 215309/S-001 provides revisions to the Prescribing Information (PI) for the proposed indication of topical treatment of vitiligo in patients 12 years of age and older. The currently approved dosage form and strength support the proposed new indication. We find the PI acceptable from a medication error perspective.

Supplement NDA 215309/S-002 provides revisions to the Prescribing Information (PI) for the inclusion of a 100 g package size and associated container label and carton labeling. (b) (4) (b) (4). We find the proposed revisions to the PI and proposed Opzelura 100 gram container label and carton labeling acceptable from a medication error perspective.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed Prescribing Information (PI) for both supplements as well as the container label and carton labeling for Opzelura 100 gram presentation are acceptable from a medication error perspective. We have no recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Opzelura received on October 18, 2021 and December 17, 2021 from Incyte Corporation.

Table 2. Relevant Product Information for Opzelura	
Initial Approval Date	September 21, 2021
Active Ingredient	ruxolitinib
Indication	Current 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 Proposed the topical treatment of vitiligo in patients 12 years of age and older
Route of Administration	topical
Dosage Form	cream
Strength	1.5%
Dose and Frequency	(b) (4) [redacted]

How0 Supplied	(b) (4)
Storage	20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F)
Container Closure	(b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On February 15, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, 'ruxolitinib'. Our search identified two previous reviews[a,b], and we considered our previous recommendations to see if they are applicable for this current review.

[a] Patel, M. Label and Labeling Review for ruxolitinib (NDA 215309). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAR 30. RCM No.: 2020-2688.

[b] Patel, M. Label and Labeling Review for Opzelura (NDA 215309). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 SEP 16. RCM No.: 2020-2688-1.

APPENDIX G. LABELS AND LABELING

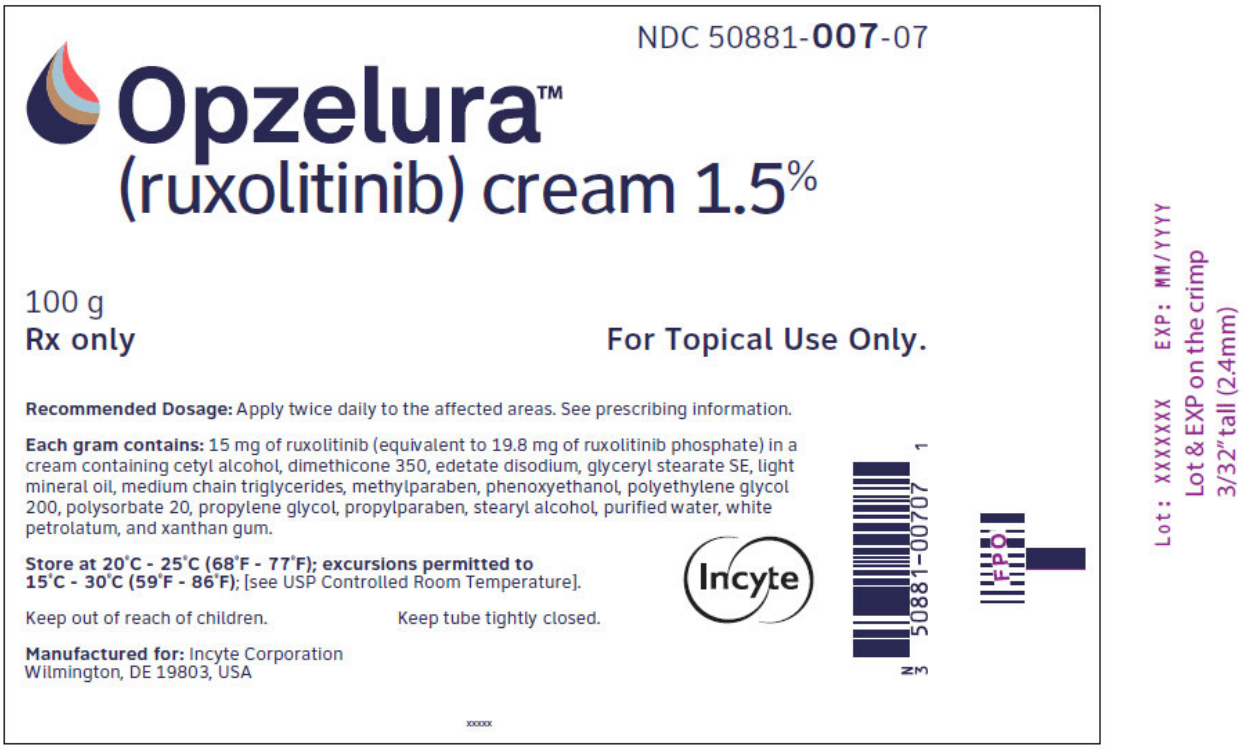
G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Opzelura labels and labeling submitted by Incyte Corporation.

- Container label received on December 17, 2021
- Carton labeling received on December 17, 2021
- Prescribing Information (Images not shown) received on October 18, 2021 and December 17, 2021, available from \\CDSESUB1\evsprod\nda215309\0021\m1\us\draft-labeling-text-redline.pdf and \\CDSESUB1\evsprod\nda215309\0023\m1\us\draft-labeling-text-redline.pdf

G.2 Label and Labeling Images

Container Label



[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Carton Labeling

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

/s/

MADHURI R PATEL
03/08/2022 09:20:54 AM

SEVAN H KOLEJIAN
03/08/2022 09:59:47 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA21530Orig1s001,3

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: May 25, 2022

To: Brenda Carr, MD, Clinical Reviewer,
Division of Dermatology and Dentistry (DDD)
Snezana Trajkovic, MD, Clinical Team Leader, DDD
Matthew White, Regulatory Project Manager, DDD

From: Laurie Buonaccorsi, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments OPZELURA™ (ruxolitinib) cream, for topical use.

NDA: 215309

In response to DDD's consult request dated November 17, 2021, OPDP has reviewed the proposed product labeling (PI) and Medication Guide for the supplemental NDA submission for OPZELURA™ (ruxolitinib) cream, for topical use (Opzelura). This supplement expands the indication to include the topical treatment of nonsegmental vitiligo in adult and pediatric patients 12 years of age and older.

Labeling

PI: OPDP's comments on the proposed labeling are based on the draft PI and Medication Guide received by electronic mail from DDD on May 18, 2022, and our comments are provided below.

Medication Guide: A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Laurie Buonaccorsi at (240) 402-6297 or laurie.buonaccorsi@fda.hhs.gov.

Following this page, 16 Pages of Draft Labeling have been Withheld in Full as (b)(4)

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

/s/

LAURIE J BUONACCORSI
05/25/2022 01:33:36 PM